

Evaluation and management of patients with coronary chronic total occlusions considered for revascularisation. A clinical consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC, the European Association of Cardiovascular Imaging (EACVI) of the ESC, and the ESC Working Group on Cardiovascular Surgery

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ABSTRACT

Chronic total occlusions (CTOs) of coronary arteries can be found in the context of chronic or acute coronary syndromes; sometimes they are an incidental finding in those apparently healthy individuals undergoing imaging for preoperative risk assessment. Recently, the invasive management of CTOs has made impressive progress due to sophisticated preinterventional assessment, including advanced non-invasive imaging, the availability of novel and dedicated tools for CTO percutaneous coronary intervention (PCI), and experienced interventionalists working in specialised centres. Thus, it is crucial that referring physicians who see patients with CTO be aware of recent developments and of the initial evaluation requirements for such patients. Besides a careful history and clinical examination, electrocardiograms, exercise tests, and non-invasive imaging modalities are important for selecting the patients most suitable for CTO PCI, while others may be referred to coronary artery bypass graft or optimal medical therapy only. While CTO PCI improves angina and reduces the use of antianginal drugs in patients with symptoms and proven ischaemia, hibernation and/or wall motion abnormalities at baseline or during stress, the effect of CTO PCI on major cardiovascular events is still controversial. This clinical consensus statement specifically focuses on referring physicians, providing a comprehensive algorithm for the preinterventional evaluation of patients with CTO and the current evidence for the clinical effectiveness of the procedure. The proposed care track has been developed by members and with the support of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Association of Cardiovascular Imaging (EACVI), and the European Society of Cardiology (ESC) Working Group on Cardiovascular Surgery.

KEYWORDS: chronic coronary total occlusion; left ventricular dysfunction; Heart Team; multiple vessel disease; stable angina

The management of coronary chronic total occlusions (CTOs) is clinically and technically challenging and requires a close collaboration between referring physicians and specialised centres¹. The therapeutic options for patients with CTOs have expanded immensely thanks to sophisticated preinterventional planning, including advanced cardiac imaging, advanced percutaneous coronary intervention (PCI) equipment, cardiac surgery, and effective anti-ischaemic optimal medical therapy (OMT). Because of these developments, the success rate of CTO PCI today exceeds 80-90% in the hands of expert operators working at specialised CTO referral centres^{2,3}. According to the CTO Academic Research Consortium (CTO-ARC), a CTO is defined as an occlusion of an epicardial coronary artery without antegrade flow through the lesion and with a probable or definite duration of ≥ 3 months, based on angiographic criteria such as a Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow through the lesion with no evidence of a thrombus, no staining at the proximal cap, and the presence of mature collaterals⁴. Contemporary, consecutive series of patients undergoing invasive coronary angiography (ICA) reported the presence of at least one CTO in 15-20% of cases^{5,6}.

However, the decision-making process for the management of such patients requires a thorough clinical evaluation with initial examinations including electrocardiograms (ECGs), echocardiography, exercise tests, or cardiac imaging stress tests.

This clinical consensus statement, involving the European Society of Cardiology (ESC) Association of Percutaneous Cardiovascular Interventions (EAPCI), the ESC Association of Cardiovascular Imaging (EACVI), as well as the ESC Working Group on Cardiovascular Surgery, proposes a comprehensive algorithm for patients in whom a CTO has been diagnosed, providing a preinterventional evaluation targeted to the patient's condition and needs.

The CTO patient: characteristics and clinical phenotypes

CTOs may be discovered in different clinical settings, such as acute coronary syndromes (ACS), in the context of chest pain evaluation, as a consequence of documented ischaemia using different imaging modalities¹ or incidentally, during a coronary angiography workup before surgical valve replacement or vascular surgery, among others^{1,5,6}. While patients complaining of exertional symptoms (e.g., angina, dyspnoea) have a clear diagnostic and therapeutic path to be followed, asymptomatic patients must be carefully evaluated based on further examinations usually not available to the treating physician at the time of presentation (**Figure 1**).

In both circumstances, it is desirable to carefully evaluate the patient's age, frailty, and comorbidities (e.g., significant concomitant valvular heart disease, large aortic aneurysms, non-cardiac limitations of functional capacity, ongoing oncological treatment and/or cognitive deficits, among others). These clinical elements should concur with technical considerations to guide the decision between OMT or revascularisation and, in the latter group, between PCI and surgery. Of note, patients with CTO are older, more often diabetic and with a greater impairment of left ventricular ejection fraction (LVEF), compared with patients without CTO⁶.

Other patients may present with ACS, including ST-segment elevation myocardial infarction (STEMI). In the case of type 1 myocardial infarction (MI), with either a plaque rupture or erosion in the culprit artery providing collaterals to another coronary artery with a CTO, prognosis is poor because of the double injury due to interruption of collateral flow from the culprit artery to the CTO territory⁷. Notably, about one-third of patients who are resuscitated because of a cardiac arrest have a CTO⁸. If severe acute ischaemia has led to cardiogenic shock, complete revascularisation beyond the infarct-related artery should be avoided. Indeed, the initial suggestion of the SHOCK trial that complete revascularisation should be attempted in this setting was refuted by later trials^{9,10}. Conversely, there is convincing evidence supporting complete revascularisation for STEMI without cardiogenic shock and multivessel disease¹¹. However, these trials were not specifically targeted for patients with CTO in non-culprit arteries (**Table 1**).

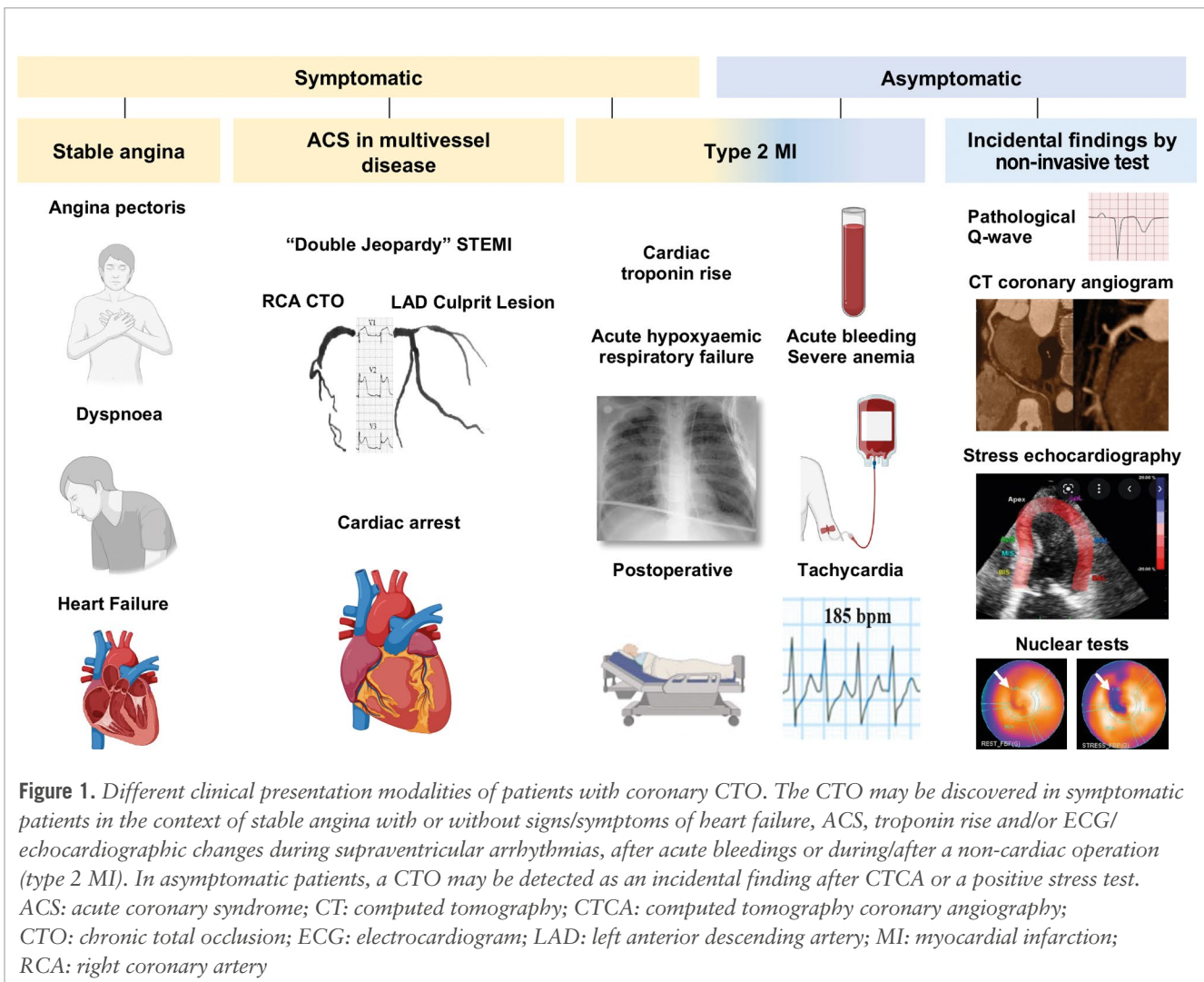
Patients with non-STEMI-ACS also require immediate treatment of the culprit artery, with the added challenge of ruling out the CTO as the cause of or contributor to the acute event¹² (**Table 1**). Besides clinical clues, the absence of contrast staining, which is typical of fresh thrombotic occlusions, and the presence of well-developed collaterals towards the distal segment of the CTO normally allow a distinction between acute and chronic coronary occlusions. A particularly interesting subgroup includes patients with type 2 MI (i.e., MI secondary to ischaemia due to either increased oxygen demand or decreased supply). They typically present with increased troponin levels, ECG changes and/or regional wall motion abnormalities, with or without symptoms^{1,13}. In such cases, the treatment should focus on the acute trigger disrupting a previously stable situation with no immediate need of an urgent or emergent CTO revascularisation, but with consideration of it at a later stage (**Table 1**).

Initial examination

The main indication for CTO recanalisation is to relieve exercise-limiting symptoms such as angina. Thus, the initial

Abbreviations

ACS	acute coronary syndromes	ECG	electrocardiogram	PCI	percutaneous coronary intervention
CABG	coronary artery bypass grafting	LVEF	left ventricular ejection fraction	STEMI	ST-segment elevation myocardial infarction
CTCA	computed tomography coronary angiography	MACE	major adverse cardiovascular events	VA	ventricular arrhythmias
CTO	chronic total occlusion	MI	myocardial infarction		
		MRI	magnetic resonance imaging		



clinical examination requires a comprehensive and careful assessment of the symptomatic status, as well as possible changes in the customary exercise levels over the past months or years, taking in account that, often, CTO patients may adapt to their limited exercise capacity and may not perceive or report their functional status limitation appropriately. Furthermore, symptoms are not limited to chest pain only; indeed, dyspnoea is at least as frequent as angina, and this improves after successful recanalisation¹⁴.

The assessment of exercise-induced symptoms can be objectively performed in a “patient-centred” fashion, using tools such as the modified Seattle Angina Questionnaire (SAQ)¹⁵, the EuroQol quality-of-life 5-dimensional score (EQ-5D)¹⁶ or Rose Dyspnea Scale (RDS)¹⁷ (Figure 2). Depression may also be more prevalent in patients with CTO¹⁸ and may mask exercise-related symptoms. After blood tests, ECGs and echocardiography, different imaging modalities are useful to assure that an angiographically documented CTO serves viable myocardium and indeed induces significant ischaemia during stress¹⁹ (Central illustration). If an imaging stress test is not feasible or locally unavailable, a bicycle or treadmill exercise tolerance test might be carried out to determine the patient’s true functional capacity, the severity of exercise-induced

angina and/or dyspnoea, and their reproducibility compared to the patient’s history.

Furthermore, many patients may have silent ischaemia in the CTO territory as well. In such cases, collaterals commonly prevent regional myocardial dysfunction or MI, but their functional capacity to increase myocardial blood flow to the CTO territory during exercise may be limited. Typically, fractional flow reserve (FFR) assessed distal to a CTO is usually below 0.5^{20,21}. Thus, the use of non-invasive ischaemia tests should be strongly encouraged, especially in patients with atypical symptoms or in those complaining of dyspnoea, to ascertain their ischaemic origin. Finally, in asymptomatic patients with left ventricular (LV) dysfunction, the assessment of inducible ischaemia/viability may have a prognostic value²² and might be considered during follow-up to guide coronary revascularisation in selected cases only (Central illustration).

If ischaemia leads to regional wall motion abnormalities, as assessed by imaging, the functional recovery of LV function depends on the extent of hibernating or stunned, but viable, myocardium. However, the evaluation of hibernation or stunning in patients with CTO has led to conflicting results²³⁻²⁶ (Table 1).

Table 1. Expert panel statements.

	Evidence available
The CTO recanalisation success rate has dramatically increased (85-90%), provided that expert operators are offered the full availability of dedicated interventional tools.	RCTs and registries: uncontroversial ^{2,3,5,6,25,26,29,48,49,54-56, 59,60}
Frequency and severity of complications is higher (1-3%) compared with most PCI procedures in CCS. This requires careful consideration of the benefit and risk balance before embarking upon CTO recanalisation or moving to recanalisation modalities (ADR, retrograde) that pose higher complication risks.	Registries and meta-analyses: uncontroversial ^{2,3,5,6,25,48,49}
A specific consent form listing the differences with other PCI procedures (duration, double access, lack of certainty of success, slightly higher risk of complications) should be submitted to patients and discussed with the main operator before the procedure.	Expert consensus
<i>Ad hoc</i> CTO PCI (i.e., during the same diagnostic angiogram) is discouraged. CTO PCI should be started only after having ensured that sufficient time is available, experienced operators are present and a well-defined strategy has been developed. The treating physicians will have the opportunity to review indications, perform additional tests if needed, and inform the patient and his family, leaving enough time for decision-making.	Expert consensus
The complexity of CTO procedures can be graded, and the most complex (stumpleless, ostial, very calcified, or long and tortuous, previously failed) should be reserved for dedicated operators or performed with proctorship.	Expert consensus
The presence of a CTO during ACS (especially STEMI) increases the risk that the patient develops cardiogenic shock, but attempts at recanalisation in the acute phase should be discouraged.	Randomised trials ^{9,10,11}
Complete revascularisation appears beneficial in STEMI and, with less compelling evidence, in NSTEMI. CTO PCI during primary angioplasty should be discouraged.	Randomised trial ¹¹ . Expert consensus on timing and modalities of CTO treatment
In CCS patients with multivessel disease with clinical or anatomical preference for PCI over CABG, the timing of CTO PCI and the sequence of treatment of non-CTO and CTO lesions deserve careful consideration.	Expert consensus
Symptoms of angina or dyspnoea likely caused by the persistence of a CTO and resistant to medical therapy should be the main driver of CTO recanalisation.	Randomised trials and registries ⁵¹⁻⁵⁵
Myocardial revascularisation decision, in the context of left main/multivessel disease, including CTO lesions, is optimised by a Heart Team approach.	ESC and ACC guidelines on myocardial revascularisation ^{43,44}
Current evidence does not support the use of CTO PCI to improve prognosis (reduce mortality and incidence of myocardial infarction). Randomised trials have limitations in terms of sample size, patient selection bias and trial design, and it is worth noting the opposite results in large, nationwide, long-term registries comparing patients who had successful or failed CTO with those patients undergoing revascularisation or left under medical treatment.	Consensus that the conflicting evidence from randomised trials and large registries ⁵¹⁻⁶¹ is still insufficient to draw firm conclusions
Current evidence is still not sufficient to draw firm conclusions on the use of CTO PCI to improve left ventricular function.	Evidence from meta-analyses ²⁴ and registries ^{25,32} was not confirmed in a randomised ⁶⁴ trial
The assessment of inducible ischaemia and viability in the CTO territory is advisable in case of LV dysfunction. MRI, if available, should be preferred over nuclear tests and stress echocardiography for viability assessment.	Expert consensus

ACC: American College of Cardiology; ACS: acute coronary syndromes; ADR: antegrade dissection and re-entry; CABG: coronary artery bypass grafting; CCS: chronic coronary syndrome; CTO: chronic total occlusion; ESC: European Society of Cardiology; LV: left ventricular; MRI: magnetic resonance imaging; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; RCT: randomised controlled trials; STEMI: ST-segment elevation myocardial infarction

One aspect that is often not routinely evaluated is the incidence of ventricular arrhythmias (VA) in patients with CTO and ischaemic cardiomyopathy. Indeed, among patients with VA on admission, the presence of a coronary CTO is independently associated with increased midterm all-cause mortality²⁷. Furthermore, among patients with ischaemic cardiomyopathy and an 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 therapy²⁸.

Imaging

A comprehensive imaging workup in patients with CTO ideally aims at defining the anatomy of the involved coronary artery,

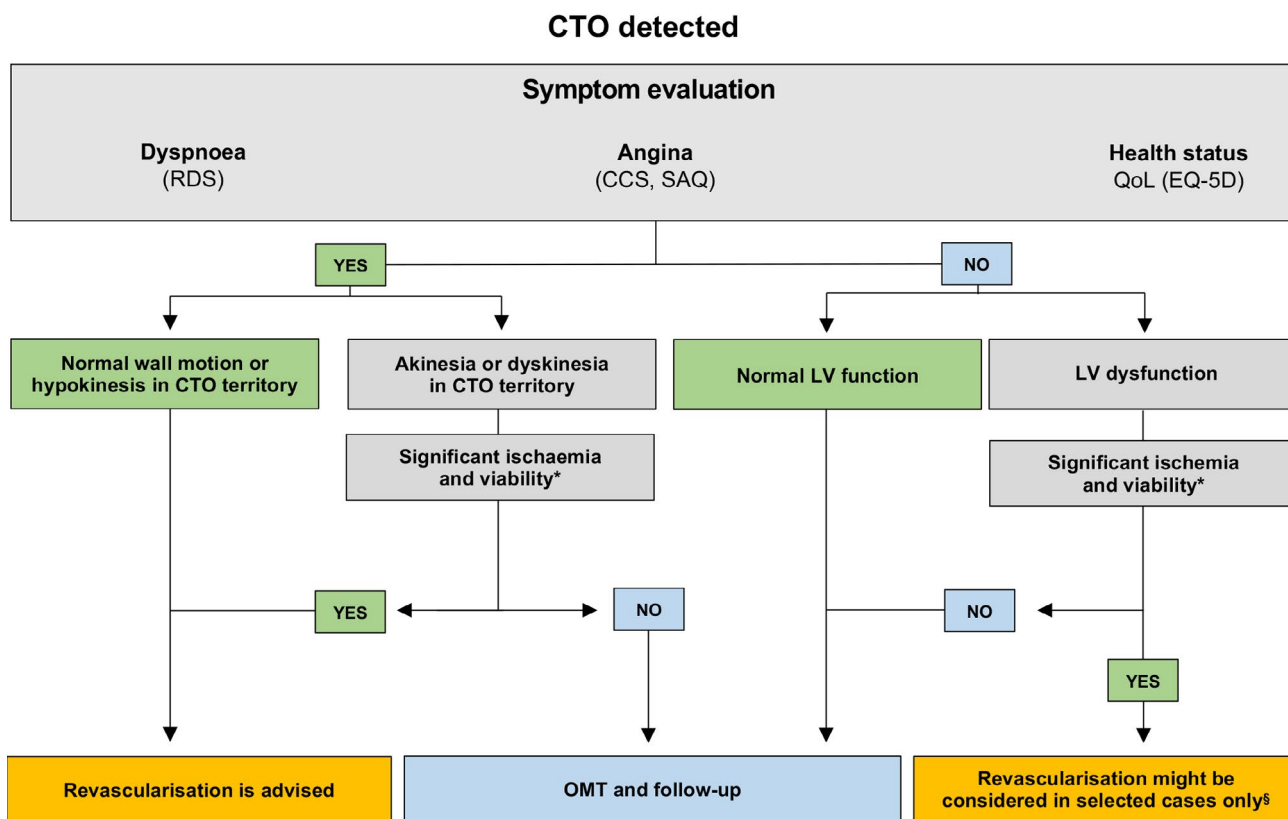
the amount of inducible ischaemia, and the viability of the myocardial segments supplied by it as a basis for decision-making and for procedural guidance, and eventually to predict the effect of CTO revascularisation on LV remodelling and/or residual ischaemia at follow-up (**Table 2**).

This section provides practical advice regarding the use of all these different imaging modalities, alone or in combination, each of them with their advantages and weaknesses.

LV STRUCTURE AND FUNCTION

The primary goal of assessing left ventricular function is risk assessment for a planned CTO procedure because complications increase as LVEF decreases²⁹. Echocardiography, especially if refined with myocardial strain imaging, is the first choice due to its wide availability³⁰. Furthermore,

Flowchart of patients with CTO.



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*see Table 2 for inducible ischaemia/viability cutoff of each imaging modality. [§] E.g., young patients, with proximal LAD CTO, and demonstration of significant silent inducible ischaemia and viability. CCS: Canadian Cardiovascular Society; CTO: chronic total occlusion; EQ-5D: EuroQol five-dimensional; LV: left ventricular; MRI: magnetic resonance imaging; OMT: optimal medical therapy; QoL: quality of life; RDS: Rose Dyspnea Scale; SAQ: Seattle Angina Questionnaire

echocardiography can rule out other possible concomitant pathologies, such as heart valve disease or aortic aneurysms, that must be considered before coronary revascularisation.

ISCHAEMIA QUANTIFICATION AND MYOCARDIAL VIABILITY

The revascularisation of a CTO should only be indicated if the myocardial segments supplied by it are viable and ischaemic upon pharmacological stress or exercise.

Nowadays, many different imaging tests can be used for these purposes, each of them with advantages and drawbacks (Table 2). However, the local availability of such technologies and the local imagers' expertise can drive the preferential choice of one test over another.

Patients with a large area of viable and ischaemic myocardium are likely symptomatic and would likely derive benefit from CTO revascularisation; conversely, minor degrees of ischaemia commonly respond well to OMT^{31,32}. Furthermore, patients with extensive ischaemic burden reduction and no residual ischaemia after CTO PCI have lower rates of

all-cause death and non-fatal myocardial infarction as compared with those with significant residual perfusion defect. Moreover, long-term cardiac symptom relief was associated with normalisation of hyperaemic myocardial blood flow (hMBF) levels after CTO PCI³³. Stress cardiac magnetic resonance imaging (cMRI) perfusion, using a gadolinium-based contrast agent and pharmacological vasodilation, is currently considered state-of-the-art for detecting ischaemia and viability, providing precise information about fibrosis and scarring^{34,35}. Indeed, after successful revascularisation, myocardial contractility recovery of those segments supplied by the CTO vessel is likely if transmural late gadolinium enhancement (LGE) is <25%, while it is very unlikely if LGE is >75%. Unfortunately, for segments in the intermediate range, the predictive accuracy of LGE transmural is limited; this aspect might explain why successful CTO PCI of a dysfunctional but viable myocardium does not lead to the expected left ventricular function recovery in all patients^{35,36}. Beyond cMRI, stress echocardiography is widely used for the

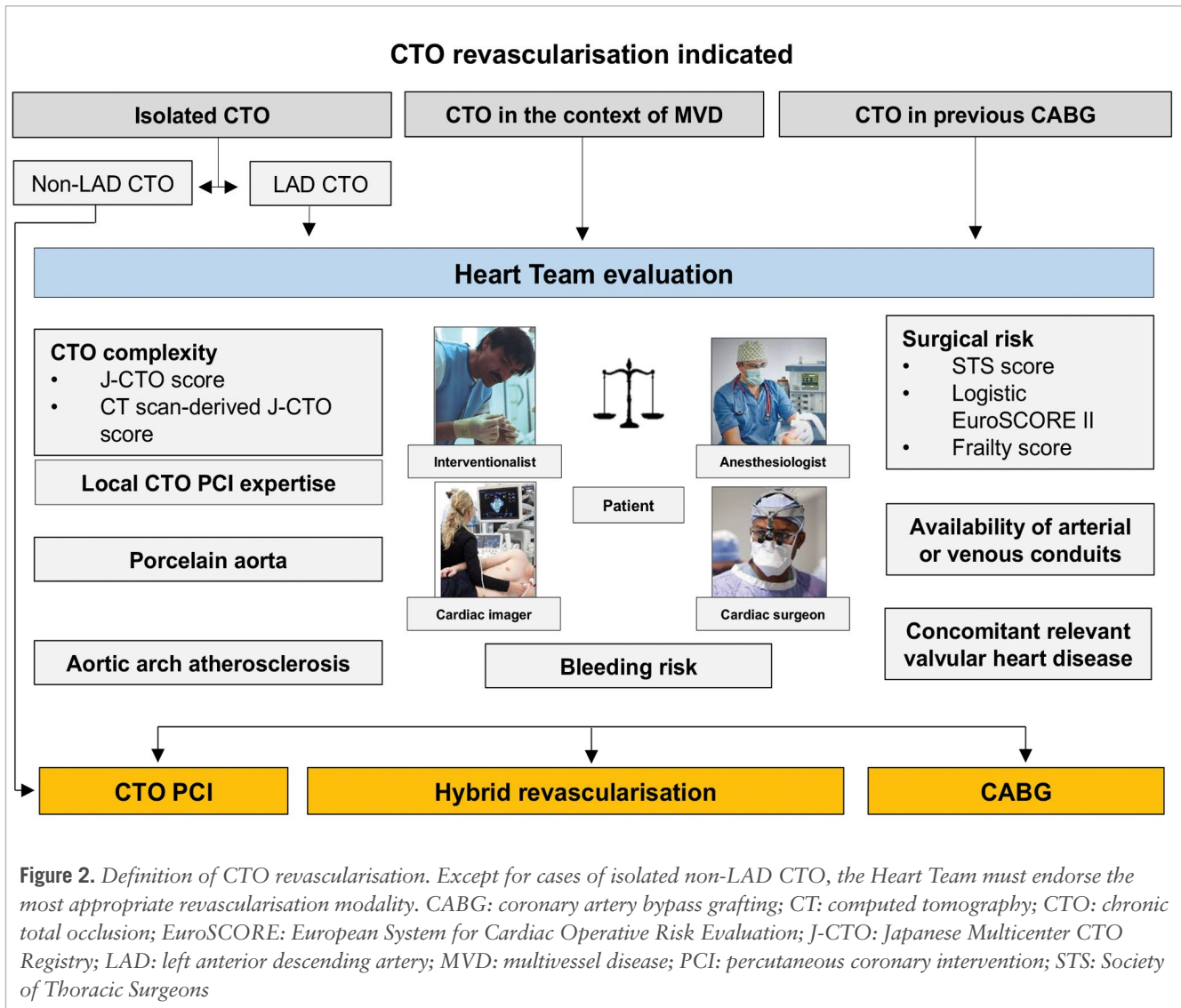


Table 2. Evaluation of myocardial ischaemia and viability by different imaging modalities.

	Inducible ischaemia	Myocardial viability	Limitations
ECHO	<ul style="list-style-type: none"> Stress-induced wall motion abnormalities in >3 out of 17 segments Stress-induced perfusion defect with contrast echo in >3 out of 17 segments 	<ul style="list-style-type: none"> Low-dose dobutamine/low-load exercise echo wall motion abnormalities improvement in >3 out of 17 segments Reversibility of rest or stress-induced perfusion defect with contrast echo in >3 out of 17 segments 	<ul style="list-style-type: none"> Image quality Reproducibility Reduced sensitivity for viability assessment
CMR	<ul style="list-style-type: none"> Stress-induced wall motion abnormalities in ≥3 out of 16 segments Stress-induced perfusion defect in ≥2 out of 17 segments 	<ul style="list-style-type: none"> Low-dose dobutamine/low-load exercise echo wall motion abnormalities improvement in ≥3 out of 16 segments LGE <25-50% transmural in >4 out of 17 segments 	<ul style="list-style-type: none"> Availability Time-consuming Not suitable for patients with claustrophobia Costs
SPECT and PET	<ul style="list-style-type: none"> Stress-induced SPECT Tc-99m: >10% of global myocardium area Pharmacologically induced [¹⁵O] H₂O- or [¹³N]-ammonia PET imaging in >3 out of 17 segments 	<ul style="list-style-type: none"> [¹⁸F]FDG PET resting uptake ≥50% 201-Tl or Tc-99m SPECT resting uptake >50% 	<ul style="list-style-type: none"> Ionising radiation exposure Time-consuming
CTCA	<ul style="list-style-type: none"> Stress-induced perfusion defect with contrast FFR-CT <0.8 	<ul style="list-style-type: none"> Perfusion CT <75% transmural in >3 out of 17 segments 	<ul style="list-style-type: none"> Ionising radiation exposure Ventricular performance

CMR: cardiac magnetic resonance imaging; CT: computed tomography; CTCA: computed tomography coronary angiography; ECHO: echocardiography; FDG: fluorodeoxyglucose; FFR-CT: fractional flow reserve computed tomography; LGE: late gadolinium enhancement; PET: positron emission tomography; SPECT: single-photon emission computed tomography

assessment of myocardial viability and inducible ischaemia with treadmill exercise or dobutamine protocols. However, dobutamine echocardiography, besides its high specificity, showed reduced sensitivity in predicting the recovery of dysfunctional myocardium supplied by totally occluded vessels³⁷. Finally, among nuclear tests, positron emission tomography (PET) should be the preferred technique for the myocardial viability assessment due to its higher spatial and temporal resolution, lower radiation dose, and shorter scan duration than single-photon emission computed tomography (SPECT)³⁸.

GUIDANCE FOR PROCEDURAL PLANNING

For a definitive diagnosis of CTO, coronary angiography remains the gold standard. Thus, for guidance of procedural planning, a dual coronary angiography should be performed unless coronary collateral circulation originates exclusively from the ipsilateral vessel³⁹. However, coronary computed tomography (CT) scans, particularly with three-dimensional reconstructions, are used more and more frequently, providing important complementary information to the conventional coronary angiography (location and extent of calcification, definition of morphology of proximal and distal CTO caps, occlusion length, CTO tortuosity) especially in very complex CTOs⁴⁰. Such anatomical information may influence the PCI strategy and material selection for PCI. For example, in cases of heavily calcified lesions, the use of calcium modification treatment (e.g., rotational atherectomy or intravascular lithotripsy), as well as the vessel course in a very long CTO segment, can be anticipated. Furthermore, a computed tomography coronary angiography (CTCA)-derived score, such as the Computed Tomography Registry of Chronic Total Occlusion Revascularization (CT-RECTOR), was shown to be more accurate than the angiography-based Japanese Multicenter CTO Registry (J-CTO) score for grading CTO difficulty before PCI, as assessed by the time-efficient guidewire crossing^{41,42}.

Decision-making: the Heart Team

Both European and American guidelines recommend the concept of an interdisciplinary Heart Team involving cardiac surgeons, interventional and general cardiologists, cardiovascular (CV) imagers and anaesthesiologists for decision-making with different levels of evidence^{43,44}. Especially in those complex scenarios where multiple comorbidities, advanced patient age, left main and 3-vessel disease, including CTOs, make the choice of the best treatment option challenging, the Heart Team is of value to endorse the treatment strategy (**Figure 2**). Indeed, PCI has a low risk of immediate complications, while coronary artery bypass grafts (CABGs) showed improved long-term, event-free survival if an internal mammary artery graft to the left anterior descending artery is used⁴⁵.

Beyond the anatomical (e.g., coronary structure, calcification, access to occluded segment, among others) and functional data (i.e., ischaemia and viability) relevant to assess the appropriateness of a CTO procedure, the patient's clinical profile and their wishes also have to be taken into account when considering coronary revascularisation of CTOs. The patient must be made aware that they will undergo an intervention with a much longer duration and a higher complication rate (e.g., coronary perforations) than for non-CTO

PCI (**Table 1**). Finally, the patient should be aware that while a symptomatic improvement or a reduction in antianginal drugs are both plausible, there is not sufficient evidence to suggest that the CTO revascularisation will prolong their survival or decrease the risk of major adverse CV events at follow-up (**Table 1**).

Clinical outcomes

Despite the high prevalence of CTO and the higher CV risk associated with it, CTO recanalisation traditionally represents only a small fraction of the overall volume of PCIs⁴⁶. In the past, this was mainly due to a combination of low success rates, high incidence of complications, long procedural times, high costs and perceived lack of clinical benefit. However, in the last decade, along with an increased revascularisation success rate^{2,3}, the pooled estimate of complication rates has decreased over time, now at a maximum of 3%, yet still remaining higher than that of non-CTO PCI^{47,48}.

Given this, the most important questions to be answered after PCI-based CTO revascularisation are the following:

- 1) Is there any improvement in angina, exercise capacity and/or quality of life?
- 2) Is there any reduction in major adverse cardiovascular events (MACE) at long-term follow-up?
- 3) What is the role of CTO revascularisation in patients with left ventricular dysfunction?

SYMPTOMS, QUALITY OF LIFE AND FUNCTIONAL STATUS

In stable coronary artery disease, the prevalence of angina, despite OMT, was approximately 20% in one of the largest contemporary European registries where anginal symptoms were associated with an increased risk of MACE, including cardiovascular death and non-fatal MI⁴⁹. Furthermore, a non-negligible proportion of patients still complained of refractory angina despite multiple CABGs and/or PCIs¹. Besides OMT and revascularisation of non-CTO lesions, CTO PCI represents an additional tool for symptom relief and improvement in quality of life^{50,51}.

Recently, the OPEN-CTO registry demonstrated that CTO PCI improved patients' health status, as assessed by the SAQ and mean RDS scores at 1-month follow-up¹⁸. Furthermore, 3 out of the 4 main randomised trials available on this topic, EuroCTO⁵², COMET-CTO⁵³, and IMPACTOR-CTO⁵⁴, demonstrated that patients' health status improved more significantly after CTO PCI than with OMT, while the DECISION-CTO trial⁵¹ did not. In the EuroCTO trial, patients undergoing PCI for CTO not only showed a marked improvement in the SAQ score (angina frequency and quality of life) compared to OMT (hazard ratios [HR] 5.23 and 6.62, respectively), but also a higher rate of complete freedom from angina (71.6% vs 57.8%; $p < 0.001$) and a lower burden of antianginal drugs taken at 1-year follow-up⁵². Similarly, the COMET-CTO trial, at a mean follow-up of 275±88 days, showed a significant improvement of symptoms and quality of life measured by the SAQ in the CTO PCI group compared to the OMT group⁵³. Finally, in the IMPACTOR-CTO trial, where 94 patients with isolated right coronary artery CTO were randomised, CTO PCI led to a significantly greater improvement in the 6-min walk distance and quality of life as assessed by the 36-Item Short

Form Health Survey (SF-36) at 1-year follow-up, compared with OMT alone⁵⁴.

In summary, evidence supporting CTO PCI as an effective tool for symptom relief (both angina and dyspnoea) and improvement in quality of life is based on several observational studies and on 4 randomised controlled trials, of which 3 are in favour of endovascular revascularisation, while one (DECISION-CTO) was neutral. Based on this, symptoms such as angina or dyspnoea, resistant to the best medical therapy tolerated by the patient, should be the main driver of CTO recanalisation (**Table 1**).

MACE REDUCTION AT LONG-TERM FOLLOW-UP

Different observational studies using a propensity score-matched analysis have demonstrated a lower incidence of MACE after CTO revascularisation as compared with OMT alone at long-term follow-up⁵⁵⁻⁵⁷. Similarly, two large prospective registries, the Korean registry⁵⁸ and the Canadian Multicenter Chronic Total Occlusion Registry⁵⁹, showed a significant clinical benefit of CTO revascularisation over OMT alone at very long-term follow-up. The first is a single-centre, propensity-matched cohort of 1,547 consecutive patients with CTO who underwent either PCI or routine OMT. At 10 years, a significant mortality benefit was shown in the CTO PCI group as compared with OMT (13.6% vs 20.8%, HR 0.64; $p=0.01$)⁵⁸. Similarly, in the Canadian Registry, which enrolled 1,624 patients, CTO revascularisation was associated with a lower 10-year incidence of MACE, including all-cause mortality (22.7% vs 36.6%), future revascularisation (14.0% vs 22.8%), and ACS hospitalisation (10.0% vs 16.6%) as compared with OMT⁵⁹. Similarly, at 3-year follow-up, the EuroCTO trial confirmed no differences in the rates of cardiovascular death or myocardial infarction between PCI or OMT among patients with a remaining single coronary CTO, but the MACE rate was higher in the OMT group due to more ischaemia-driven revascularisations⁶⁰.

Conversely, the two other randomised trials, DECISION-CTO⁵¹ and EXPLORE⁶¹, did not confirm a long-term MACE reduction with CTO revascularisation as compared with OMT. However, many caveats exist for both trials, which have been described in detail previously⁶².

Therefore, although randomised controlled trials provide the highest level of evidence in the currently used guidelines, they also have some limitations and give conflicting results. Moreover, propensity-matched analysis studies and registries are prone to undetected bias and often have a lack of an independent MACE adjudication. As such, registries can only be considered hypothesis-generating. Furthermore, CTO revascularisation compared with OMT now faces fierce competition by effective anti-ischaemic, antithrombotic and hypolipidaemic remedies (**Table 1**). Nevertheless, further large-scale, randomised trials, with long-term follow-up, including patients with depressed LVEF, comorbidities and significant symptoms, are needed to determine whether CTO revascularisation is indeed superior to OMT in terms of long-term MACE reduction.

CTO REVASCLARISATION OF PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTION

Although some previous studies have shown LVEF recovery after successful revascularisation of the CTO territory,

especially among patients with more severe LV dysfunction, significant myocardial inducible perfusion defect and viability, these data were not confirmed in the randomised REVASC trial^{24,25,32,63}. In this study, the mean baseline LVEF was only mildly/moderately reduced in both the OMT and CTO PCI groups (59.6 [45.8 to 64.3] and 54.7 [42.9 to 65.1], respectively), with one possible explanation for this being the neutral effect of coronary revascularisation on LV recovery (**Table 1**).

Similarly, the relationship between LVEF recovery and long-term patient outcomes is still debated (**Table 1**). In the REVASC trial, the CTO PCI group showed a higher MACE rate reduction, as compared with the group managed by OMT, driven mostly by lower repeated intervention rate at 1-year follow-up (16.3% vs 5.9%; $p=0.02$)⁶³.

Furthermore, Schumacher et al have recently demonstrated that while extensive ischaemia reduction after CTO PCI led to significantly better survival, free of death and MI, among patients with LV dysfunction, this was not the case among patients with preserved LV function⁶⁴.

Of course, the present study is not randomised and should be considered as hypothesis-generating. Therefore, despite successful CTO revascularisation of dysfunctional myocardium not being systematically followed by LVEF recovery, future large randomised studies are warranted to conclusively define whether CTO revascularisation of patients with severe LV dysfunction may be beneficial at long-term follow-up. Indeed, this population is not adequately represented in the current studies.

Conclusions

Percutaneous CTO interventions have reached a high level of success with acceptable complication rates when in the hands of expert operators. Symptom improvement, on top of medical therapy, is the main goal of CTO PCI, while MACE reduction at follow-up remains uncertain, as the currently available trials were underpowered and led to conflicting results. A rational patient selection, based on clinical symptoms, different imaging modalities and a multidisciplinary approach, is key for a successful CTO revascularisation. Finally, in situations where multiple comorbidities make the choice of the best treatment option challenging, the Heart Team is essential to endorse the treatment strategy.

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Conflict of interest statement

N. Bonaros: Medtronic and Edwards Lifesciences; B. Cosyns: research funding from Abbott; C. Di Mario: Boston Scientific, Medtronic, Behring, Idorsia, Philips, Shockwave Medical, Edwards Lifesciences; D. Z. Dudek: Abbott, Balton, Mac's Medical, Chemie AG, Ferrer Internacional, Aspironix, Abiomed, Hemolens, AstraZeneca, Biotronik, Boston Scientific, Bracco Pharmaceutical, Edwards Lifesciences, GE Healthcare, Medtronic, Procardia, B. Braun, Teleflex, Sanofi Aventis, Philips, SMT, Gedeon Richter, Cardinalhealth, Siemens Healthcare, Terumo Inc; B.L.M. Gerber: Pfizer, Daiichi Sankyo, Bristol-Myers Squibb, Sanofi Aventis; J. Hill: Abbott Vascular, Shockwave Medical, Neovasc, Boston Scientific, Abiomed; T.F. Lüscher: Acthera, Daiichi Sankyo, Amgen, Novartis, Boehringer-Ingelheim, Philips, e-therapeutics, Open Health, Novo Nordisk, AstraZeneca, Vifor International, Abbott; M. McEntegart: Boston Scientific, Teleflex, Shockwave Medical, Medtronic, Biosensors; B. Vaquerizo Montilla: Boston Scientific, Medtronic, Lifetech; G.S. Werner: Abbott Vascular, Daiichi Sankyo, Shockwave Medical, Terumo Inc, Siemens Healthcare, Philips, Orbus, Asahi. The other authors have no conflicts of interest to declare.

References

- Davies A, Fox K, Galassi AR, Banai S, Ylä-Herttua S, Lüscher TF. Management of refractory angina: an update. *Eur Heart J*. 2021;42:269-83.
- Brilakis ES, Mashayekhi K, Tsuchikane E, Abi Rafeh N, Alaswad K, Araya M, Avran A, Azzalini L, Babunashvili AM, Bayani B, Bhandi R, Boudou N, Boukhris M, Božinović NŽ, Bryniarski L, Bufe A, Buller CE, Burke MN, Büttner HJ, Cardoso P, Carlino M, Christiansen EH, Colombo A, Croce K, Damas de Los Santos F, De Martini T, Dens J, Di Mario C, Dou K, Egreg M, ElGuindy AM, Escaned J, Furkalo S, Gagnor A, Galassi AR, Garbo R, Ge J, Goel PK, Goktekin O, Grancini L, Grantham JA, Hanratty C, Harb S, Harding SA, Henriques JPS, Hill JM, Jaffer FA, Jang Y, Jussila R, Kalnins A, Kalyanasundaram A, Kandzari DE, Kao HL, Karpaliotis D, Kassam HH, Knaepen P, Kornowski R, Krestyaninov O, Kumar AVG, Laanmets P, Lamelas P, Lee SW, Lefevre T, Li Y, Lim ST, Lo S, Lombardi W, McEntegart M, Munawar M, Navarro Lecaro JA, Ngo HM, Nicholson W, Olivecrona GK, Padilla L, Postu M, Quadros A, Quesada FH, Prakasa Rao VS, Reifart N, Saghatelian M, Santiago R, Sianos G, Smith E, C Spratt J, Stone GW, Strange JW, Tammam K, Ungi I, Vo M, Vu VH, Walsh S, Werner GS, Wollmuth JR, Wu EB, Wyman RM, Xu B, Yamane M, Ybarra LF, Yeh RW, Zhang Q, Rinfret S. Guiding Principles for Chronic Total Occlusion Percutaneous Coronary Intervention. *Circulation*. 2019;140:420-33.
- Galassi AR, Werner GS, Boukhris M, Azzalini L, Mashayekhi K, Carlino M, Avran A, Konstantinidis NV, Grancini L, Bryniarski L, Garbo R, Bozinovic N, Gershlick AH, Rathore S, Di Mario C, Louvard Y, Reifart N,

Sianos G. Percutaneous recanalisation of chronic total occlusions: 2019 consensus document from the EuroCTO Club. *EuroIntervention*. 2019;15:198-208.

- Ybarra LF, Rinfret S, Brilakis ES, Karpaliotis D, Azzalini L, Grantham JA, Kandzari DE, Mashayekhi K, Spratt JC, Wijeyesundera HC, Ali ZA, Buller CE, Carlino M, Cohen DJ, Cutlip DE, De Martini T, Di Mario C, Farb A, Finn AV, Galassi AR, Gibson CM, Hanratty C, Hill JM, Jaffer FA, Krucoff MW, Lombardi WL, Maehara A, Magee PFA, Mehran R, Moses JW, Nicholson WJ, Onuma Y, Sianos G, Sumitsuji S, Tsuchikane E, Virmani R, Walsh SJ, Werner GS, Yamane M, Stone GW, Rinfret S, Stone GW; Chronic Total Occlusion Academic Research Consortium. Definitions and Clinical Trial Design Principles for Coronary Artery Chronic Total Occlusion Therapies: CTO-ARC Consensus Recommendations. *Circulation*. 2021;143:479-500.
- Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, Sparkes JD, Wright GA, Strauss BH. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol*. 2012 59:991-7.
- Azzalini L, Jolicœur EM, Pighi M, Millán X, Picard F, Tadros VX, Fortier A, L'Allier PL, Ly HQ. Epidemiology, Management Strategies, and Outcomes of Patients With Chronic Total Coronary Occlusion. *Am J Cardiol*. 2016;118:1128-35.
- Nagalli S, Kikkeri NS, Nasir U, Rai Ahuja K, Ali Waheed T, Bhatia N. Trends and In-Hospital Outcomes of Patients Admitted with ST Elevation Myocardial Infarction and Chronic Total Occlusions: Insights from a National Database. *Curr Probl Cardiol*. 2023;48:101132.
- Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen MM, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak RR, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stael M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans TACM, de Ruijter W, Delnoij TSR, Crijns HJGM, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, Spoormans EM, van de Ven PM, Oudemans-van Straaten HM, van Royen N. Coronary Angiography After Cardiac Arrest Without ST Segment Elevation: One-Year Outcomes of the COACT Randomized Clinical Trial. *JAMA Cardiol*. 2020;5:1358-65.
- Hochman JS, Sleeper LA, Godfrey E, McKinlay SM, Sanborn T, Col J, LeJemtel T. Should we emergently revascularize Occluded Coronaries for cardiogenic shock: an international randomized trial of emergency PTCA/CABG-trial design. The SHOCK Trial Study Group. *Am Heart J*. 1999;137:313-21.
- Thiele H, de Waha-Thiele S, Freund A, Zeymer U, Desch S, Fitzgerald S. Management of cardiogenic shock. *EuroIntervention*. 2021;17:451-65.
- Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, López-Sendón J, Faxon DP, Mauri L, Rao SV, Feldman L, Steg PG, Avezum Á, Sheth T, Pinilla-Echeverri N, Moreno R, Campo G, Wrigley B, Kedev S, Sutton A, Oliver R, Rodés-Cabau J, Stanković G, Welsh R, Lavi S, Cantor WJ, Wang J, Nakamya J, Bangdiwala SI, Cairns JA; COMPLETE Trial Steering Committee and Investigators. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med*. 2019;381:1411-21.
- Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliquet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289-367.
- Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237-69.
- Qintar M, Grantham JA, Sapontis J, Gosch KL, Lombardi W, Karpaliotis D, Moses J, Salisbury AC, Cohen DJ, Spertus JA, Arnold SV. Dyspnea Among Patients With Chronic Total Occlusions Undergoing Percutaneous Coronary Intervention: Prevalence and Predictors of Improvement. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003665.
- Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Fihn SD. Monitoring the quality of life in patients with coronary artery disease. *Am J Cardiol*. 1994;74:1240-4.

16. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20:1727-36.
17. Rose GA, Blackburn H. Cardiovascular survey methods. *Monogr Ser World Health Organ.* 1968;56:1-188.
18. Yeh RW, Tamez H, Secemsky EA, Grantham JA, Sapontis J, Spertus JA, Cohen DJ, Nicholson WJ, Gosch K, Jones PG, Valsdottir LR, Bruckel J, Lombardi WL, Jaffer FA. Depression and Angina Among Patients Undergoing Chronic Total Occlusion Percutaneous Coronary Intervention: The OPEN-CTO Registry. *JACC Cardiovasc Interv.* 2019;12:651-8.
19. Galassi AR, Brilakis ES, Boukhris M, Tomasello SD, Sianos G, Karpaliotis D, Di Mario C, Strauss BH, Rinfret S, Yamane M, Katoh O, Werner GS, Reifart N. Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. *Eur Heart J.* 2016;37:2692-700.
20. Werner GS, Fritzenwanger M, Prochnau D, Schwarz G, Ferrari M, Aarnoudse W, Pijls NH, Figulla HR. Determinants of coronary steal in chronic total coronary occlusions donor artery, collateral, and microvascular resistance. *J Am Coll Cardiol.* 2006;48:51-8.
21. Werner GS, Surber R, Ferrari M, Fritzenwanger M, Figulla HR. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. *Eur Heart J.* 2006;27:2406-12.
22. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD, Hachamovitch R. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging.* 2013;6:363-72.
23. Camici PG, Wijns W, Borgers M, De Silva R, Ferrari R, Knuuti J, Lammertsma AA, Liedtke AJ, Paternostro G, Vatner SF. Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). *Circulation.* 1997;96:3205-14.
24. Megaly M, Saad M, Tajti P, Burke MN, Chavez I, Gössl M, Lips D, Mooney M, Poulouse A, Sorajja P, Traverse J, Wang Y, Kohl LP, Bradley SM, Brilakis ES. Meta-analysis of the impact of successful chronic total occlusion percutaneous coronary intervention on left ventricular systolic function and reverse remodeling. *J Interv Cardiol.* 2018;31:562-71.
25. Galassi AR, Boukhris M, Toma A, Elhadj Z, Laroussi L, Gaemperli O, Behnes M, Akin I, Lüscher TF, Neumann FJ, Mashayekhi K. Percutaneous Coronary Intervention of Chronic Total Occlusions in Patients With Low Left Ventricular Ejection Fraction. *JACC Cardiovasc Interv.* 2017;10:2158-70.
26. Elias J, van Dongen IM, Hoebers LP, Ouweneel DM, Claessen BEPM, Råmunddal T, Laanmets P, Eriksen E, van der Schaaf RJ, Ioanes D, Nijveldt R, Tijssen JG, Hirsch A, Henriques JPS; EXPLORE investigators. Improved recovery of regional left ventricular function after PCI of chronic total occlusion in STEMI patients: a cardiovascular magnetic resonance study of the randomized controlled EXPLORE trial. *J Cardiovasc Magn Reson.* 2017;19:53.
27. Behnes M, Akin I, Kuche P, Schupp T, Reiser L, Bollow A, Taton G, Reichelt T, Ellguth D, Engelke N, El-Battrawy I, Lang S, Brilakis ES, Azzalini L, Galassi AR, Boukhris M, Neuser H, Neumann FJ, Nienaber C, Weiß C, Borggreffe M, Mashayekhi K. Coronary chronic total occlusions and mortality in patients with ventricular tachyarrhythmias. *EuroIntervention.* 2020;15:1278-85.
28. Nombela-Franco L, Iannaccone M, Anguera I, Amat-Santos IJ, Sanchez-Garcia M, Bautista D, Calvelo MN, Di Marco A, Moretti C, Pozzi R, Scaglione M, Cañadas V, Sandin-Fuentes M, Arenal A, Bagur R, Perez-Castellano N, Fernandez-Perez C, Gaita F, Macaya C, Escaned J, Fernández-Lozano I. Impact of Chronic Total Coronary Occlusion on Recurrence of Ventricular Arrhythmias in Ischemic Secondary Prevention Implantable Cardioverter-Defibrillator Recipients (VACTO Secondary Study): Insights From Coronary Angiogram and Electrogram Analysis. *JACC Cardiovasc Interv.* 2017;10:879-88.
29. Simsek B, Kostantinis S, Karacsonyi J, Alaswad K, Krestyaninov O, Khelinskii D, Davies R, Rier J, Goktekin O, Gorgulu S, ElGuindy A, Chandwaney RH, Patel M, Abi Rafeh N, Karpaliotis D, Masoumi A, Khatri JJ, Jaffer FA, Doshi D, Poommipanit PB, Rangan BV, Sanvodal Y, Choi JW, Elbarouni B, Nicholson W, Jaber WA, Rinfret S, Koutouzis M, Tsiafoutis I, Yeh RW, Burke MN, Allana S, Mastrodemos OC, Brilakis ES. Predicting Periprocedural Complications in Chronic Total Occlusion Percutaneous Coronary Intervention: The PROGRESS-CTO Complication Scores. *JACC Cardiovasc Interv.* 2022;15:1413-22.
30. Amzulescu MS, De Craene M, Langet H, Pasquet A, Vancraeynest D, Pouleur AC, Vanoverschelde JL, Gerber BL. Myocardial strain imaging: review of general principles, validation, and sources of discrepancies. *Eur Heart J Cardiovasc Imaging.* 2019;20:605-19.
31. Rossello X, Pujadas S, Serra A, Bajo E, Carreras F, Barros A, Cinca J, Pons-Lladó G, Vaquerizo B. Assessment of Inducible Myocardial Ischemia, Quality of Life, and Functional Status After Successful Percutaneous Revascularization in Patients With Chronic Total Coronary Occlusion. *Am J Cardiol.* 2016;117:720-6.
32. Bucciarelli-Ducci C, Auger D, Di Mario C, Locca D, Petryka J, O'Hanlon R, Grasso A, Wright C, Symmonds K, Wage R, Asimacopoulos E, Del Furia F, Lyne JC, Gatehouse PD, Fox KM, Pennell DJ. CMR Guidance for Recanalization of Coronary Chronic Total Occlusion. *JACC Cardiovasc Imaging.* 2016;9:547-56.
33. Schumacher SP, Stuijzand WJ, de Winter RW, van Diemen PA, Bom MJ, Everaars H, Driessen RS, Kamperman L, Kockx M, Hagen BSH, Rajmakers PG, van de Ven PM, van Rossum AC, Polowski MP, Nap A, Knaapen P. Ischemic Burden Reduction and Long-Term Clinical Outcomes After Chronic Total Occlusion Percutaneous Coronary Intervention. *JACC Cardiovasc Interv.* 2021;14:1407-18.
34. Patel AR, Salerno M, Kwong RY, Singh A, Heydari B, Kramer CM. Stress Cardiac Magnetic Resonance Myocardial Perfusion Imaging: JACC Review Topic of the Week. *J Am Coll Cardiol.* 2021;78:1655-68.
35. Almeida AG, Carpenter JP, Cameli M, Donal E, Dweck MR, Flachskampf FA, Maceira AM, Muraru D, Neglia D, Pasquet A, Plein S, Gerber BL; Reviewers: This document was reviewed by members of the 2018–2020 EACVI Scientific Documents Committee; chair of the 2018–2020 EACVI Scientific Documents Committee; 2018–2020 EACVI President. Multimodality imaging of myocardial viability: an expert consensus document from the European Association of Cardiovascular Imaging (EACVI). *Eur Heart J Cardiovasc Imaging.* 2021;22:e97-125.
36. Gerber BL, Darchis J, le Polain de Waroux JB, Legros G, Pouleur AC, Vancraeynest D, Pasquet A, Vanoverschelde JL. Relationship between transmural extent of necrosis and quantitative recovery of regional strains after revascularization. *JACC Cardiovasc Imaging.* 2010;3:720-30.
37. Piscione F, Perrone-Filardi P, De Luca G, Prastaro M, Indolfi C, Golino P, Dellegrottaglie S, Chiariello M. Low dose dobutamine echocardiography for predicting functional recovery after coronary revascularisation. *Heart.* 2001;86:679-86.
38. Nakazato R, Berman DS, Gransar H, Hyun M, Miranda-Peats R, Kite FC, Hayes SW, Thomson LE, Friedman JD, Rozanski A, Slomka PJ. Prognostic value of quantitative high-speed myocardial perfusion imaging. *J Nucl Cardiol.* 2012;19:1113-23.
39. Wu EB, Brilakis ES, Mashayekhi K, Tsuchikane E, Alaswad K, Araya M, Avran A, Azzalini L, Babunashvili AM, Bayani B, Behnes M, Bhandi R, Boudou N, Boukhris M, Bozinovic NZ, Bryniarski L, Bufe A, Buller CE, Burke MN, Buttner A, Cardoso P, Carlino M, Chen JY, Christiansen EH, Colombo A, Croce K, de Los Santos FD, de Martini T, Dens J, di Mario C, Dou K, Eged M, Elbarouni B, ElGuindy AM, Escaned J, Furkalo S, Gagnor A, Galassi AR, Garbo R, Gasparini G, Ge J, Ge L, Goel PK, Goktekin O, Gonzalo N, Grancini L, Hall A, Hanna Quesada FL, Hanratty C, Harb S, Harding SA, Hatem R, Henriques JPS, Hildick-Smith D, Hill JM, Hoye A, Jaber W, Jaffer FA, Jang Y, Jussila R, Kalnins A, Kalyanasundaram A, Kandzari DE, Kao HL, Karpaliotis D, Kassem HH, Khatri J, Knaapen P, Kornowski R, Krestyaninov O, Kumar AVG, Lamelas PM, Lee SW, Lefevre T, Leung R, Li Y, Li Y, Lim ST, Lo S, Lombardi W, Maran A, McEntegart M, Moses J, Munawar M, Navarro A, Ngo HM, Nicholson W, Oksnes A, Olivecrona GK, Padilla L, Patel M, Pershad A, Postu M, Qian J, Quadros A, Rafah NA, Råmunddal T, Prakasa Rao VS, Reifart N, Riley RE, Rinfret S, Saghatelian M, Sianos G, Smith E, Spaedy A, Spratt J, Stone G, Strange JW, Tammam KO, Thompson CA, Toma A, Tremmel JA, Trinidad RS, Ungi I, Vo M, Vu VH, Walsh S, Werner G, Wojcik J, Wollmuth J, Xu B, Yamane M, Ybarra LF, Yeh RW, Zhang Q. Global Chronic Total Occlusion Crossing Algorithm: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2021;78:840-53.

40. Hong SJ, Kim BK, Cho I, Kim HY, Rha SW, Lee SH, Park SM, Kim YH, Chang HJ, Ahn CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y; CT-CTO Investigators. Effect of Coronary CTA on Chronic Total Occlusion Percutaneous Coronary Intervention: A Randomized Trial. *JACC Cardiovasc Imaging*. 2021;14:1993-2004.
41. Opolski MP, Achenbach S, Schubäck A, Rolf A, Möllmann H, Nef H, Rixe J, Renker M, Witkowski A, Kepka C, Walther C, Schlundt C, Debski A, Jakubczyk M, Hamm CW. Coronary computed tomographic prediction rule for time-efficient guidewire crossing through chronic total occlusion: insights from the CT-RECTOR multicenter registry (Computed Tomography Registry of Chronic Total Occlusion Revascularization). *JACC Cardiovasc Interv*. 2015;8:257-67.
42. Tan Y, Zhou J, Zhang W, Zhou Y, Du L, Tian F, Guo J, Chen L, Cao F, Chen Y. Comparison of CT-RECTOR and J-CTO scores to predict chronic total occlusion difficulty for percutaneous coronary intervention. *Int J Cardiol*. 2017;235:169-75.
43. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
44. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, Fremes SE, Gaudino MF, Goldberger ZD, Grant MC, Jaswal JB, Kurlansky PA, Mehran R, Metkus TS Jr, Nnacheta LC, Rao SV, Sellke FW, Sharma G, Yong CM, Zwischberger BA. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e4-17.
45. Banning AP, Serruys P, De Maria GL, Ryan N, Walsh S, Gonzalo N, Jan van Geuns R, Onuma Y, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Piek JJ, Appleby C, Fath-Ordoubadi F, Zaman A, Van Mieghem NM, Uren N, Zueco J, Buszman P, Iniguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, de Vries T, Taggart D, Farooq V, Spitzer E, Tijssen J, Escaned J. Five-year outcomes after state-of-the-art percutaneous coronary revascularization in patients with de novo three-vessel disease: final results of the SYNTAX II study. *Eur Heart J*. 2022;43:1307-16.
46. Jeroudi OM, Alomar ME, Michael TT, El Sabbagh A, Patel VG, Mogabgab O, Fuh E, Sherbet D, Lo N, Roesle M, Rangan BV, Abdullah SM, Hastings JL, Grodin J, Banerjee S, Brilakis ES. Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. *Catheter Cardiovasc Interv*. 2014;84:637-43.
47. Patel VG, Brayton KM, Tamayo A, Mogabgab O, Michael TT, Lo N, Alomar M, Shorrock D, Cipher D, Abdullah S, Banerjee S, Brilakis ES. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. *JACC Cardiovasc Interv*. 2013;6:128-36.
48. Brilakis ES, Banerjee S, Karpaliotis D, Lombardi WL, Tsai TT, Shunk KA, Kennedy KF, Spertus JA, Holmes DR Jr, Grantham JA. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2015;8:245-53.
49. Steg PG, Greenlaw N, Tendera M, Tardif JC, Ferrari R, Al-Zaibag M, Dorian P, Hu D, Shalnova S, Sokn FJ, Ford I, Fox KM; Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) Investigators. Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: data from the International Observational CLARIFY Registry. *JAMA Intern Med*. 2014;174:1651-9.
50. Safley DM, Grantham JA, Hatch J, Jones PG, Spertus JA. Quality of life benefits of percutaneous coronary intervention for chronic occlusions. *Catheter Cardiovasc Interv*. 2014;84:629-34.
51. Lee SW, Lee PH, Ahn JM, Park DW, Yun SC, Han S, Kang H, Kang SJ, Kim YH, Lee CW, Park SW, Hur SH, Rha SW, Her SH, Choi SW, Lee BK, Lee NH, Lee JY, Cheong SS, Kim MH, Ahn YK, Lim SW, Lee SG, Hiremath S, Santoso T, Udayachalerm W, Cheng JJ, Cohen DJ, Muramatsu T, Tsuchikane E, Asakura Y, Park SJ. Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. *Circulation*. 2019;139:1674-83.
52. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, Rumoroso JR, Erglis A, Christiansen EH, Escaned J, di Mario C, Hovasse T, Teruel L, Bufe A, Lauer B, Bogaerts K, Goicolea J, Spratt JC, Gershlick AH, Galassi AR, Louvard Y; EUROCTO trial investigators. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. 2018;39:2484-93.
53. Juricic SA, Tesic MB, Galassi AR, Petrovic ON, Dobric MR, Orlic DN, Vukcevic VD, Stankovic GR, Aleksandric SB, Tomasevic MV, Nedeljkovic MA, Beleslin BD, Jelic DD, Ostojic MC, Stojkovic SM. Randomized Controlled Comparison of Optimal Medical Therapy with Percutaneous Recanalization of Chronic Total Occlusion (COMET-CTO). *Int Heart J*. 2021;62:16-22.
54. Obedinskiy AA, Kretov EI, Boukhris M, Kurbatov VP, Osiev AG, Ibn Elhadj Z, Obedinskaya NR, Kasbaoui S, Grazhdankin IO, Prokhorikhin AA, Zubarev DD, Biryukov A, Pokushalov E, Galassi AR, Baystrukov VI. The IMPACTOR-CTO Trial. *JACC Cardiovasc Interv*. 2018;11:1309-11.
55. Jang WJ, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Kim WS, Lee YT, Gwon HC. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. *JACC Cardiovasc Interv*. 2015;8:271-9.
56. Ladwiniec A, Allgar V, Thackray S, Alamgir F, Hoye A. Medical therapy, percutaneous coronary intervention and prognosis in patients with chronic total occlusions. *Heart*. 2015;101:1907-14.
57. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900-7.
58. Park TK, Lee SH, Choi KH, Lee JM, Yang JH, Song YB, Hahn JY, Choi JH, Gwon HC, Lee SH, Choi SH. Late Survival Benefit of Percutaneous Coronary Intervention Compared With Medical Therapy in Patients With Coronary Chronic Total Occlusion: A 10-Year Follow-Up Study. *J Am Heart Assoc*. 2021;10:e019022.
59. Strauss BH, Knudtson ML, Cheema AN, Galbraith PD, Elbaz-Greener G, Abuzeid W, Henning KA, Qiu F, Wijesundera HC. Canadian Multicenter Chronic Total Occlusion Registry: Ten-Year Follow-Up Results of Chronic Total Occlusion Revascularization. *Circ Cardiovasc Interv*. 2021;14:e010546.
60. Werner GS, Hildick-Smith D, Martin Yuste V, Boudou N, Sianos G, Gelev V, Rumoroso JR, Erglis A, Christiansen EH, Escaned J, Di Mario C, Teruel L, Bufe A, Lauer B, Galassi AR, Louvard Y. Three-year outcomes of A Randomized Multicentre Trial Comparing Revascularization and Optimal Medical Therapy for Chronic Total Coronary Occlusions (EuroCTO). *EuroIntervention*. 2023;19:571-9.
61. Henriques JP, Hoebbers LP, Råmunddal T, Laanmets P, Eriksen E, Bax M, Ioanes D, Suttorp MJ, Strauss BH, Barbato E, Nijveldt R, van Rossum AC, Marques KM, Elias J, van Dongen IM, Claessen BE, Tijssen JG, van der Schaaf RJ; EXPLORE Trial Investigators. Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI: The EXPLORE Trial. *J Am Coll Cardiol*. 2016;68:1622-32.
62. Walker M, Kumbhani DJ. An Open (Up the Vessel) and Shut (Up the Critics) Case or Fake News?: Long-Term Outcomes Following Percutaneous Coronary Intervention of Chronic Total Occlusions. *J Am Heart Assoc*. 2021;10:e020448.
63. Mashayekhi K, Nührenberg TG, Toma A, Gick M, Ferenc M, Hochholzer W, Comberg T, Rothe J, Valina CM, Löffelhardt N, Ayoub M, Zhao M, Bremicker J, Jander N, Minners J, Ruile P, Behnes M, Akin I, Schäufele T, Neumann FJ, Büttner HJ. A Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion: The REVASC Trial. *JACC Cardiovasc Interv*. 2018;11:1982-91.
64. Schumacher SP, Nap A, Knaapen P. Prognostic Impact of Left Ventricular Dysfunction and Ischemia Reduction After Chronic Total Occlusion Percutaneous Revascularization. *JACC Cardiovasc Interv*. 2022;15:1096-8.