Percutaneous Coronary Intervention of Chronic Total Occlusion

Subjects: Cardiac & Cardiovascular Systems
Contributor: Kevin Hamzaraj , Andreas Kammerlander , Mariann Gyöngyösi , Bernhard Frey , Klaus Distelmaier , Senta Graf

Percutaneous coronary intervention of chronic total occlusion (CTO PCI) is a challenging procedure with high complication rates and, as not yet fully understood long-term clinical benefits. Ischemic symptom relief in patients with high ischemic burden is to date the only established clinical indication to undergo CTO PCI, supported by randomized controlled trials.

chronic total occlusion | cardiac magnetic resonance | echocardiography | Percutaneous coronary intervention | Coronary artery disease

1. Introduction to Chronic Total Occlusion and Revascularization Recommendations

Chronic total occlusion (CTO) of coronary arteries represents an advanced form of atherosclerotic coronary artery disease, which is currently prevalent in circa one-fifth of patients presenting for diagnostic coronary angiography [1]. CTO is defined as a chronic occlusion of the artery for longer than 3 months with a TIMI 0 flow and is associated with the development of collateral conduits from donor vessels that maintain a certain perfusion level to the CTO-related myocardial segments [2][3]. However, these collaterals are very often insufficient to provide adequate myocardial perfusion, which often leads to the typical manifestation of ischemic heart disease [2]. A growing body of evidence suggests that the revascularization of CTO using coronary artery bypass grafting or percutaneous coronary intervention (PCI) has several clinical benefits, including ischemic symptom relief and quality of life improvement. These findings are supported to date by limited randomized controlled studies assessing the effects of CTO PCI upon clinical indication [4][5][6][7] (**Table 1**). Yet it is still unclear whether revascularization of CTO provides a survival benefit or long-term freedom from cardiac events, compared to receiving optimal medical therapy alone–indeed, the few available randomized controlled trials have reported no benefit in this context [5][7]. However, large observational studies on CTO patients have concordantly been reporting positive effects of CTO PCI on long-term survival and freedom from cardiac events. Of note, most of these studies compared patients that underwent successful vs. unsuccessful revascularization attempts on CTO vessels [8][9][10].

Table 1. Randomized studies comparing CTO PCI with OMT [4][5][6][7][8] CTO PCI—percutaneous coronary intervention of chronic total occlusion, OMT—optimal medical therapy, MACE—major adverse cardiac events, QOL—quality of life, LVEF—left ventricular ejection fraction, CMR—cardiac magnetic resonance, LVEDV—left

ventricular end-diastolic volume, SWT—segmental wall thickening, (I)—primary endpoint, (II)—secondary endpoint, (subgroup)–results derived from subgroup analysis; **—reporting of viability or ischemia data.

Study	Time	Number of Patients	Success Rate	Follow-Up (Median)	Findings
DECISION-CTO	2010–2016	834 (1:1)	90.6%	4 years	- No difference in MACE occurence (I) - Better QOL in CTO PCI group (II) - ** no data on ischemia and viability detection
EURO-CTO	2012–2015	396 (2:1)	86.6%	1 year	- Better QOL and Angina reduction in CTO PCI group (I) - No difference in MACE occurence (II) - ** Ischemia PCI arm 65%, Viability PCI arm 86%
EXPLORE	2007–2015	304 (1:1)	77%	4 months	- No benefit in LVEF (CMR) nor in LVEDV (I) - LAD CTO PCI had higher LVEF (subgroup) - No benefit in terms of MACE (II) - ** no data on ischemia and viability detection
REVASC	2007–2015	205 (1:1)	86% at first attempt (99% overall)	1 year	- No benefit in terms of SWT, regional and global LVEF (CMR) (I) -

Study	Time	Number of Patients	Success Rate	Follow-Up (Median)	Findings
					CTO PCI had less MACE driven by repeat PCI (II) - Single vessel disease CTO patients benefited from PCI in terms of SWT (subgroup) - ** no data in ischemia and viability detection
IMPACTOR (RCA CTO)	2010–2014	94 (1:1)	83%	1 year [10][12][13][14]	- CTO PCI group had a significant MIB decrease compared to OMT [11] - Better QOL in the CTO PCI group - No difference in terms of MACE - ** myocardial ischemic burden documented, no data on viability

However, -elevation operator e last few O PCI–#, operating racterized ul patient selection and benefit-risk evaluation before attempting CTO PCI, adapted to operator experience and expected symptom and prognostic benefits [3][15][16].

The European Society of Cardiology (ESC) guidelines on myocardial revascularization suggest choosing patients for CTO PCI in a similar manner to those who need treatment for non-CTO lesions, and explain that clinical benefits are analogous among these patient groups–hence, the rationale and criteria for decision-making in the revascularization of stable CAD should apply to the CTO subset [16]. As stated in the guidelines, prognostic benefits of revascularization may be granted to patients with a significant left main and/or left anterior descending artery (LAD) stenosis, multi-vessel disease or in patients with an ischemic territory exceeding 10% of the left ventricle. For this reason, they suggest an objective quantification of ischemia using non-invasive diagnostic imaging as a first-line test before revascularization. In left ventricular dysfunction, guidelines recommend viability testing to be performed appropriately for the detection of stunned or hibernating myocardium causing heart failure with the potential of functional recovery [16].

Most importantly, CTO PCI is currently recommended by the ESC in selected patients with angina symptoms resistant to medical therapy (class of recommendation II-a, level of evidence B) [16] (**Table 2**). However, the 2017 American College of Cardiology/American Heart Association guidelines on myocardial revascularization recommend CTO PCI only upon clinical indication and in the hands of appropriately experienced operators, as a class II-a of recommendation and level of evidence B [15]. The recent 2021 American guidelines downgraded the clinical recommendation for CTO PCI to a class II-b level of evidence B due to equivocal evidence based on

randomized trials: “In patients with suitable anatomy who have refractory angina on medical therapy, after treatment of non-CTO lesions, the benefit of PCI of a CTO to improve symptoms is uncertain”. They also encourage CTO PCI after shared-decision and potential benefits [17] (**Table 2**). Of note, no randomized trials comparing CTO PCI and CABG are available to date.

Table 2. Guideline recommendations for CTO PCI [16][17].

Gudielines	Class of Recommendation	Level of Evidence	Recommendation
European 2018	II-a	B	“Percutaneous revascularization of CTOs should be considered in patients with angina resistant to medical therapy or with a large area of documented ischaemia in the territory of the occluded vessel”
American 2021	II-b	B	“In patients with suitable anatomy who have refractory angina on medical therapy, after treatment of non-CTO lesions, the benefit of PCI of a CTO to improve symptoms is uncertain”

Pre-interventional evaluation of CTO lesions has indeed to be well elaborated as the main characteristics of this specific lesion subset, such as collateral vessels and complete antegrade flow impairment, restrict diagnostic availability or alter the interpretations for clinical indication. For example, the use of the broadly recommended FFR or the novel CT-FFR measurements is not routinely possible in CTO vessels [16]. Thus, non-invasive imaging takes on greater significance and the choice of techniques and interpretation of imaging-derived information require special attention.

In this context, suitable candidates to undergo CTO PCI should be carefully identified and selected taking into consideration diverse clinical factors and supported by appropriate cardiac imaging techniques evaluating viability and ischemia.

Guided by current recommendations and clinical practice, researchers opted to review the available evidence on benefits of CTO PCI and shed light on pre-interventional requirements for the consideration of revascularization. researchers used the term revascularization to reference PCI as the primary focus, if not stated otherwise. Furthermore, researchers summarised the available non-invasive imaging methods that support the physician to guide the patient selection process.

2. Which Patient May Benefit from CTO PCI?

2.1. Viability

In patients with coronary artery disease and normal ventricular function without regional wall motion abnormalities assessed by echocardiography, intact myocardial viability can be presumed [18]. In these patients, several benefits of revascularization have been reported. In patients with preserved systolic left ventricular function and one single

vessel disease randomized in the ORBITA trial, revascularization improved the stress wall motion score index as assessed by cardiac echocardiography after 6 weeks as a secondary endpoint [19]. Furthermore, a large meta-analysis described better outcomes of revascularization in patients with viable myocardium and normal left ventricular function, as compared to medical therapy [20].

On the other hand, the clinical benefit of revascularization in patients with left ventricular dysfunction is still ambivalent. A considerable proportion of CTO patients manifest heart failure with a reduction of left ventricular function [10] but it is unclear still whether CTO PCI is able to induce recovery. One large randomized controlled trial (*n* = 205) investigated the left ventricular recovery in terms of wall thickness and ejection fraction and found no differences between CTO patients who underwent revascularization and those who received optimal medical therapy alone. However, the results were limited by the low rates of ventricular dysfunction at baseline and the revascularization of diseased donor vessels in the control group [6]. However, previous studies have reported positive results in the general CAD population. A large meta-analysis of 3088 patients studied the role of myocardial viability in the revascularization of CAD patients with severe left ventricular dysfunction (as assessed by the left ventricular ejection fraction) [21]. Researchers underlined that viable myocardium benefits immensely from revascularization as compared to medical therapy and paved the way for further research and clinical applications. Its implications may have a slightly different meaning nowadays, as, during the few past years, medical therapy for heart failure has witnessed massive improvements; patients treated medically in the current era have a better prognosis with the new heart failure therapies, as reported in large randomized controlled studies [22][23]. However, the interpretation for clinical practice was limited by the observational nature of the study and the lack of information on the method of revascularization. Later on, most solid data came from randomized trials on patients receiving coronary artery bypass grafting (CABG), suggesting that ischemic but viable myocardium with left ventricular dysfunction has a better long-term prognosis after CABG [24]. A viability sub-study of the STICH trial on patients with reduced left ventricular function receiving CABG reported at first less cardiac mortality and cardiac hospitalization within 5 years when myocardial viability was preserved. However, in the multivariable analysis, the correlation was lost [25]. On the other hand, in an extended 10-year follow-up, freedom from cardiac death and hospitalization was significantly higher in the STICH trial patients when myocardial viability was preserved [26].

It seems that revascularization in ventricular dysfunction has prognostic benefits, but it has been long debated if this implication depends on the revascularization method. Indeed, in the general CAD population, the recent FAME-3 trial reported a non-inferiority of functionally-guided PCI vs. CABG in 1-year follow-up. However, patients with left ventricular dysfunction were underrepresented with ca. 18% in both treatment arms [27].

Recently, one randomized trial recently addressed the evidence gap. The REVIVED trial investigated patients with viable dysfunctional left ventricles undergoing PCI and reported no benefit in survival or cardiac events in 3 years compared to the control group which received optimal medical therapy alone. Moreover, the trial showed no improvement in left ventricular ejection fraction after PCI [28]. However, the clinical endpoint observation time might have been too early in the REVIVED trial: As seen in the STICH trial, prognostic benefits of revascularization may be detected only after a longer observational period. Another issue might be the non-adequate selection of patients with left ventricular dysfunction for myocardial revascularization. In the PARR-2 randomized trial, patients identified

using PET before undergoing PCI had better hard outcomes than those selected using the standard of care protocol [29]. Despite studying a smaller cohort than REVIVED, researchers emphasized the need for a more careful clinical indication by highly sensitive methods of non-invasive cardiac imaging.

On the other hand, non-randomized data suggest PCI survival benefits in left ventricular dysfunction: Gerber et al., reported a higher 3-year survival in patients with severe left ventricular dysfunction and viable myocardium who received revascularization. Overall, the study reported similar 3-year mortality as the REVIVED trial [30]. Although emerging data may lead to discussions in the next guidelines, current practices and indications for patients with myocardial dysfunction undergoing revascularization (including CTO patients) will most probably remain unaltered [31].

In patients with ventricular dysfunction, PCI benefits may be found mostly in the presence of hibernation. An observational study on 648 patients reported that an extent of hibernating myocardium exceeding 10% was associated with the benefits of revascularization [32]. Physiologically, improvement in left ventricular function may be physiologically explained by reversed myocardial hibernation after restored perfusion, with enhanced reversibility in those patients who have less fibrotic tissue [33][34]. When left untreated, hibernation can be a progressive condition with subsequent development of fibrosis, myocardial thinning and akinesia [35]. A prospective trial found progressive loss of myocardial viability in patients with ventricular dysfunction receiving neither revascularization nor medical treatment, resulting in scar formation in former hibernating myocardial segments [36]. Of note, revascularization of hibernating myocardium has been associated with improved long-term prognosis in viable areas larger than 10% of the left ventricle [32]. As such, quantification of viability has prognostic value, but is only possible non-invasively.

2.2. Ischemia

Revascularization of ischemic but viable myocardium aims to minimize residual ischemia and subsequently improves symptoms and prognosis. Patients with a large ischemic burden (more than 10%) are considered to benefit the most from PCI [37]. This statement is supported mainly by the randomized COURAGE trial, which reported a survival benefit and reduced myocardial infarction rates in patients with an ischemic burden of more than 10% at the baseline and less than 5% after revascularization [38]. Ischemia was evaluated non-invasively using SPECT. On the other hand, a sub-study of the PARR-2 trial using PET reported fewer cardiac events after revascularization in CAD patients with an ischemic but viable myocardial area of more than 7% of the left ventricle [39]. However, the threshold of ischemia in 10% of the myocardium remains standard of care, as this amount of ischemic burden is associated with prognostic benefits of revascularization in the general CAD population [16].

Nowadays, invasive functional assessment of coronary artery stenoses can derive information related to the extent of ischemia in the distal supply region. Treatment of functionally significant stenoses, as assessed by fractional flow reserve, has been proven to be superior to revascularization guided by anatomical evaluation alone. The FAME trial reported better 2-year MACE rates after revascularization of ischemic myocardium, as assessed invasively with FFR [40]. However, for quantitative measurement of myocardial ischemia, coronary flow reserve using PET

represents the most reliable parameter due to the detection of ischemia in the whole myocardium, which surpasses the invasive tool of FFR measuring the pressure drop solely [41]. In fact, invasive functional measurement does not apply to CTO lesions, as collateral vessels rather than CTO vessels themselves supply the corresponding myocardial regions.

Indeed, CTO-related myocardium can be an ischemic area even in well-developed collaterals. Werner et al., reported a sufficient collateral flow in only 5% of CTO patients with preserved left ventricular function [42]. When patients report typical symptoms, ischemia is mostly present. A quantitative correlation between ischemic burden and clinical benefits in CTO patients is not specifically stated. The IMPACTOR-CTO trial aimed to stratify patients according to their ischemic burden, guided by the belief that large ischemic CTO-related areas will benefit most from revascularization [43]. This was the only randomized study to report a significant myocardial ischemia reduction in patients undergoing CTO PCI. However, myocardial ischemia reduction remains the primary benefit of CTO PCI.

References

1. Brilakis, E.S.; Mashayekhi, K.; Burke, M.N. How DECISION-CTO Can Help Guide the Decision to Perform Chronic Total Occlusion Percutaneous Coronary Intervention. Circulation 2019, 139, 1684–1687.
2. Seiler, C.; Stoller, M.; Pitt, B.; Meier, P. The human coronary collateral circulation: Development and clinical importance. Eur. Heart J. 2013, 34, 2674–2682.
3. Brilakis, E.S.; Mashayekhi, K.; Tsuchikane, E.; Rafeh, N.A.; Alaswad, K.; Araya, M.; Avran, A.; Azzalini, L.; Babunashvili, A.M.; Bayani, B.; et al. Guiding Principles for Chronic Total Occlusion Percutaneous Coronary Intervention. Circulation 2019, 140, 420–433.
4. Henriques, J.P.; Hoebers, L.P.; Råmunddal, T.; Laanmets, P.; Eriksen, E.; Bax, M.; Ioanes, D.; Suttorp, M.J.; Strauss, B.H.; Barbato, E.; et al. Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients with STEMI. J. Am. Coll. Cardiol. 2016, 68, 1622–1632.
5. Werner, G.S.; Martin-Yuste, V.; Hildick-Smith, D.; Boudou, N.; Sianos, G.; Gelev, V.; Rumoroso, J.R.; Erglis, A.; Christiansen, E.H.; Escaned, J.; et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. Eur. Heart J. 2018, 39, 2484–2493.
6. Mashayekhi, K.; Nührenberg, T.G.; Toma, A.; Gick, M.; Ferenc, M.; Hochholzer, W.; Comberg, T.; Rothe, J.; Valina, C.M.; Löffelhardt, N.; et al. A Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion. JACC Cardiovasc. Interv. 2018, 11, 1982–1991.

7. Lee, S.-W.; Lee, P.H.; Ahn, J.-M.; Park, D.-W.; Yun, S.-C.; Han, S.; Kang, H.; Kang, S.-J.; Kim, Y.-H.; Lee, C.W.; et al. Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. Circulation 2019, 139, 1674–1683.
8. Tajti, P.; Burke, M.N.; Karmpaliotis, D.; Alaswad, K.; Werner, G.S.; Azzalini, L.; Carlino, M.; Patel, M.; Mashayekhi, K.; Egred, M.; et al. Update in the Percutaneous Management of Coronary Chronic Total Occlusions. JACC Cardiovasc. Interv. 2018, 11, 615–625.
9. Mashayekhi, K.; Neuser, H.; Kraus, A.; Zimmer, M.; Dalibor, J.; Akin, I.; Werner, G.; Aurel, T.; Neumann, F.-J.; Behnes, M. Successful Percutaneous Coronary Intervention Improves Cardiopulmonary Exercise Capacity in Patients with Chronic Total Occlusions. J. Am. Coll. Cardiol. 2017, 69, 1095–1096.
10. Sapontis, J.; Salisbury, A.C.; Yeh, R.W.; Cohen, D.J.; Hirai, T.; Lombardi, W.; McCabe, J.M.; Karmpaliotis, D.; Moses, J.; Nicholson, W.J.; et al. Early Procedural and Health Status Outcomes After Chronic Total Occlusion Angioplasty. JACC Cardiovasc. Interv. 2017, 10, 1523–1534.
11. Claessen, B.E.; Dangas, G.D.; Weisz, G.; Witzenbichler, B.; Guagliumi, G.; Möckel, M.; Brener, S.J.; Xu, K.; Henriques, J.P.; Mehran, R.; et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. Eur. Heart J. 2012, 33, 768–775.
12. Tajti, P.; Karmpaliotis, D.; Alaswad, K.; Jaffer, F.A.; Yeh, R.W.; Patel, M.; Mahmud, E.; Choi, J.W.; Burke, M.N.; Doing, A.H.; et al. The Hybrid Approach to Chronic Total Occlusion Percutaneous Coronary Intervention. JACC Cardiovasc. Interv. 2018, 11, 1325–1335.
13. Wilson, W.M.; Walsh, S.J.; Yan, A.T.; Hanratty, C.G.; Bagnall, A.J.; Egred, M.; Smith, E.; Oldroyd, K.G.; McEntegart, M.; Irving, J.; et al. Hybrid approach improves success of chronic total occlusion angioplasty. Heart 2016, 102, 1486–1493.
14. Brilakis, E.S.; Banerjee, S.; Karmpaliotis, D.; Lombardi, W.L.; Tsai, T.T.; Shunk, K.A.; Kennedy, K.F.; Spertus, J.A.; Holmes, D.R.; Grantham, J.A. Procedural Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention. JACC Cardiovasc. Interv. 2015, 8, 245–253.
15. Patel, M.R.; Calhoon, J.H.; Dehmer, G.J.; Grantham, J.A.; Maddox, T.M.; Maron, D.J.; Smith, P.K. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients with Stable Ischemic Heart Disease. J. Am. Coll. Cardiol. 2017, 69, 2212–2241.
16. Neumann, F.J.; Sousa-Uva, M.; Ahlsson, A.; Alfonso, F.; Banning, A.P.; Benedetto, U.; Byrne, R.A.; Collet, J.P.; Falk, V.; Head, S.J.; et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur. Heart J. 2019, 40, 87–165.
17. Lawton, J.S.; Tamis-Holland, J.E.; Bangalore, S.; Bates, E.R.; Beckie, T.M.; Bischoff, J.M.; Bittl, J.A.; Cohen, M.G.; DiMaio, J.M.; Don, C.W.; et al. 2021 ACC/AHA/SCAI Guideline for Coronary

Artery Revascularization. J. Am. Coll. Cardiol. 2022, 79, e21–e129.

18. Camici, P.G.; Prasad, S.K.; Rimoldi, O.E. Stunning, Hibernation, and Assessment of Myocardial Viability. Circulation 2008, 117, 103–114.
19. Al-Lamee, R.; Thompson, D.; Dehbi, H.-M.; Sen, S.; Tang, K.; Davies, J.; Keeble, T.; Mielewczik, M.; Kaprielian, R.; Malik, I.S.; et al. Percutaneous coronary intervention in stable angina (ORBITA): A double-blind, randomised controlled trial. Lancet 2018, 391, 31–40.
20. Windecker, S.; Stortecky, S.; Stefanini, G.; da Costa, B.R.; Rutjes, A.W.S.; Di Nisio, M.; Siletta, M.G.; Maione, A.; Alfonso, F.; Clemmensen, P.M.; et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: Network meta-analysis. BMJ 2014, 348, g3859.
21. Allman, K.C.; Shaw, L.J.; Hachamovitch, R.; E Udelson, J. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: A meta-analysis. J. Am. Coll. Cardiol. 2002, 39, 1151–1158.
22. Zannad, F.; Ferreira, J.P.; Pocock, S.J.; Anker, S.D.; Butler, J.; Filippatos, G.; Brueckmann, M.; Ofstad, A.P.; Pfarr, E.; Jamal, W.; et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: A meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet 2020, 396, 819–829.
23. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur. Heart J. 2021, 42, 3599–3726.
24. Ryan, M.; Morgan, H.; Chiribiri, A.; Nagel, E.; Cleland, J.; Perera, D. Myocardial viability testing: All STICHed up, or about to be REVIVED? Eur. Heart J. 2022, 43, 118–126.
25. Velazquez, E.J.; Lee, K.L.; Deja, M.A.; Jain, A.; Sopko, G.; Marchenko, A.; Ali, I.S.; Pohost, G.; Gradinac, S.; Abraham, W.T.; et al. Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction. N. Engl. J. Med. 2011, 364, 1607–1616.
26. Howlett, J.G.; Stebbins, A.; Petrie, M.C.; Jhund, P.S.; Castelvecchio, S.; Cherniavsky, A.; Sueta, C.A.; Roy, A.; Piña, I.L.; Wurm, R.; et al. CABG Improves Outcomes in Patients with Ischemic Cardiomyopathy. JACC Heart Fail. 2019, 7, 878–887.
27. Fearon, W.F.; Zimmermann, F.M.; De Bruyne, B.; Piroth, Z.; van Straten, A.H.; Szekely, L.; Davidavičius, G.; Kalinauskas, G.; Mansour, S.; Kharbanda, R.; et al. Fractional Flow Reserve–Guided PCI as Compared with Coronary Bypass Surgery. N. Engl. J. Med. 2022, 386, 128–137.
28. Perera, D.; Clayton, T.; O'Kane, P.D.; Greenwood, J.P.; Weerackody, R.; Ryan, M.; Morgan, H.P.; Dodd, M.; Evans, R.; Canter, R.; et al. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. N. Engl. J. Med. 2022, 387, 1351–1360.

29. Beanlands, R.S.; Nichol, G.; Huszti, E.; Humen, D.; Racine, N.; Freeman, M.; Gulenchyn, K.Y.; Garrard, L.; Dekemp, R.; Guo, A.; et al. F-18-Fluorodeoxyglucose Positron Emission Tomography Imaging-Assisted Management of Patients with Severe Left Ventricular Dysfunction and Suspected Coronary Disease: A Randomized, Controlled Trial (PARR-2). J. Am. Coll. Cardiol. 2007, 50, 2002–2012.
30. Gerber, B.L.; Rousseau, M.F.; Ahn, S.A.; Waroux, J.-B.L.P.D.; Pouleur, A.-C.; Phlips, T.; Vancraeynest, D.; Pasquet, A.; Vanoverschelde, J.-L.J. Prognostic Value of Myocardial Viability by Delayed-Enhanced Magnetic Resonance in Patients with Coronary Artery Disease and Low Ejection Fraction: Impact of Revascularization Therapy. J. Am. Coll. Cardiol. 2012, 59, 825–835.
31. Safley, D.M.; Koshy, S.; Grantham, J.A.; Bybee, K.A.; House, J.A.; Ms, K.F.K.; Rutherford, B.D. Changes in myocardial ischemic burden following percutaneous coronary intervention of chronic total occlusions. Catheter. Cardiovasc. Interv. 2011, 78, 337–343.
32. Ling, L.F.; Marwick, T.H.; Flores, D.R.; Jaber, W.A.; Brunken, R.C.; Cerqueira, M.D.; Hachamovitch, R. Identification of Therapeutic Benefit from Revascularization in Patients with Left Ventricular Systolic Dysfunction. Circ. Cardiovasc. Imaging 2013, 6, 363–372.
33. Frangogiannis, N.G. The pathological basis of myocardial hibernation. Histol. Histopathol. 2003, 18, 647–655.
34. Lim, S.P.; Mc Ardle, B.A.; Beanlands, R.S.; Hessian, R.C. Myocardial Viability: It is Still Alive. Semin. Nucl. Med. 2014, 44, 358–374.
35. Roes, S.D.; Mollema, S.A.; Lamb, H.J.; van der Wall, E.E.; de Roos, A.; Bax, J.J. Validation of Echocardiographic Two-Dimensional Speckle Tracking Longitudinal Strain Imaging for Viability Assessment in Patients with Chronic Ischemic Left Ventricular Dysfunction and Comparison with Contrast-Enhanced Magnetic Resonance Imaging. Am. J. Cardiol. 2009, 104, 312–317.
36. Cleland, J.; Pennell, D.; Ray, S.; Coats, A.; Macfarlane, P.; Murray, G.; Mule, J.D.; Vered, Z.; Lahiri, A. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): Randomised controlled trial. Lancet 2003, 362, 14–21.
37. Hachamovitch, R.; Rozanski, A.; Shaw, L.J.; Stone, G.W.; Thomson, L.E.J.; Friedman, J.D.; Hayes, S.W.; Cohen, I.; Germano, G.; Berman, D.S. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. Eur. Heart J. 2011, 32, 1012–1024.
38. Boden, W.E.; O'Rourke, R.A.; Teo, K.K.; Hartigan, P.M.; Maron, D.J.; Kostuk, W.J.; Knudtson, M.; Dada, M.; Casperson, P.; Harris, C.L.; et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. N. Engl. J. Med. 2007, 356, 1503–1516.

39. D'Egidio, G.; Nichol, G.; Williams, K.A.; Guo, A.; Garrard, L.; Dekemp, R.; Ruddy, T.D.; DaSilva, J.; Humen, D.; Gulenchyn, K.Y.; et al. Increasing Benefit From Revascularization Is Associated with Increasing Amounts of Myocardial Hibernation: A Substudy of the PARR-2 Trial. JACC Cardiovasc. Imaging 2009, 2, 1060–1068.
40. van Nunen, L.X.; Zimmermann, F.M.; Tonino, P.A.L.; Barbato, E.; Baumbach, A.; Engstrøm, T.; Klauss, V.; A MacCarthy, P.; Manoharan, G.; Oldroyd, K.G.; et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet 2015, 386, 1853–1860.
41. Johnson, N.P.; Gould, K.L. Physiological Basis for Angina and ST-Segment Change: PET-Verified Thresholds of Quantitative Stress Myocardial Perfusion and Coronary Flow Reserve. JACC Cardiovasc. Imaging 2011, 4, 990–998.
42. Werner, G.S.; Surber, R.; Ferrari, M.; Fritzenwanger, M.; Figulla, H.R. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. Eur. Heart J. 2006, 27, 2406–2412.
43. Obedinskiy, A.A.; Kretov, E.I.; Boukhris, M.; Kurbatov, V.P.; Osiev, A.G.; Ibn Elhadj, Z.; Obedinskaya, N.R.; Kasbaoui, S.; Grazhdankin, I.O.; Prokhorikhin, A.A.; et al. The IMPACTOR-CTO Trial. JACC Cardiovasc. Interv. 2018, 11, 1309–1311.