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Review

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Expanding indications: hybrid surgical-percutaneous coronary intervention (PCI) coronary revascularization of chronic total occlusions in patients with multivessel coronary artery disease (CAD)

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Abstract
Hybrid revascularization of multivessel coronary artery disease by combining coronary artery bypass grafting (CABG) and chronic total occlusion (CTO) percutaneous coronary intervention (PCI) is a relatively novel concept. Hybrid CABG-CTO PCI aims to combine the durable clinical benefits of a left internal mammary artery graft (ideally minimally invasively) with the durability of CTO PCI in non-left anterior descending vessels. This review assesses the current evidence for performing hybrid CTO PCI-CABG and pre-procedural planning considerations.

Keywords: Chronic total occlusion (CTO), percutaneous coronary intervention(PCI), coronary artery bypass grafting(CABG), hybrid revascularization, coronary artery disease

INTRODUCTION
Revascularization for multivessel coronary artery disease
Current guidelines recommend revascularization for most patients with multivessel coronary artery disease

(MVCAD) for both prognostic and symptomatic benefits[1,2]. With increasing anatomical complexity and lesion burden, such as left main disease, bifurcation lesions, calcified lesions, chronic total occlusions (CTOs), and SYNTAX score > 22 coronary artery bypass grafting (CABG) is recommended over percutaneous coronary intervention (PCI)[3]. CABG is also recommended over PCI for patients with ischemic cardiomyopathy or diabetes[4,5]. Independent of revascularization strategy, complete revascularization (residual Syntax Score ≤ 8) is usually desired, as incomplete revascularization is an important predictor of adverse outcomes after CABG and PCI[6-8].

Revascularization of CTO lesions

One third of patients with multivessel CAD have at least one CTO lesion[9]. CTO lesions are more prevalent in patients with diabetes, chronic kidney disease, or especially a history of CABG surgery[10].

CABG for CTO lesions

CABG in the setting of multivessel disease with the goal of complete revascularization may often include bypassing CTO lesions. Observational data suggest that complete revascularization provides superior outcomes compared to incomplete revascularization[7,11], and poses few risks during CABG[12]. A paucity of data is available examining the outcome of CABG for CTOs as the primary reason for revascularization, although CTOs have traditionally been a major reason to refer patients for CABG[13,14]. In an analysis of patients with a CTO lesion in the randomized SYNTAX trial, the CTO was only grafted in 68.1% of patients[15]. This may be partly due to diffuse disease and difficulties in identifying and grafting the target vessel, which appears small and underfilled if it has been chronically occluded. If CTOs are grafted, long-term graft failure may be more than twice as likely as grafts of non-CTO vessels[16]. Conversely, observational data demonstrate a reduction of angina after CABG for CTOs[17].

PCI for CTOs

The primary indication for CTO PCI is the relief of angina. The success rate and safety of CTO PCI are high in centers with expertise in CTO PCI programs. Registries demonstrate 85%-90% success rates with a major complication rate ranging from 1.8%-7%, and more recent data confirm a contemporary complication rate of about 2%[18-21]. This is in line with the general trend of improving outcomes after PCI[22].

The efficacy of CTO PCI for angina relief has been shown in multiple observational trials and two randomized trials, the EuroCTO trial (Randomized Multicentre Trial to Compare Revascularization With Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) and the IMPACTOR-CTO trial (Impact on Inducible Myocardial Ischemia of Percutaneous Coronary Intervention versus Optimal Medical Therapy in Patients with Right Coronary Artery Chronic Total Occlusion)[20,23,24]. Two other randomized trials showed a neutral effect of CTO PCI on left ventricular ejection fraction in CTOs was found to be present in patients presenting with ST-elevation myocardial infarction, and on major adverse cardiovascular events (MACE) in stable patients presenting for CTO PCI[25,26]. Other potential indications for CTO PCI have been investigated in observational studies. Left ventricular ejection fraction improved after CTO PCI in patients with depressed baseline function, especially in patients with viable myocardium supplied by the target vessel[27,28]. Recent observational trials have suggested that, compared to incomplete revascularization, after successful CTO PCI, there is an improvement in 3-year event-free survival and a decrease in 2-year MACE and cardiogenic death when complete revascularization is achieved[29,30].

Rationale for hybrid CTO-PCI and CABG with left internal mammary artery to left anterior descending artery (LIMA-LAD)

The concept of hybrid coronary revascularization (HCR) in the cases of LAD CTO and multivessel disease has been established, usually involving minimally invasive LIMA-LAD grafting and PCI for the remaining vessels[31-33]. Because CTO and non-CTO lesions in the setting of HCR are treated with a LIMA-LAD bypass, CTO PCI in the context of HCR therefore aims to combine the benefits of the LIMA-LAD bypass and the potential for similar or increased durability of CTO PCI for non-LAD vessels to achieve complete revascularization[24]. In addition, in centers that perform minimally invasive CABG (e.g., totally endoscopic coronary artery bypass (TECAB), minimally invasive direct coronary artery bypass (MIDCAB), and the newer minimally invasive coronary surgery CABG (MICS CABG)), such a hybrid approach might be less invasive than traditional CABG[34-36].

Grafting of the LIMA to LAD provides a survival benefit in patients with MVCAD, and is highly durable with a > 95% 15-year patency rate[37,38]. CABG is - therefore - the preferred revascularization strategy for many patients except those with one or two-vessel disease without proximal LAD involvement, or those with excessive high surgical risk[2,39].

On the other hand, bypass grafting of CTOs is associated with challenges as described above and possibly suboptimal patency rates, especially in non-LAD vessels[16]. In the PRAGUE-4 trial, grafted non-LAD CTO vessels were found to have 1-year patency rates of only 23%[40]. A limitation of prior CTO grafting studies is the limited use of non-saphenous vein graft (SVG) conduits which might confer improved outcomes, such as the radial artery or right internal mammary artery (RIMA).

The 10-year patency of saphenous vein grafts is about 50%[41]. Although not directly comparable, one measure of the long-term success of PCI is target lesion revascularization. Patients receiving drug-eluting stents have historically experienced a 10% target lesion revascularization (TLR) rate at 5 years[42]. With contemporary ultra-thin drug eluting stents (DES), a further reduction in TLR rates may be possible, as demonstrated by TLR rates of 3.2% at 3 years[43]. In the absence of a randomized trial comparing CABG *vs.* PCI for revascularization of CTO lesions, we hypothesize that CTO PCI may be superior to saphenous vein grafting of non-LAD CTO lesions.

Taken together, hybrid CABG-CTO PCI revascularization is an attractive solution in the setting of multivessel disease with LAD involvement and a non-LAD CTO, especially when minimally invasive surgical techniques such as TECAB or MICS CABG are feasible.

STUDIES INVESTIGATING HYBRID REVASCULARIZATION INVOLVING CTOS

Retrospective studies

Only one retrospective study reported on outcomes of patients undergoing CTO PCI as part of a hybrid CABG-PCI revascularization procedure[44]. Hybrid coronary revascularization with robotic beating-heart multivessel TECAB and PCI was performed in 57 patients. The mean follow-up period was 21.5 ± 13.4 months. The mean length of hospital stay was 3.0 ± 1.3 days, a short duration compared to typical CABG inpatient rates of 5-7 days. In the majority of patients (98.2%), off-pump beating-heart CABG was performed. A CTO was present in 17/57 (29.8%) patients. Of these, 6/17 were treated with TECAB and 11/17 patients underwent CTO PCI after CABG. The overall success rate was 73% and no complications occurred. No outcomes were reported specifically for the CTO subgroup, but only for the entire group of 57 patients. At 36 months, freedom from mortality and major adverse cardiac events were 92.8% and 80.2%, respectively, with 8.8% repeat revascularization, one (1.8%) myocardial infarction, one in-stent restenosis, and four graft occlusions.

Case report

More recently, a case of an 80-year-old man with stable angina, multivessel coronary artery disease, an ejection fraction of 32%, and a high SYNTAX score of 45 was reported[45]. He had a short but calcified and angulated mid-RCA CTO. During a heart team discussion, he was deemed to be a good candidate for hybrid coronary revascularization given his high SYNTAX score, which made him a good candidate for CABG, and his short CTO, which made successful PCI more likely. First, CTO-PCI of the mid right coronary artery (RCA) was performed, followed two months later by total endoscopic coronary artery bypass grafting with the LIMA to the LAD and a diagonal branch, and RIMA to an obtuse marginal branch. He was discharged with a residual SYNTAX score of 1 and has remained free of angina with normalized ejection fraction on a follow-up echocardiogram.

TIMING OF CTO PCI AND CABG

Timing of CTO PCI (or any PCI) in relation to cardiac surgery is an important consideration. In theory, CTO PCI can be performed prior to, at the time of, or after cardiac surgery. However, each option has different risks and benefits, discussed next.

CTO PCI prior to CABG

Advantages of performing CTO PCI prior to CABG include the potential to obtain complete revascularization with LIMA-LAD at a later date (in contrast, incomplete CABG without CTO grafting could increase the chance for a demand-induced perioperative myocardial infarction)[46]. Particularly for CTO PCI of lesions with high Japanese CTO (J-CTO) scores and therefore increased technical difficulty, lower chance of success, and higher risk of complications, it may also be beneficial to attempt PCI prior to surgery, because should CTO PCI be unsuccessful, complete CABG including revascularization of the CTO territory with another graft conduit could remain an option.

On the other hand, performing CTO PCI prior to CABG in the setting of high-grade lesions may not always be well-tolerated, especially with retrograde CTO PCI or if a PCI complication occurs. Furthermore, if CABG is indicated soon after successful CTO PCI, managing DAPT after PCI may require some care and coordination, even when implanting a stent that is approved for shorter DAPT duration in high bleeding risk patients (e.g., 1-3 months). For example, it still may be necessary to consider bridging with cangrelor or glycoprotein IIb/IIIa antagonists in the perioperative setting, followed by resumption of oral DAPT as soon as permissible after CABG. Alternatively, if CABG (LIMA-LAD) can be deferred for 6-12 months after CTO PCI, DAPT can likely be stopped, allowing the usual monotherapy aspirin to be prescribed during the perioperative period. In our opinion, bare-metal stents with 1-month DAPT are not a good alternative, given their much higher restenosis rate and the recent availability of Food and Drug Administration (FDA)-approved DES for one month of DAPT in high-bleeding risk patients, which would likely include those undergoing future CABG.

Another strategy is to perform CABG and CTO PCI in the same setting on the same day, especially in a hybrid operating room with fluoroscopic capabilities. In this approach, CTO PCI is performed first and DAPT is loaded, followed by immediate CABG[46]. This approach may avoid operating on fully therapeutic DAPT and minimizes the number of separate procedures the patient has to undergo. Another option in the current era may be to perform CTO PCI and continue bridging with cangrelor until CABG can be performed. However, coordination between the surgical and interventional teams may be logistically challenging, and ideally, a hybrid operating room is needed. Bleeding can also be an issue because DAPT is required after CABG for the stented vessels. In summary, CTO PCI at the time of CABG does not seem to be preferable due to logistics and time requirements and may be more difficult to manage complications;

therefore, it is not preferred.

CTO PCI after CABG

CTO PCI after CABG is the preferred hybrid coronary revascularization strategy in most cases as it has several advantages. However, in the current practice of conventional CABG, this opportunity would arise only when bypass of a CTO is known to be unsuccessful (e.g., technical limitations in the OR, absence of conduit) or when a patient experiences post-CABG ischemic symptoms leading to a diagnosis of ischemia in the CTO territory, and/or CTO graft failure.

Second, if planned hybrid CTO PCI is to be performed after CABG with LIMA:LAD grafting only, an additional advantage is that the larger (LAD) territory has already been revascularized, offering additional protection from CTO PCI-induced myocardial stress. A LIMA:LAD +/- other graft presence may also simplify the treatment of other lesions that previously were not amenable or at high risk for PCI, such as left main bifurcation lesions, proximal diagonal branches with calcified LAD bifurcation lesions, which can now potentially be treated with a provisional instead of a bifurcation stenting strategy. In addition, graft patency can be confirmed at the time of the PCI and possible early graft occlusions can be treated.

CASE REPORT

A 53-year-old man was referred to our office. His medical history included hyperlipidemia with high lipoprotein (a) and Canadian Cardiovascular Society (CCS) class 2-3 angina for two years. A stress echocardiogram revealed basal to mid-inferior and anterior lateral ischemia. Medical therapy with Aspirin 81 mg daily, rosuvastatin 20 mg daily, ezetimibe 10 mg, and metoprolol 25 mg daily was initiated. Isosorbide mononitrate 30 mg daily was added at a subsequent visit, with symptoms improved to CCS class 1-2. For further risk stratification and to define the burden of atherosclerosis, computed cardiac tomography angiography (CCTA) and calcium scoring were performed. His calcium score was 28 (LM: 0, LAD: 1, LCx: 0, RCA: 27). CCTA demonstrated high-risk anatomy and he was referred for coronary angiography, which revealed a 55% mid LAD lesion and diffuse up to 50% of distal LAD disease, a proximal OM2 CTO, 80% of mid RCA and 70% of distal RCA disease. Diastolic hyperemia-free ratio (DFR) of the distal LAD was 0.82 (positive), and of the mid LAD, 0.90 (negative). The SYNTAX score was 25. Given the lack of severe angiographic LAD stenosis, de novo medical therapy, no diabetes, normal ejection fraction, younger age with potential for saphenous vein graft occlusion in his 60s, the decision was made in a heart team meeting to proceed with PCI of the RCA and OM2 CTO.

Heart team meetings at our institution generally include multiple interventional cardiologists and cardiothoracic surgeons and, depending on the case, may also involve the patient's primary cardiologist, cardiologists specialized in cardiac imaging to review cardiac magnetic resonance imaging, cardiac computed tomography angiography, and echocardiography studies, as well as colleagues from radiology to comment on these studies. The heart team makes a treatment recommendation based on a thorough discussion of all participants that includes but is not limited to procedural risk, feasibility, as well as short- and long-term risk/benefit, considering the individual patient's presentation and risk factor profile. The recommendation of the heart team is then presented to the patient, the ultimate decision maker.

The RCA PCI was uncomplicated with the placement of two everolimus-eluting stents (3.0 × 48 mm and 3.5 × 38 mm). The OM2 CTO was wired using a microcatheter and antegrade wire escalation with the ultimate placement of a 2.75 × 38 mm everolimus-eluting stent with an excellent angiographic result.

We planned to re-evaluate the patient for CABG with LIMA-LAD given his diffuse mid to distal DFR-positive LAD disease with CABG tentatively planned for 6 months after PCI, if symptoms persisted. However, the patient was completely angina-free during the 3-month follow-up and has felt much more energetic since then.

This case highlights the feasibility of non-LIMA multivessel PCI with the option for CABG to LAD or potentially failed CTO lesions at a later point in time. In our experience, this flexible strategy has proven to be very effective as it allows for state-of-the-art treatment of CTO lesions without the need for immediate CABG, while still allowing for the option of a LIMA-LAD depending on symptoms or lesion severity. With the availability of more data and the experience of other centers, this strategy can be further refined in the future.

DISCUSSION

Hybrid coronary revascularization for patients with multivessel coronary artery disease that includes a CTO in a non-LAD vessel is an attractive strategy that potentially offers several advantages. The benefits of CABG (LIMA:LAD) and PCI (non-LAD CTO PCI) may be realized with a hybrid procedure. The patient presumably receives the prognostic benefit of the LIMA-LAD graft, possibly through less invasive cardiac surgery (TECAB/MICS CABG), resulting in shorter recovery times. In addition, the patient may benefit from potentially better long-term results with CTO PCI compared to vein grafting of CTO vessels; however, it should be noted that to date, there have been no trials directly comparing long-term patency of vessels after CTO-PCI versus CABG. Therefore, hybrid CABG-CTO PCI in patients with a non-LAD CTO and LAD disease may present a desirable alternative to current standard treatment with either standalone PCI or standalone CABG. We surmise that further clinical studies of hybrid CABG-CTO PCI compared to traditional CABG, including the grafting of CTOs, would be of substantial interest to the interventional and surgical communities.

While the benefits of a hybrid approach may be greater, limitations must be considered as well. As opposed to undergoing complete revascularization during CABG, in a hybrid procedure, the patient will undergo a single vessel or two vessel CABG and separate CTO PCI. In principle, this means that the risk of the two separate procedures (each having a 2% major risk for the average risk patient) may be greater than a single CABG procedure alone. If CTO PCI is straightforward, then a hybrid approach may be favorable, but less so for CTO patients with highly calcified bifurcation lesions requiring atherectomy, or a high J-CTO score, which implies a lower likelihood of success and higher complication rates, especially coronary artery perforation. In our opinion, a heart team approach is an ideal way to decide the best revascularization strategy for these complex patients, which is affirmed by current guidelines[2,39,47].

If a hybrid approach is chosen and CTO PCI is planned, timing is an important consideration, as discussed above. CTO PCI prior to CABG offers a bailout option should PCI be unsuccessful, as the patient may still be able to undergo bypass grafting of the chronically occluded vessel after an unsuccessful attempt. Hence, CTO PCI prior to CABG may be the preferred option for patients with technically difficult CTOs (Japanese CTO (JCTO) score ≥ 3), where the chance for failure is higher. Downsides of such an approach include the potential higher procedural risk of performing CTO PCI in the setting of other unrevascularized ischemic lesions, and the future need to stop DAPT if CABG is to be performed in less than 6-12 months, potentially requiring intravenous anti-platelet therapy bridging in the periprocedural setting.

Timing and strategy will also depend on the experience, the success rate of the individual operator and the center where the procedure is performed. While the average success rate of CTO PCI in the United States is

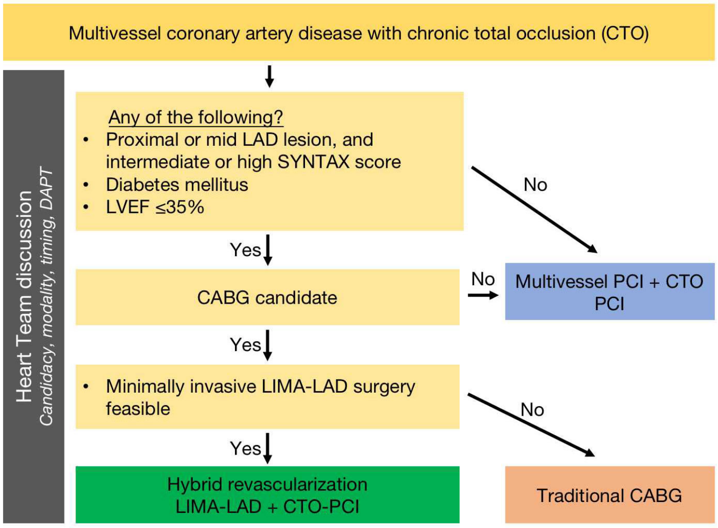

Figure 1. Approaches to hybrid CTO PCI and CABG. Patients presenting with multivessel coronary artery disease and at least one CTO are discussed by the heart team to decide on the most appropriate revascularization strategy considering SYNTAX score, CTO location, CTO PCI and CABG technical difficulty, and comorbidities. Revascularization approaches are to be discussed with consideration of hybrid revascularization for patients with non-LAD CTO lesions amenable to PCI, where LIMA-LAD (ideally minimally invasive TECAB or MIDCAB) is feasible as well. Timing of CTO PCI and CABG, as well as DAPT plan, should also be addressed by the heart team. CTO: Chronic total occlusion; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; LIMA: left internal mammary artery; LAD: left anterior descending artery; TECAB: totally endoscopic coronary artery bypass; MIDCAB: minimally invasive direct coronary artery bypass; DAPT: dual-antiplatelet therapy; LVEF: left ventricular ejection fraction.

about 60%, it rises to 90% in experienced centers[48]. Experienced operators achieve higher success rates with fewer complications[49]. These factors may affect the choice of hybrid revascularization or complete CABG, and whether CTO PCI should be attempted before or after CABG if success rates are low. Therefore, for more complicated CTO (J-CTO scores > 0-1), it is recommended to discuss hybrid CABG-PCI approaches with experienced CTO operators.

The complexity of disease is an important consideration in deciding if a patient should be offered hybrid revascularization, CABG, or multivessel PCI. Hybrid revascularization with CTO PCI will likely benefit the patients with a high SYNTAX score or intermediate SYNTAX score with diabetes mellitus or low left ventricular ejection fraction where the current guidelines favor traditional CABG over PCI. Patients with low SYNTAX score or intermediate SYNTAX score without diabetes can be offered multivessel PCI after without hybrid revascularization after a detailed risk and benefit discussion.

Finally, we would like to remark that there is currently a paucity of data regarding hybrid coronary revascularization with LIMA-LAD and CTO-PCI of a non-LAD vessel. Therefore, more research is required to understand if hybrid revascularization compared to traditional CABG will provide superior durability and clinical outcomes in patients with intermediate to high SYNTAX score, while not increasing the overall risk for two combined procedures.

CONCLUSIONS

Hybrid coronary revascularization combining LIMA-LAD CABG with PCI of CTOs in patients with multivessel CAD is an intriguing approach with the potential benefits of greater durability with PCI compared to saphenous vein grafting of CTO vessels. Patient selection and timing of the procedures are important considerations and are best addressed in a heart team forum [Figure 1]. Additional observational and randomized clinical trial data are necessary to understand whether hybrid revascularization approaches will prove superior to standalone CABG or standalone multivessel PCI.

DECLARATIONS

Authors' contributions

Made substantial contributions to writing several drafts, revising drafts, creating and editing the figure, adding references, reviewing literature: Bode MF, Jaffer FA

Availability of data and materials

Not applicable.

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Conflicts of interest

FAJ has received sponsored research support from Canon, Siemens, Teleflex, Shockwave, Amarin, Mercator, and Boston Scientific; and is consultant/speaker for Boston Scientific, Biotronik, Siemens, Magenta Medical, IMDS, and Philips. FAJ has equity in Intravascular Imaging, Inc. and DurVena, Inc. Massachusetts General Hospital has a patent licensing arrangement with Terumo, Canon, and Spectrawave. All other authors have no relevant conflicts of interest to disclose.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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