JTD JOURNAL OF THORACIC DISEASE
A PEER-REVIEWED, OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN THORACIC DISEASES
IMPACT FACTOR 2.895

Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-21-681

Reviewer A

In general, this paper shows interesting data but no completely new results.

Comment : The fact that incomplete revascularisation is associated with a higher risk of mortality is well known and widely accepted. Even in CTOs it has been shown that even if well collateralised the myokardium is still at risk and needs revascularising. It therefore does not surprise me, that the patients with incomplete revascularisation show higher mortality and a higher risk of MACCE.

Adding to that the risk factors should be balanced in this cohort. Especially the significantly higher rate of Diabetes and End Stage Renal Disease in the incompletely revascularised group makes it hard to compare the groups and even harder to draw conclusions.

I suggest balancing the groups using propensity score matching to make them comparable. If this is impossible due to low sample size, obtaining the STS-Risk scores could shed more light on differences in mortality risk between the groups independent of revasclarisation. This might make it possible to draw the conclusions that revscularisation in CTOs should be achieved if ever possible.

Reply: I agree with the points you've raised and appreciate your suggestion. As you mentioned, balancing the groups using the propensity score matching was not possible, because of the small sample size. Instead of the STS risk score, I would like to show the EuroSCORE II, which was routinely calculated prior to each surgery at our institution. The latest version of the EuroSCORE II is known to have better predictive discrimination for operative morality than EuroSCORE I, and it is more suitable for complex cardiac surgical patients than the STS score (Reference 1).

Changes in the Text: I added the EuroSCORE II in Table 1.

Reference 1) Ad N et al. Comparison of EuroSCORE II, Original EuroSCORE, and

The Society of Thoracic Surgeons Risk Score in Cardiac Surgery Patients. Ann Thorac Surg. 2016 Aug;102(2):573-9

Reviewer B

This paper reports a retrospective study of a single institution evaluating the incidence and clinical outcome of revascularization on chronic total occlusion (CTOs) in patients undergoing coronary artery bypass grafting (CABG).

This reviewer has some remarks:

Comment 1: In the materials methods section, there is lack of information concerning the type of conduits used (i.e., arterial, or venous) to revascularize CTOs., neither where the conduits were placed (i.e., left anterior descending artery, circumflex artery or right coronary artery).

Reply: I appreciate your critical comment. I added CTO revascularization strategy including the type of conduit and territory in the method section.

Changes in the text:

3) Surgical revascularization of CTOs

In our institution, we primarily perform conventional CABG with standard cardiopulmonary bypass and cardiac arrest, but off-pump CABG was considered in patients with significant atherosclerotic aortic disease. Decisions for whether to bypass a CTO lesion or not were mainly based on the quality of the conduit, the anatomical complexity such as the diameter of the native coronary artery, the degree of calcification. Severely calcified CTO lesion requiring thromboendarterectomy was not revascularized. Left internal mammary artery (LIMA) was the first choice of conduit to revascularize CTOs in LAD territory. For non-LAD territory, we selected the radial artery over the saphenous vein graft, especially for LCX territory to revascularize CTOs.

The intraoperative mean graft flow and pulsatility index (PI) were measured with a transit time flow measurement (TTFM) device (MedStim, Oslo, Norway) for all anastomosis at the time of CPB weaning or haemodynamic stabilization with a systolic blood pressure of 100–120 mmHg. According to the European Association for Cardiothoracic Surgery and European Society of Cardiology (EACTS/ESC)

guideline, we followed the TTFM cut-off threshold values; mean flow ≥ 20 ml/min, PI ≤ 5. If TTFM value shows suboptimal or outside the threshold value, then we consider to revise the anastomosis.

Comment 2: There is lack of information on how the vessels with CTOs were managed. Did the surgeons make use of thromboendarterectomy (TEA)?

Reply: In our institution, decisions for whether to bypass a CTO lesion or not were mainly based on the quality of the conduit, the anatomical complexity, such as the diameter of the native coronary artery, and the degree of calcification. Therefore, diffuse severely calcified CTO lesions requiring TEA were not bypassed, which contributed to incomplete revascularization in our study. TEA was not done in any CTO revascularization in our study. I added our institution's revascularization strategy in the Method section.

Changes in the text:

3) Surgical revascularization of CTOs

In our institution, we primarily perform conventional CABG with standard cardiopulmonary bypass and cardiac arrest, but off-pump CABG was considered in patients with significant atherosclerotic aortic disease. Decisions for whether to bypass a CTO lesion or not were mainly based on the quality of the conduit, the anatomical complexity such as the diameter of the native coronary artery, the degree of calcification. Severely calcified CTO lesion requiring thromboendarterectomy was not revascularized. Left internal mammary artery (LIMA) was the first choice of conduit to revascularize CTOs in LAD territory. For non-LAD territory, we selected the radial artery over the saphenous vein graft, especially for LCX territory to revascularize CTOs.

The intraoperative mean graft flow and pulsatility index (PI) were measured with a transit time flow measurement (TTFM) device (MedStim, Oslo, Norway) for all anastomosis at the time of CPB weaning or haemodynamic stabilization with a systolic blood pressure of 100–120 mmHg. According to the European Association for Cardiothoracic Surgery and European Society of Cardiology (EACTS/ESC) guideline, we followed the TTFM cut-off threshold values; mean flow ≥ 20 ml/min, PI ≤ 5. If TTFM value shows suboptimal or outside the threshold value, then we consider to revise the anastomosis.

Comment 3: There is lack of information on patient's cause of death (cardiac or not). Patients in the Incomplete Revascularization (ICR) group appears to have higher operative risk because of the advance age and increase numbers of co-morbidities. This can be bias towards the results and the conclusions.

Reply: 30-day and overall mortality included all causes of death. This explanation was added in the Method section. I agree with your observation about the imbalance of co-morbidities between the ICR and CR groups. Unfortunately, balancing the groups using propensity score matching was not possible because of the small sample size. Rather, I would like to add the EuroSCORE II, which was routinely calculated prior to surgery in our institution. EuroSCORE II is one of the most commonly used and reliable risk prediction algorithms based on co-morbidities and the complexity of the surgery. The EuroSCORE II between the two groups were comparable. I added this result in Table 1.

Comment 4: Aline 32: must be: undergoing Coronary Artery Bypass Grafting (CABG) instead of CABG.

Reply: I appreciate your comment. I added ' coronary artery bypass grafting ' in the revised manuscript.

Reviewer C

In this manuscript, the authors evaluate the incidence and clinical outcomes of patients with chronic total occlusions (CTO) undergoing revascularization via coronary artery bypass grafting (CABG). The manuscript is well written, thorough, and the authors present the results from their single center.

Major Comments

Comment 1: The authors of this manuscript have produced an interesting article. Although notably, there are important results that are absent. In this manuscript, MACCE was defined as all-cause mortality, stroke or transient ischemic attack, and acute coronary syndrome requiring repeated revascularization. These individual results are essential to understanding the outcomes of this patient population. While the combined end point of MACCE is an appropriate outcome to include, the

individual outcomes of stroke or transient ischemic attack, myocardial infarction or acute coronary syndrome, required revascularization, readmission to hospital, and sepsis, among other outcomes, are important to understanding the outcomes of this patient population. If the authors have access to these outcomes, they should be included in this study.

Reply: I agree with your comment and appreciate your valuable suggestion. I added individual results of MACCE in table 1.

Minor Comments

Comment 2: In lines 64-66 the authors state "However, because of the lower initial success rate with angioplasty and a higher frequency of restenosis, reocclusion, and adverse clinical events, PCI for CTOs remains controversial." It is unclear what the lower initial success rates with angioplasty are referring to. Does angioplasty have a lower initial success rate than coronary artery bypass grafting, PCI with bare metal or drug eluting stents? This should be specified.

Reply: I revised that sentence in the manuscript to make it clearer.

Comment 3: In line 72 the authors state, "Even though several studies of revascularization on CTOs with coronary arteries demonstrated favorable outcomes of CABG over PCI". It is unclear what is meant when stating "revascularization on CTOs with coronary arteries". The authors should consider removing the "with coronary arteries" or revising this statement for clarity.

Reply: I deleted 'with coronary arteries'.

Comment 4: In the introduction, the authors state that one of their objectives is to evaluate the clinical outcomes of patients with CTO. While the authors provide data for patients with CTO who received complete or incomplete revascularization, it does not necessarily indicate the impact of CTO on outcomes. A comparison to other CABG patients from the same center without CTO would provide insight into the impact CTO has on outcomes. By only providing data from CTO patients, it is unclear what the significance of CTO is. If the authors have access to data from their center or previously published data for CABG patients without CTO, it may be useful to provide this data for context.

Reply: I agree with your comment. Our study's aim was not to evaluate the impact of CTOs on outcomes, but to assess the impact of complete revascularization on CTOs upon performing CABG. Fefer et al. (reference 10 in the original manuscript) narrowed down their study from comparing CABG outcomes with CTO's and without CTOs to comparing complete bypass and incomplete bypass among patients with CTOs. Our study is focusing on the latter issue only. I am afraid that it is not possible to provide specific data or previously published data for CABG without CTOs in this revision. Hopefully, I will consider to evaluate the impact of CTOs by comparing outcomes of CABG without CTOs in a further study.

Reviewer D

First I would like to applaud the others for conducting this important study. Their data set is large and they performed a comprehensive analysis of CABG for CTO. The long term analysis of this study is very important and their investigation of prior research is quite strong. I do have however some key questions which may really help better understand CTO and the use of CR v ICR.

Comment 1: In this study ICR was shown to have increased mortality at both short and long term compared with CR. They demonstrated this with multivariate analysis and used a considerable number of variables such as age, DM, LVEF, etc.. However, I would like to see two other variables in their calculations: LVEF < 35 and Rentrop (collateral supply). I think categorizing by LVEF <35 will help us see if ICR is particularly bad in low LVEF patients. Also, the Rentrop score was assessed in their background, but they didn't show any univariate analysis on how Rentrop affects mortality. This is important as better collateral supply may decrease the need for CR. There is increased mortality with increased CBP time. Therefore, decreasing the length of the surgery by not performing CR when necessary may be beneficial to the patient.

Reply: I appreciate your insightful feedback. In the case of LVEF, we considered the data a continuous variable as shown in the Table 1-4. LVEF, as a continuous variable, showed significant association with 30-day and overall mortality, as well as MACCE in the multivariate analysis. When we performed the same analysis with dichotomized LVEF (<35%, ≥35%) as you suggested, LVEF<35% was identified as a risk factor for

30-day mortality (OR 4.03, 95% C.I. 1.15-14.15, p=0.03), however, it did not show any significant association with overall mortality and MACCE (HR 1.66, 95%C.I. 0.72-3.82, p=0.23, and HR 1.34, 95% C.I. 0.63-2.85, p=0.43, respectively). In addition, statistically, categorizing a continuous variable seems to not be recommended unless the distribution is clearly multimodal or there is a theoretically justified borderline, because categorizing a continuous independent variable has many consequences, such as loss of information and statistical power, etc (reference 1). Therefore, I propose that considering LVEF as continuous variable, as shown in our manuscript, would be more appropriate than dichotomizing it.

Regarding the Rentrop grade for collateral flow, we referred to 'Rentrop grade ≥2' as 'good collateral' in table 1 (please, see the footnote of the table 1 in the original manuscript). I completely agree with your suggestion that Rentrop grades should be included in the multivariate analysis, which I missed in the original manuscript. Unfortunately, in the univariate and multivariate analyses, Rentrop grade >2 showed no association with any outcomes. (30-day mortality p=0.20, overall mortality p=0.35 (in the multivariate analysis), and MACCE p=0.92). I added these results in the table 2-4. I also changed the variable 'good collateral' to 'Rentrop grade ≥2' in the tables for more clarity

Reference 1) Altman D.G., Royston P.Statistics Notes: The cost of dichotomizing continuous variables. BMJ 2006;332:1080.

Comment 2: In the baseline characteristics, it is important that probe/doppler flow or some more unbiased standard for effective revascularization in the other bypassed vessels is shown. As stated, ICR patients may have more difficult anatomy. Producing this data may help delineate the cause of worse outcomes in ICR patients. Is it because the surgery is more technically challenging or because the lack of blood flow in the CTO?

Reply: In our institution, we routinely check transit-time flow measurement (TTFM) at the time of CPB weaning and after CPB off. According to the EACTS/ESC guideline, we follow the TTFM cut-off threshold values; mean flow ≥ 20 ml/min, PI ≤ 5. If TTFM value shows suboptimal or outside the threshold value, then we consider revising the anastomosis. Decisions for whether to bypass a CTO lesion or not were mainly based on the quality of the conduit, the anatomical complexity, such as the diameter of the native coronary artery and the degree of calcification, but once a CTO

lesion was bypassed, effective revascularization was assessed by the TTFM, same as described above. Even though technically revascularization was performed appropriately in the CTO lesions, graft occlusion in the revascularized CTO lesion occurred in the CR group (n=6, 3.1%). I think this may imply that anatomical complexity in the CTO lesion does not necessarily correlate with functional ischemia or viability of the myocardium on CTO lesions. Unfortunately, use of MRI or PET prior to revascularization to assess viability, especially for CTO lesions, is not part of routine clinical decision making because of the practicality of obtaining these images, partly due to expense and also limited and uncertain accuracy (reference 12 in the original manuscript). As we mentioned in our study limitation, assessment of viability of the myocardium on CTO lesions was not included in our study. Functional assessment of CTO lesions may be necessary in the further study.

Comment 3: Also, as stated in the introduction, not all CTO lesions are similar. It would be beneficial to show which CTO lesions have worse outcomes in ICR and CR patients? Maybe certain lesions are particularly more suitable for ICR as their outcomes are similar to CR and maybe certain lesions should be performed with ICR as they are too risky for CR.

Reply: I appreciate your critical comment. As an observational study, available data about CTO lesions were limited to the degree of collateral flow (Rentrop grade), territory, and conduits used for revascularization, and completeness of revascularization. Unfortunately, all of these were not associated with clinical outcomes except for completeness of revascularization. Hopefully, in a further study with a larger cohort, this important issue that you mentioned may be resolved.

Comment 4: Finally, the number of CTO lesions are compared throughout the analysis. However, the more important question is how many CTO lesions were left un revascularized. This should be further categorized as ICR with 2 unrevascularized CTO lesions may have significant worse outcomes than ICR with 1. ICR with 1 may even be more comparable to CR in terms of mortality.

Reply: While I agree with your point, I'd like to state that among the patients in ICR group, 47 patients (92.1%) had 1 unrevascularized CTO lesion (subgroup1), and 4 patients had 2 unrevascularized CTO lesions (subgroup2). There was no statistical difference between these subgroups in terms of 30-day and overall mortality, as well

as MACCE (p=0.49, 0.46, and 0.77, respectively). When comparing the subgroup 1 to the CR group, in terms of mortalities and MACCE, it showed the similar results to those found in our original manuscript. Number of CTO lesions left unrevascularized may not affect the main outcomes.

Again, I would like to thank the authors for investigating this topic.