Revascularization for Stable Chronic Total Occlusion is Essential for Diabetic Patient with Heart Failure

Yunfeng Yan
Beijing Anzhen Hospital, Capital Medical University
Mingduo Zhang
Beijing Anzhen Hospital, Capital Medical University
Zhuo Ma
Beijing Zhongguancun Hospital
Zilong Zhang
Emergency General Hospital
Fei Yuan
Beijing Anzhen Hospital, Capital Medical University
Hong Liu
Beijing Anzhen Hospital, Capital Medical University
Feng Xu
Beijing Anzhen Hospital, Capital Medical University
Min Zhang
Beijing Anzhen Hospital, Capital Medical University
Wei Wang
Beijing Anzhen Hospital, Capital Medical University
Kuo Zhou
Beijing Anzhen Hospital, Capital Medical University
Quanming Zhao
Beijing Anzhen Hospital, Capital Medical University
Shuzheng Lyu (shuzheng023@163.com)
Capital Medical University Affiliated Anzhen Hospital https://orcid.org/0000-0002-4243-2341

Research article

Keywords: chronic total occlusion, diabetes, revascularization, medical therapy, heart failure.

Posted Date: November 1st, 2019

DOI: https://doi.org/10.21203/rs.2.16708/v1

Abstract

Background Revascularization is the recommended treatment strategy for patients with heart failure (HF) and coronary artery disease (CAD). However, chronic total occlusion (CTO) is less attempt. Furthermore, there were conflicting debates on if diabetic HF patients gained benefits from revascularization. As to CTO revascularization, no study answered if it offered benefits to diabetic HF patients.

Methods Diabetic patients with stable CTO and HF were consecutively enrolled in this retrospective cohort study. Based on treatment strategies to the CTO vessel, patients were assigned to successful revascularization (CTO-SR) or medical therapy (CTO-MT) group. The primary endpoints were major adverse cardiac events (MACE). Subgroup analysis were performed based on left ventricular ejection fraction (LVEF) and relevant baseline variables.

Results A population of 680 patients were enrolled in the present study: 344 patients in the CTO-MT group, and 336 patients in the CTO-SR group. After a median follow-up of 34 months, CTO-SR was superior to CTO-MT in MACE (adjusted hazard ratio [HR]: 0.462, 95% conference interval [CI]: 0.337-0.634), which could mainly due to the superiority in cardiac-death and TVR. Propensity matching analysis also confirmed CTO-SR's superiority (HR: 0.494 [0.337-0.725]). Subgroup analysis further confirmed a consistent superiority in patients with LVEF≥40%, but not in those with LVEF<40%.

Conclusions For patients with diabetes, HF and stable CTO, CTO-SR was superior to CTO-MT. CTO-SR's superiority was consistent in patients with LVEF≥40%, but not for patients with LVEF<40%. Trial registration This study was not registered in an open access database.

Background

Even though heart failure (HF) occurred only 1-2% [1-3] in western world, the prevalence increased to as high as 12%-27% in diabetic population [4, 5]. Furthermore, for HF patients with diabetes, clinical adverse outcomes occurred more frequently than those without [6, 7]. Some experts thought the worse clinical prognosis might mainly due to the high incidence of coronary artery disease (CAD) in diabetic patients [8, 9]. Such notion is supported by some studies [10-12]. Thus, the comorbidity of CAD, diabetes and HF is common and related to worse clinical prognosis. Treatment strategies were also popularly discussed. The ESC/EACTS guideline [13] recommended coronary revascularization for patients with ischemic heart failure due to positive outcomes obtained from revascularization [14, 15]. However, a sub-analysis of the STICH trial [16], which evaluated the impact of diabetes on patients with ischemic HF who were treated with coronary artery bypass grafting (CABG) or medical therapy (MT), showed that CABG did not exert benefits in diabetic population. We wonder if diabetic HF patients obtain improved clinical outcomes after ischemia was relieved.

On the other hand, revascularization for chronic total occlusion (CTO) is a challenge to both HF patients and doctors. PCI for CTO only accounts for 3.8% of the entire PCI procedure [17]. When taking HF and diabetes into consideration, the attempt of revascularization might further decrease due to the inherited

high-risk features. However, Professor Galassi [18] found that even for CTO patients with LVEF≤35%, CTO-PCI could offer patients LVEF improvement and midterm clinical benefits. Thus, the risk/benefit ratio is favorable for this high-risk procedure. Urgent evidences are needed to answer if diabetic patients with HF need an invasive CTO revascularization procedure. By now, no study directly focused on this.

Thus, we designed the present study which enrolled stable CTO patients with diabetes and HF. We try to answer if successful CTO revascularization (CTO-SR) offered patients clinical benefits when comparing with conservative medicine therapy (CTO-MT).

Methods

Study design and population

Between January 2007 to December 2017, 2502 diabetic patients with one CTO were enrolled in an all-comer, retrospective cohort study. This present study extracted only patients with heart failure. Inclusion criteria were: (1) Only one CTO (American Heart Association segment maps 1, 2, 3, 6, 7, 8,11 and 13) diagnosed by coronary angiography; (2) Patients who had stable clinical presentations of symptomatic stable angina or silent ischaemia; (3) Diabetic patients with heart failure. Exclusion criteria includes: (1) History of CABG; (2) Acute myocardial infarction (MI) due to non-CTO vessel within 1 month. (3) Left main coronary artery disease; (4) History of cancer or other diseases which would confuse the endpoints. Of note, CTO was defined as total occlusion of the native coronary artery (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0) with a duration of at least 3 months. Occlusion duration was calculated from previous angiography or first episode of angina. For those who express no symptoms, we artificially consider them meeting our criteria.

Grouping

CABG, PCI and MT were all alternative treatment methods for CTOs, and the final decision was based on both physician's and patient's choice. Patients were assigned to different groups based on their final treatment strategy to the CTO: successful revascularization (CTO-SR) or medical therapy (CTO-MT). To sum up, CTO-SR included patients with CTO-CABG and successful CTO-PCI. CTO-MT contained patients with failed CTO-PCI, failed CTO-CABG and initial CTO-MT. Successful CTO-PCI was defined as a residual stenosis of <20% and a TIMI flow ≥2 [19] after drug eluting stents implantation. Failed CTO-CABG was defined as grafting to other arteries but not the CTO.

Based on LVEF, patients were subdivided into three groups: subgroup 1: LVEF<40%, subgroup 2: 40%≤LVEF<50% and subgroup 3: LVEF≥50%.

Procedure

Baseline information was extracted from a hospital information system (HIS) by independent investigators who were trained beforehand to ensure consistent. Basic and procedural cine angiograms were all re-reviewed by two experienced interventional physicians using standard definition.

We performed a minimum of 12 months follow-up procedure (around January 2019) by phone call. For patients with records of re-hospitalization in Beijing Anzhen Hospital, interesting information was also extracted from the HIS. We set up an adjudication board (Shuzheng Lyv, Hong Liu, Quanming Zhao, and Fei Yuan) who were blind to patients groups. Certifications of clinical endpoints were based on the board.

For all patients, an optimal medical therapy is recommended. Of note, antiplatelet drugs with aspirin at 100mg/day, and/or clopidogrel at a dose of 75mg/day or ticagrelor at 90 mg twice daily. High dose statin or/and ezetimibe to reduce the level of low-density lipoprotein cholesterol was needed. Other therapies, like antianginal therapy, angiotensin-converting enzyme inhibitor, diuretics, digitalis glycosides, aldosterone receptor antagonist, cardiac resynchronization therapy, et al. were recommended in needed patients.

Definition and endpoints

HF [3] was defined as the presence of dyspnea or equivalent symptoms due to cardiac causes. When gathering the information of heart failure, we extracted the diagnosis, NYHA grade, patients' symptom and LVEF. The certifications of HF were also based on the adjudication board.

The definition of clinical endpoints were following the Academic Research Consortium (ARC) [20] and the third universal definition of MI [21]. The primary clinical endpoint was predefined as major adverse cardiac events which was a composite of cardiac-death, target vessel revascularization (TVR) and repeat nonfatal HF. Cardiac-death was defined as death of cardiac, unwitnessed or unknow cause. TVR was defined as repeat revascularization to the previous CTO vessel. Only those with a record of rehospitalization due to heart failure was considered as repeat heart failure. Other clinical endpoints included all-cause death, repeat revascularization and repeat nonfatal myocardial infarction (MI). all-cause death was defined as death of any cause. Repeat revascularization was defined as revascularization to both previous CTO and non-CTO vessels. Repeat MI was defined as an overall consideration of angina or equivalent symptoms, electrocardiogram variation and changes in myocardial damage biomarkers. We used only repeat nonfatal MI and repeat nonfatal HF as our endpoint.

Diabetes was defined as a previous diagnosis or a new diagnosis (a fasting blood glucose level ≥7.0 mmol/L or a glucose level two hours after a meal of ≥11.1 mmol/L detected on more than 2 occasions) [22].

Statistic analysis

Continuous variables are presented as means±SDs (normal distribution) or medians with interquartile ranges (skewed distribution). Comparisons were calculated by using the Mann-Whitney U test or the Student's *t* test, where appropriate. Categorical items are presented as counts (percentages) and were analysed by using the chi-square test or the Fisher exact text.

For clinical endpoints, the Kaplan-Meier method were used to draw survival curves and comparisons were performed by using the log-rank tests. The unadjusted hazard ratios (HRs) were analysed by using the

univariate Cox proportional hazard regression model. We also performed a multivariate Cox regression. Potential adjusted variables were selected based on both the univariate Cox regression (by evaluating all variables in **Table 1** and applying a threshold of P≤0.1) and the relevant clinical implications. The adjusted hazard ratio (HR) was calculated based on: age, chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), prior MI, hyperuricemia, left ventricular end diastolic diameter (LVEDD), ventricular aneurysm, reginal wall motion abnormality (RWMA), single vessel disease, left anterior descending CTO (LAD-CTO) and Rentrop grade≥2.

A propensity score-matched analysis was also performed. All variables listed in **Table 1** (except for the retrograde approach) was included in the model. A 1:1 matching was performed by applying the nearest-neighbour method (calliper value=0.02). Absolute standardised differences (ASDs) were used to evaluate the effect of matching. ASDs <10.0% showed a relatively good balance. Baseline variables and clinical endpoints after propensity matching were re-compared.

Subgroup analysis was performed based on LVEF in all clinical endpoints.

Another subgroup analysis, including age (<60-years-old/≥60-years-old), sex (male/female), prior MI (yes/no), single-vessel disease (yes/no), Rentrop grade ≥2 (yes/no), syntax score (<22/≥22), RWMA (yes/no) and ventricular aneurysm (yes/no), was performed by using a multivariate Cox regression model based on the same variables described before. Of note, we only performed the subgroup analysis for the primary clinical endpoint: MACE.

Statistical analyses were performed by utilizing SPSS 24.0 (SPSS Inc., Chicago, Illinois, USA) and Stata 14.0 (Stata, College Station, TX, USA). A P-value ≤0.05 was deemed to be statistically significant.

Results

Baseline characteristics

Patients enrollment was shown as **Figure 1.** To reiterate, 680 HF patients were selected from 2502 patients: 344 patients in the CTO-MT group, and 336 patients in the CTO-SR group. Patients treated with CTO-SR were younger, more likely to be male, and had a higher prevalence of smoking, aspirin uptake, LAD-CTO and good collateral circulation (Rentrop grade≥2). While patients treated with CTO-MT had a higher prevalence of Prior PCI, NYHA class Ⅲ, LCX-CTO, nitrites uptake, stain uptake and P2Y12 inhibitor uptake **(Table 1)**.

Procedural complications and in-hospital adverse events

We summarized procedural complications in patients treated with PCI. 11 patients who were treated with failed CTO-PCI (CTO-MT group) suffered coronary artery dissection. There is no contrast extravasation, pericardial effusion and emergency surgery. While for patients treated with successful CTO-PCI (CTO-SR group), five patients suffered contrast retention. There was also no other complications occurred.

In-hospital adverse events (mortality) occurred in five patients. All were treated with CTO-CABG (CTO-SR group). We excluded these five patients when analyzing long-term clinical outcomes.

Long-term clinical outcomes

Follow-up information was successfully obtained from 557 (92.74%) patients. The median follow-up period of the present study was 38 (inter-quartile range [IQR]: 23.00-74.00) months. CTO-SR was superior to CTO-MT in both univariate (hazard ratio [HR]: 0.550, 95% conference interval [CI]: 0.408-0.740) and multivariate (HR: 0.462, 95% CI: 0.337-0.634) analysis. A consistent superiority of CTO-SR was also observed in cardiac-death (adjusted HR: 0.451, 95% CI: 0.275-0.740) and TVR (adjusted HR: 0.433, 95% CI: 0.253-0.742), but not repeat nonfatal HF.

As to other endpoints, CTO-SR was also superior in all-cause death (adjusted HR: 0.551, 95% CI: 0.352-0.863), repeat revascularization (adjusted HR: 0.528, 95% CI: 0.352-0.791) and repeat nonfatal MI (adjusted HR: 0.479, 95% CI: 0.236-0.974) **(Table 2 and Figure 2)**.

Propensity score matched analysis

After matching, 402 patients were matched: 201 patients for each group. ASDs were all less than 10.0% except for hypertension (**See Additional file 1: Figure S1)**, which indicates a relatively low imbalance. Furthermore, all baseline variables showed no significant differences **(See Additional file 1: Table S1)**. As to the clinical endpoints, a consistent superiority of CTO-SR was seen in MACE (HR: 0.495, 95% CI: 0.340-0.720), cardiac-death (HR: 0.444, 95% CI: 0.247-0.799) and all-cause death (HR: 0.536, 95% CI: 0.318-0.903). As to TVR, although a statistic significance was not observed, we still saw a consistent trend ((HR: 0.563, 95% CI: 0.307-1.034) **(Table 3 and Figure 3)**.

Subgroup analysis

To further evaluate the influence of LVEF, we artificially subdivided patients into three subgroups based on LVEF. We found that in subgroup 3, CTO-SR was superior to CTO-MT in MACE (adjusted HR: 0.473, 95% CI: 0.288-0.777), cardiac-death (adjusted HR: 0.324, 95% CI: 0.129-0.811) and all-cause death (adjusted HR: 0.324, 95% CI: 0.129-0.811), which is consistent to the whole population. As to TVR and repeat revascularization, a consistent trend is also observed. In subgroup 2, CTO-SR's superiority is also consistent in MACE (adjusted HR: 0.372, 95% CI: 0.213-0.652), TVR (adjusted HR: 0.072, 95% CI: 0.014-0.374), repeat revascularization (adjusted HR: 0.331, 95% CI: 0.137-0.802), as well as cardiac-death and all-cause death. While in subgroup 1, no statistic difference was found between CTO-SR and CTO-MT, except for repeat nonfatal MI (adjusted HR: 0.047, 95% CI: 0.004-0.579). (**Table 4, Figure 4 and Additional file 1: Table S2**).

Another subgroup analysis showed that the superiority of SR did not differ in all subgroups **(Figure 5).**

Predictors of MACE

Multivariate Cox regression indicates that CTO-SR were protective factors of MACE, while PVD (HR: 2.870, 95% CI: 1,508-5.462) and hyperuricemia (HR: 1.526, 95% CI: 1,097-2.124) were risk factors **(See Additional file 1: Figure S2)**.

Discussion

Main findings

To our knowledge, this is the first study which focused on diabetic CTO patients with heart failure and try to secure which treatment strategy will benefit patients. We observed that: (1) CTO-SR benefits patients with lower risk of MACE than CTO-MT. The benefit was mainly attribute to a lower incidence of TVR and cardiac-death. (2) CTO-SR's superiority was consistent in patients with 40%≤LVEF<50% and LVEF≥50%, But not in those with LVEF<40%. (3) Patients who were treated with CTO-MT were associated with more severe situations: older and poor collateral circulation. However, age, collateral circulation, RWMA or ventricular aneurysm did not influence the superiority of CTO-SR.

CTO-SR was superior to CTO-MT for diabetic patients with HF and CTO.

Previous studies focused on HF patients caused by CAD and demonstrated that coronary revascularization is superior to medical therapy [14, 15]. Thus, the ESC/EACTS guidelines recommended coronary revascularization for such patients. However, in those studies, CTO, which represented a severe coronary situation with a relatively lower revascularization rate [17, 23], was not discussed sufficiently. Both the EURO-CTO [24] and DECISION CTO [25] demonstrated that revascularization did not provide patients survival or other clinical benefits, except for angina relief. However, diabetic patients were characterized by deficiency of angina pectoris, as well as other severe coronary situation (endothelial cell dysfunction, microcirculation disorders) [26-28]. Thus, the question if revascularization for diabetic CTO patients with heart failure was necessary was raised. Professor Galassi and colleagues [18] focused on CTO patients with HF who had viable myocardium. Comparing with failed CTO-PCI, they reported successful CTO-PCI was associated with promising clinical outcomes, as well as LVEF improvements. However, they compared successful CTO-PCI with failed CTO-PCI, and diabetes contains only 30% of enrolled patients. Furthermore, they contained only patients with viable myocardium. Thus, their results could not expand to general diabetic CTO patients with HF. In the present study, we demonstrated that diabetic patients with CTO and HF, successful CTO revascularization could offer patients survival benefits and other clinical benefits, which will surely promote the process of revascularization attempt, regardless of the high-risk feathers.

In the present study, we failed to see a consistent superiority of CTO-SR in patients with LVEF<40%, which is opposite to Professor Galassi [18] and Professor Wolff [15]. We assumed the following possibilities: (1) Sample size enrolled in subgroups of LVEF<40% were small. Even though 30 MACE occurred in CTO-MT versus 13 MACE occurred in CTO-SR, after analysis with Cox regression, no statistical difference was observed. Thus, further study with larger sample size was needed. (2) Detection of viable myocardium. Professor Galassi [18] enrolled only patients with viable myocardium and reported positive outcomes of

successful CTO-PCI. However, in the present study, viable myocardium was not routinely detected. It might be assumed that only patients with viable myocardium can get benefit from revascularization. Yet Professor Wolff and colleagues [15] reported a significant survival improvement for patients with LVEF<40% who were treated with CABG, in spite of myocardium viability. Furthermore, in the present study, we also observed clinical benefits for patients with LVEF≥40%, regardless of myocardium viability. Thus, a reasonable assumption might be for patients with diabetes, CTO and LVEF<40%, detection of myocardium viability was necessary. Further studies were required to confirm this.

On the other hand, our outcomes in the subgroup of LVEF<40% was consistent with STICH trial [16] which showed that CABG did not offer diabetic patients clinical benefits. We thought diabetic status might influenced the results. Diabetes is reported to promote the process of coronary atherosclerosis and associated with poor clinical outcomes [29-31], which surely contributed the poor therapeutic effect of CTO-SR in patients with LVEF<40%.

Is viable myocardium indispensable in diabetic patients with HF and CTO?

The ESC/EACTS guidelines recommended positron emission tomography (PET) may be considered for the evaluation of myocardial viability in HF patients, but with a low recommended level: IIb [13]. Furthermore, the correlation between viable myocardium and revascularization benefits was uncertain [13, 32]. Additionally, the detection value of PET might be limited in diabetic patients due to insulin resistance [33, 34]. Thus, it is unknown which kind of patients could get certain benefits from viability testing. In the present study, we observed both patients with RWMA and aneurysm got benefits from revascularization. However, patients with LVEF<40% failed to gain benefits. Therefore, it is safe to state that viable myocardium should be detected for diabetic CTO patients with lower LVEF.

The effect of collateral circulation on clinical outcomes

In the present study, poor collateral circulation was more common in patients treated with CTO-MT. However, collateral circulation did not influence the superiority of CTO-SR.

Collateral circulation provided blood irrigation for CTO territories. Some argued that for patients with well-developed collaterals, revascularization is dispensable. However, collaterals are not sufficient to provide enough blood supply for CTO territory. Furthermore, coronary steel [35] and lower blood pressure [36] can also decrease the protective influence of collaterals. Thus, revascularization should be performed. In the present study, we demonstrated that even for patients with well-developed collateral circulations, successful revascularization offered patients low incidence of MACE and other clinical benefits, which is consistent to previous studies [37] and offered positive evidence on revascularization attempt.

Limitation

This present study was restricted by the following items: (1), This study was a single-center, retrospective cohort study, though we performed propensity matched analysis and multivariable analysis, we could not balance all potential confounders. (2), We did not detect viable myocardium. (3), in the present study, the

validation of repeat nonfatal MI, repeat nonfatal HF and TVR was difficult. To assure accuracy, only individuals who had records of re-hospitalization in our Hospital or who provided a written proof of diagnosis (by WeChat) were identified as meeting definitions of these endpoints, which surely brought about some bias. (4), We only enrolled diabetic patients with CTO, which indicated that our results could not be expended to the entire CTO population.

Conclusions

In conclusion, for patients with diabetes, HF and stable CTO, CTO-SR was superior to CTO-MT. CTO-SR's superiority was consistent in patients with LVEF≥50%, but not for patients with LVEF<40%.

List Of Abbreviations

PCI: percutaneous transluminal coronary intervention; MT: medical therapy; CABG: coronary artery bypass grafting; PVD: peripheral vascular disease; MI: myocardial infarction; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; BMI: body mass index; CCB: calcium-channel blocker; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin-receptor blocker; CTO: chronic total occlusion; HF: heart failure; RWMA: regional wall motion abnormality; LVEDD: left ventricular end diastolic diameter.

Declarations

Ethics approval and consent to participate

The present study was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (No.:2018008X). Informed consent was waived by the committee due to the retrospective feature of the present study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed for this current study are available from the corresponding author upon reasonable request.

Competing interests

All authors declare that they have no competing interests.

Funding

The present work was supported by the Ministry of Science and Technology of the People's Republic of China, State Science and Technology Support Program (No.2011BAI11B05) and the Beijing Lab for Cardiovascular Precision Medicine, Beijing, China (PXM2019_014226_000023). The project director of all projects was professor Shuzheng Lyu (the corresponding author) and the funds were provided by the government or public institution to support medical research. All these institutions had no effect on the research process.

Authors' contributions

YFY, QMZ and SZL designed and supervised the study. ZM, MDZ, ZLZ, FX, MZ, WW and KZ made contribution to data acquisition. HL, FY, QMZ and SZL made contribution to endpoints adjudication. All authors have read and approved the manuscript.

Acknowledgements

Not applicable.

Reference

1.Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW*, et al: Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. European heart journal.* 2004; *25:*1614–9.

2.Mosterd A, Hoes AW: *Clinical epidemiology of heart failure. Heart (British Cardiac Society).* 2007; *93:*1137–46.

3.Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ*, et al: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European journal of heart failure.* 2016; *18:*891–975.

4.Seferovic PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J*, et al: Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. European journal of heart failure.* 2018; *20:*853–72.

5.Arnold SV, Echouffo-Tcheugui JB, Lam CSP, Inzucchi SE, Tang F, McGuire DK*, et al: Patterns of glucose-lowering medication use in patients with type 2 diabetes and heart failure. Insights from the Diabetes Collaborative Registry (DCR). American heart journal.* 2018; *203:*25–9.

6.Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K*, et al: The association between glucose abnormalities and heart failure in the population-based Reykjavik study. Diabetes care.* 2005; *28:*612–6.

7.MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB*, et al: Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. European heart journal.* 2008; *29:*1377–85.

8.Salisbury AC, Sapontis J, Grantham JA, Qintar M, Gosch KL, Lombardi W*, et al: Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention in Patients With Diabetes: Insights From the OPEN CTO Registry. JACC Cardiovascular interventions.* 2017; *10:*2174–81.

9.Choi KH, Yang JH, Song YB, Hahn JY, Choi JH, Gwon HC*, et al: Long-term clinical outcomes of patients with coronary chronic total occlusion treated with percutaneous coronary intervention versus medical therapy according to presence of diabetes mellitus. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology.* 2017; *13:*970–7.

10.Domanski M, Krause-Steinrauf H, Deedwania P, Follmann D, Ghali JK, Gilbert E*, et al: The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. Journal of the American College of Cardiology.* 2003; *42:*914–22.

11.Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ: *Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. Journal of the American College of Cardiology.* 2001; *38:*421–8.

12.Abdul-Rahim AH, MacIsaac RL, Jhund PS, Petrie MC, Lees KR, McMurray JJ: *Efficacy and safety of digoxin in patients with heart failure and reduced ejection fraction according to diabetes status: An analysis of the Digitalis Investigation Group (DIG) trial. International journal of cardiology.* 2016; *209:*310–6.

13.Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U*, et al: 2018 ESC/EACTS Guidelines on myocardial revascularization. European heart journal.* 2019; *40:*87–165.

14.Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA*, et al: Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. The New England journal of medicine.* 2016; *374:*1511–20.

15.Wolff G, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P*, et al: Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis. Circulation Heart failure.* 2017; *10.*

16.MacDonald MR, She L, Doenst T, Binkley PF, Rouleau JL, Tan RS*, et al: Clinical characteristics and outcomes of patients with and without diabetes in the Surgical Treatment for Ischemic Heart Failure (STICH) trial. European journal of heart failure.* 2015; *17:*725–34.

17.Brilakis ES, Banerjee S, Karmpaliotis D, Lombardi WL, Tsai TT, Shunk KA*, et al: Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). JACC Cardiovascular interventions.* 2015; *8:*245–53.

18.Galassi AR, Boukhris M, Toma A, Elhadj Z, Laroussi L, Gaemperli O*, et al: Percutaneous Coronary Intervention of Chronic Total Occlusions in Patients With Low Left Ventricular Ejection Fraction. JACC Cardiovascular interventions.* 2017; *10:*2158–70.

19.Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A*, et al: Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. Lancet (London, England).* 2011; *378:*1940–8.

20.Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA*, et al: Clinical end points in coronary stent trials: a case for standardized definitions. Circulation.* 2007; *115:*2344–51.

21.Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD*, et al: Third universal definition of myocardial infarction. Journal of the American College of Cardiology.* 2012; *60:*1581–98.

22.Shen Y, Ding FH, Dai Y, Wang XQ, Zhang RY, Lu L*, et al: Reduced coronary collateralization in type 2 diabetic patients with chronic total occlusion. Cardiovascular diabetology.* 2018; *17:*26.

23.Konstantinidis NV, Werner GS, Deftereos S, Di Mario C, Galassi AR, Buettner JH*, et al: Temporal Trends in Chronic Total Occlusion Interventions in Europe. Circulation Cardiovascular interventions.* 2018; *11:*e006229.

24.Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V*, et al: A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. European heart journal.* 2018; *39:*2484–93.

25.Lee SW, Lee PH, Ahn JM, Park DW, Yun SC, Han S*, et al: Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. Circulation.* 2019; *139:*1674–83.

26.Van de Veire NR, Djaberi R, Schuijf JD, Bax JJ: *Non-invasive imaging: Non-invasive assessment of coronary artery disease in diabetes. Heart.* 2010; *96:*560–72.

27.Vedantham S, Kluever AK, Deindl E: *Is there a Chance to Promote Arteriogenesis by DPP4 Inhibitors Even in Type 2 Diabetes? A Critical Review.* 2018; *7.*

28.Guandalini GS, Bangalore S: *The Potential Effects of New Stent Platforms for Coronary Revascularization in Patients With Diabetes. The Canadian journal of cardiology.* 2018; *34:*653–64.

29.Overgaard CB, Dzavik V, Buller CE, Liu L, Banasiak W, Devlin G*, et al: Percutaneous revascularization and long term clinical outcomes of diabetic patients randomized in the Occluded Artery Trial (OAT).*

International journal of cardiology. 2013; *168:*2416–22.

30.Schoenenberger AW, Jamshidi P, Kobza R, Zuber M, Stuck AE, Pfisterer M*, et al: Progression of coronary artery disease during long-term follow-up of the Swiss Interventional Study on Silent Ischemia Type II (SWISSI II). Clinical cardiology.* 2010; *33:*289–95.

31.Jimenez-Quevedo P, Sabate M, Angiolillo DJ, Alfonso F, Hernandez-Antolin R, SanMartin M*, et al: Long-term clinical benefit of sirolimus-eluting stent implantation in diabetic patients with de novo coronary stenoses: long-term results of the DIABETES trial. European heart journal.* 2007; *28:*1946–52.

32.Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P*, et al: Myocardial viability and survival in ischemic left ventricular dysfunction. The New England journal of medicine.* 2011; *364:*1617–25.

33.Sarikaya I, Elgazzar AH, Alfeeli MA, Sharma PN, Sarikaya A: *Status of F–18 fluorodeoxyglucose uptake in normal and hibernating myocardium after glucose and insulin loading. Journal of the Saudi Heart Association.* 2018; *30:*75–85.

34.Valentin RC, Farag A, Hage FG, Bhambhvani P: *Non-diagnostic (18)F-FDG PET myocardial viability studies in type–2 diabetic patients. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology.* 2018.

35.Werner GS, Fritzenwanger M, Prochnau D, Schwarz G, Ferrari M, Aarnoudse W*, et al: Determinants of coronary steal in chronic total coronary occlusions donor artery, collateral, and microvascular resistance. Journal of the American College of Cardiology.* 2006; *48:*51–8.

36.Shen Y, Yang ZK, Hu J, Wang XQ, Dai Y, Zhang S*, et al: Donor artery stenosis interactions with diastolic blood pressure on coronary collateral flow in type 2 diabetic patients with chronic total occlusion. Cardiovascular diabetology.* 2018; *17:*76.

37.Jang WJ, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH*, et al: Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. JACC Cardiovascular interventions.* 2015; *8:*271–9.

Tables

Table 1 Baseline Characteristics (Total Population n=680)			
	CTO-MT (n=344)	CTO-SR (n=336)	P value
Clinical Characteristics			
Age (yrs)	62.58±10.30	60.03±8.84	**0.001**
Male	239(69.5)	269(80.1)	**0.002**
Hypertension	234(68.0)	217(64.6)	0.343
Dyslipidemia	112(32.6)	117(34.8)	0.532
PVD	15(4.4)	12(3.6)	0.598
Prior MI	233(67.7)	245(72.9)	0.139
Prior PCI	79(23.0)	54(16.1)	**0.023**
Prior stoke	33(9.6)	25(7.4)	0.315
CKD	16(4.7)	13(3.9)	0.614
COPD /asthma	6(1.7)	3(0.9)	0.332
Hyperuricemia	81(23.5)	74(22.0)	0.636
Smoking	146(42.4)	172(51.2)	**0.022**
Drinking	42(12.2)	57(17.0)	0.079
BMI (kg/m^2)	26.22±3.41	26.12±2.93	0.696
LVEF (%)	50.00(41.75-62.00)	53.00(45.00-62.00)	0.385
LVEDD (mm)	51.00(48.00-56.00)	51.00(48.00-56.00)	0.535
Ventricular aneurysm	33(9.6)	32(9.5)	0.976
RWMA	172(50.0)	182(54.2)	0.277
NYHA class			
□	141(41.0)	112(33.3)	**0.039**
□	88(25.6)	97(28.9)	0.335
□	97(28.2)	106(31.5)	0.340
□	18(5.2)	21(6.3)	0.568
Medical Treatment			
Aspirin	331(96.2)	329(99.1)	**0.014**
$P2Y_{12}$ inhibitor	310(90.1)	267(80.4)	**0.000**
Statin	332(96.5)	303(91.3)	**0.004**
Nitrites	192(55.8)	103(31.0)	**0.000**
Beta-blocker	268(77.9)	269(81.0)	0.316
CCB	79(23.0)	75(22.6)	0.908
ACEI/ARB	207(60.2)	199(59.9)	0.950
Insulin	130(37.8)	119(35.4)	0.521
Location of CTO			
LAD	95(27.6)	142(42.3)	**0.000**
LCX	121(35.2)	45(13.4)	**0.000**
RCA	128(37.2)	149(44.3)	0.058
Number of Diseased Vessels			
1	70(20.3)	77(22.9)	0.416
2	118(34.3)	129(38.4)	0.267
3	156(45.3)	130(38.7)	0.079
Syntax score#	21.75(18.50-27.00)	23.00(20.00-26.50)	0.443
Rentrop grade≥2#	201(66.3)	256(84.5)	**0.000**
Abrupt stump#	139(45.9)	140(46.2)	0.935
Calcification#	63(20.8)	69(22.8)	0.555
Bending ≥45°#	99(32.7)	118(38.9)	0.107
CTO length≥20mm#	169(55.8)	173(57.1)	0.743
Procedural Characteristics			
Retrograde approach*	8(7.2)	22(12.2)	0.176

Values are n(%), mean±SD or median with interquartile range.

PCI: percutaneous transluminal coronary intervention; MT: medical therapy; CABG: coronary artery bypass grafting; PVD: peripheral vascular disease; MI: myocardial infarction; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; BMI: body mass index; CCB: calcium-channel blocker; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin-receptor blocker; CTO: chronic total occlusion; HF: heart failure; RWMA: regional wall motion abnormality; LVEDD: left ventricular end diastolic diameter.

#Cine angiograms records got from 606 (89.10%) individuals.

*Only those treated with CTO-PCI.

Table 2 HR (95%CI) in All Patients

	CTO-MT	CTO-SR	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
MACE	115(33.4)	70(21.1)	**0.550(0.408-0.740)**	**0.462(0.337-0.634)**
Cardiac-death	50(14.5)	28(8.5)	**0.496(0.312-0.789)**	**0.451(0.275-0.740)**
TVR	38(11.0)	23(6.9)	**0.546(0.325-0.917)**	**0.433(0.253-0.742)**
Repeat nonfatal HF	39(11.3)	28(8.5)	0.663(0.408-1.079)	0.677(0.399-1.150)
All-cause death	58(16.9)	35(10.6)	**0.534(0.351-0.813)**	**0.551(0.352-0.863)**
Repeat nonfatal MI	22(6.4)	15(4.5)	0.559(0.289-1.080)	**0.479(0.236-0.974)**
Repeat revascularization	63(28.3)	44(13.3)	**0.617(0.420-0.909)**	**0.528(0.352-0.791)**

MACE: major adverse cardiac events, a composite of cardiac-death, TVR and repeat nonfatal HF.

Adjusted covariates: age, COPD, PVD, prior MI, hyperuricemia, LVEDD, ventricular aneurysm, RWMA, single vessel disease, LAD-CTO and Rentrop grade≥2.

HR: hazard ratio; CI: conference interval; TVR: target vessel revascularization.

Table 3 HR (95%CI) in Propensity Matched Patients

	CTO-MT	CTO-SR	HR (95% CI)
MACE	76(37.8)	43(21.4)	**0.495(0.340-0.720)**
Cardiac-death	33(16.4)	17(8.5)	**0.444(0.247-0.799)**
TVR	27(13.4)	17(8.5)	0.563(0.307-1.034)
Repeat nonfatal HF	24(11.9)	15(7.5)	0.556(0.291-1.061)
All-cause death	37(18.4)	23(11.4)	**0.536(0.318-0.903)**
Repeat nonfatal MI	11(5.5)	9(4.5)	0.669(0.276-1.619)
Repeat revascularization	38(18.9)	31(15.4)	0.729(0.453-1.174)

MACE: major adverse cardiac events, a composite of cardiac-death, TVR and repeat nonfatal HF.

HR: hazard ratio; CI: conference interval; TVR: target vessel revascularization; other abbreviations as in **Table S1**.

Table 4 HR (95%CI) Based on LVEF (CTO-MT vs CTO-SR)

	LVER≥50%		40%≤LVEF□50%		LVEF□40%	
	Unadjusted HR (95%)	Adjusted HR (95% CI)	Unadjusted HR (95%)	Adjusted HR (95% CI)	Unadjusted HR (95%)	Adjusted HR (95% CI)
MACE	0.649(0.410-1.026)	**0.473(0.288-0.777)**	**0.392(0.237-0.648)**	**0.372(0.213-0.652)**	0.787(0.410-1.511)	0.643(0.297-1.393)
Cardiac-death	**0.357(0.155-0.822)**	**0.324(0.129-0.811)**	0.498(0.243-1.018)	0.476(0.219-1.035)	0.870(0.346-2.187)	0.451(0.156-1.309)
TVR	0.872(0.476-1.600)	0.550(0.287-1.052)	**0.138(0.039-0.487)**	**0.072(0.014-0.374)**	**0.023(0.000-366.05)**	**0.000(0.000-+∞)**
Repeat nonfatal HF	0.634(0.201-2.003)	0.434(0.122-1.541)	0.589(0.279-1.243)	0.579(0.251-1.336)	1.069(0.489-2.338)	1.449(0.543-3.867)
All-cause death	**0.372(0.176-0.786)**	**0.387(0.169-0.885)**	0.550(0.289-1.043)	0.664(0.330-1.336)	0.927(0.388-2.214)	0.532(0.194-1.461)
Repeat nonfatal MI	0.685(0.183-2.565)	0.471(0.110-2.007)	0.809(0.301-2.179)	0.610(0.170-2.188)	0.286(0.062-1.313)	**0.047(0.004-0.579)**
Repeat revascularization	0.809(0.496-1.319)	0.596(0.353-1.006)	**0.442(0.214-0.916)**	**0.331(0.137-0.802)**	0.140(0.018-1.088)	0.190(0.021-1.729)

MACE: major adverse cardiac events, a composite of cardiac-death, TVR and repeat nonfatal HF.

Adjusted covariates: age, COPD, PVD, prior MI, hyperuricemia, LVEDD, ventricular aneurysm, RWMA, single vessel disease, LAD-CTO and Rentrop grade≥2.

HR: hazard ratio; CI: conference interval; TVR: target vessel revascularization.

Figures

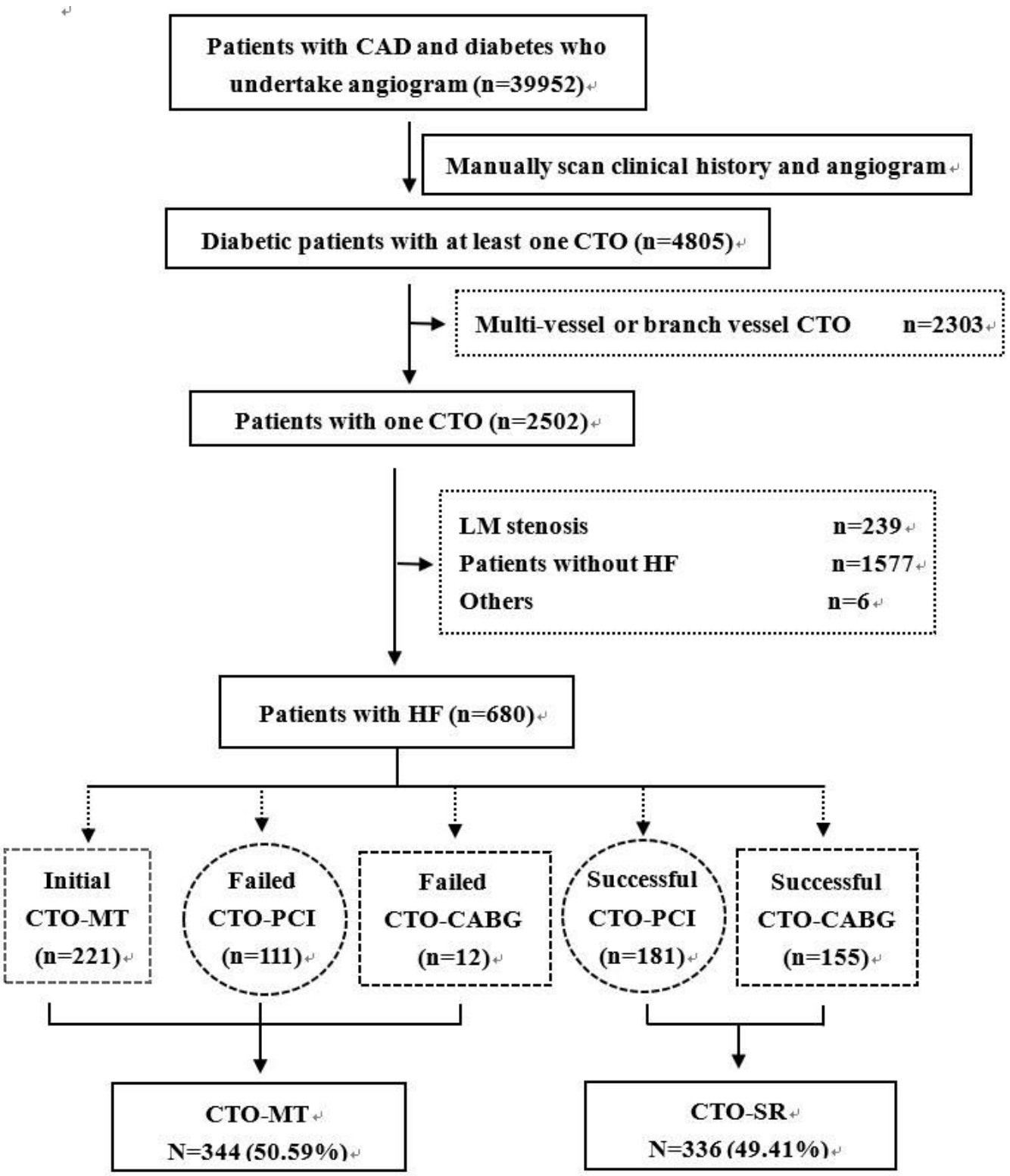

Figure 1

Flow Chart of The Present Study

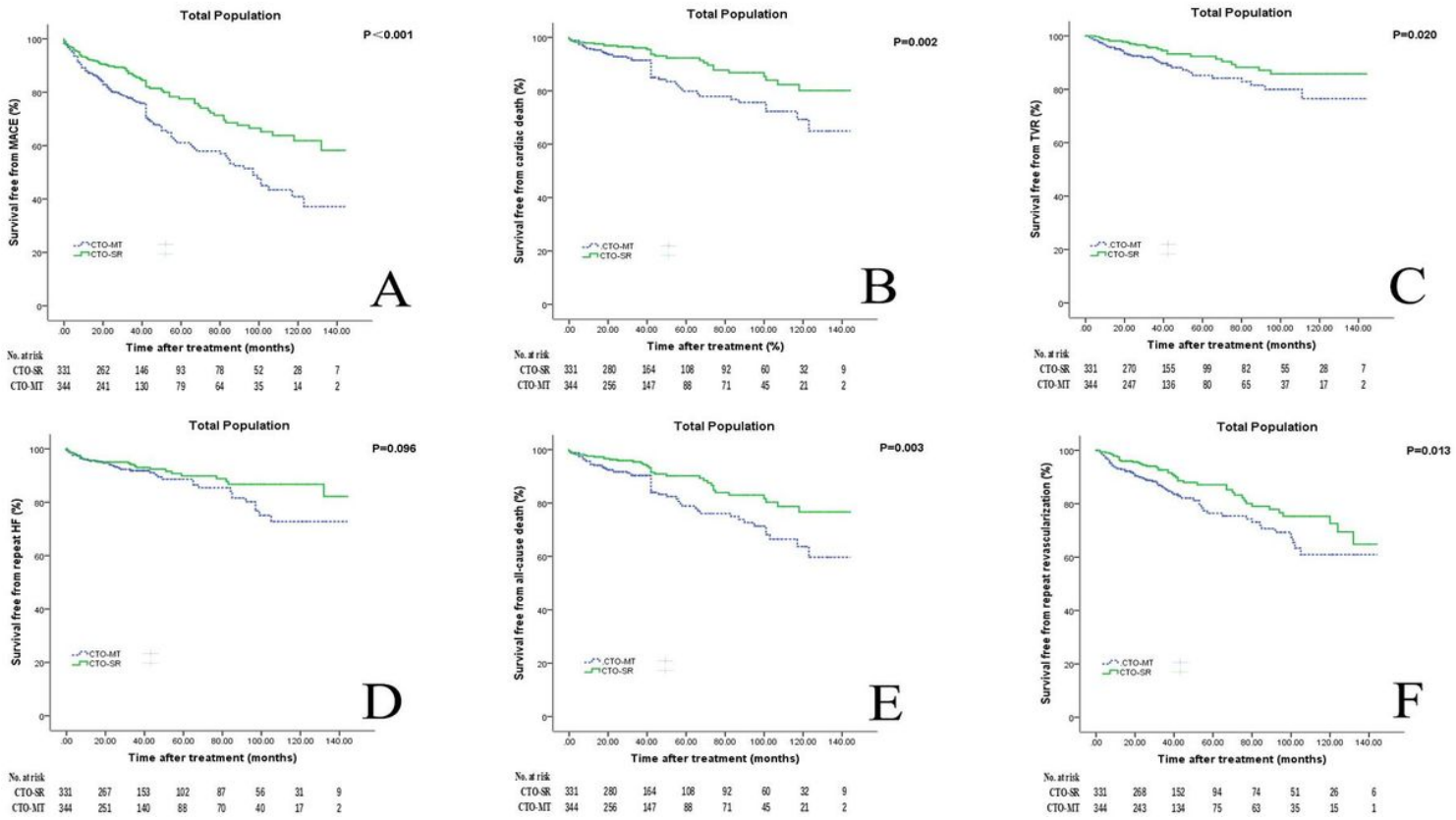

Figure 2

Kaplan-Meier Curves for Clinical Endpoints in All Patients (A), Kaplan-Meier Curves for major adverse cardiac events in patients treated with successful revascularization versus medical therapy; (B), Cardiac-death; (C), Target vessel revascularization; (D), Repeat nonfatal heart failure; (E), All-cause death; (F) Repeat revascularization.

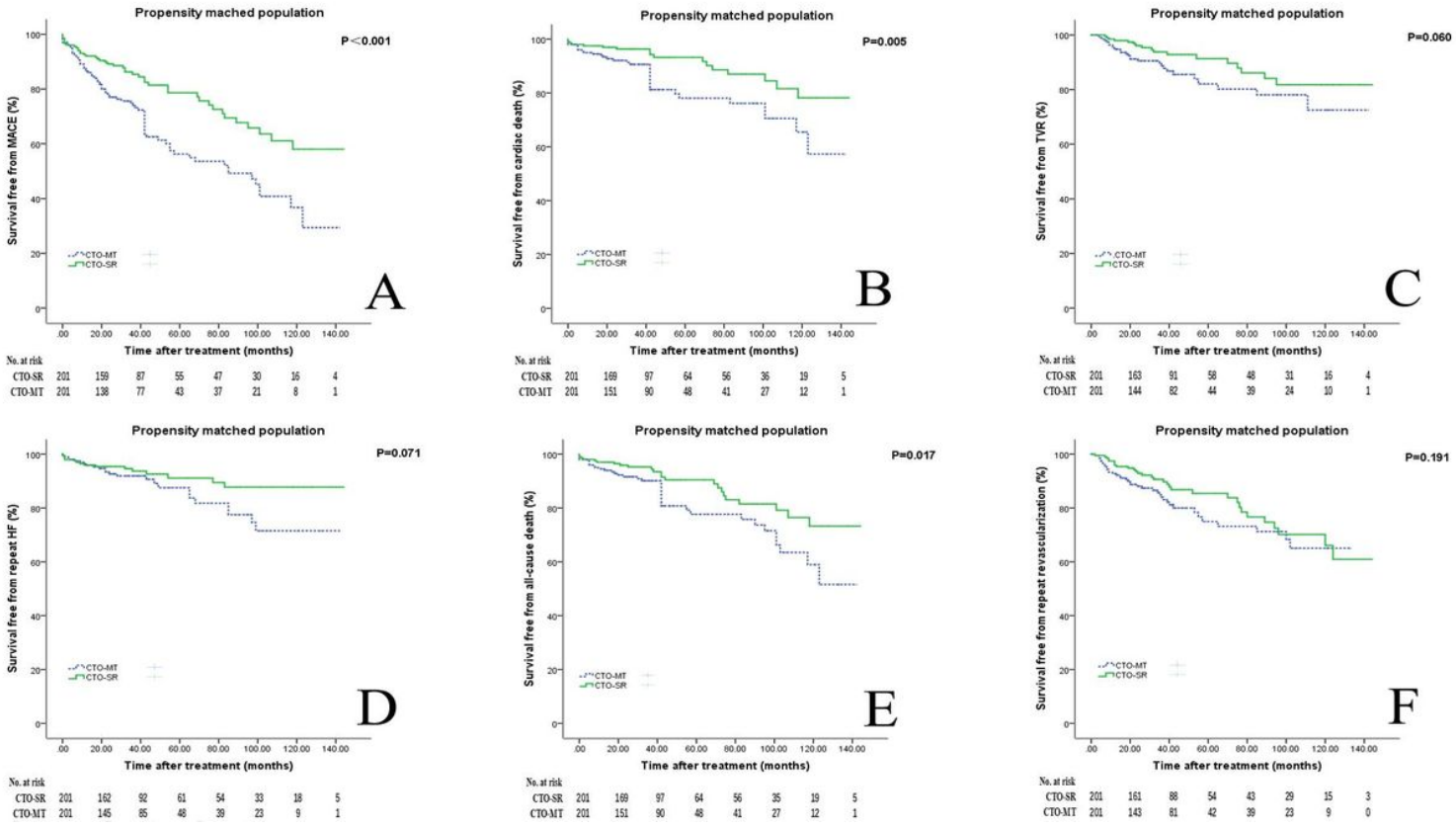

Figure 3

Kaplan-Meier Curves in Propensity-Matched Population (A), Kaplan-Meier Curves for major adverse cardiac events in patients treated with successful revascularization versus medical therapy; (B), Cardiac-death; (C), Target vessel revascularization; (D), Repeat nonfatal heart failure; (E), All-cause death; (F) Repeat revascularization.

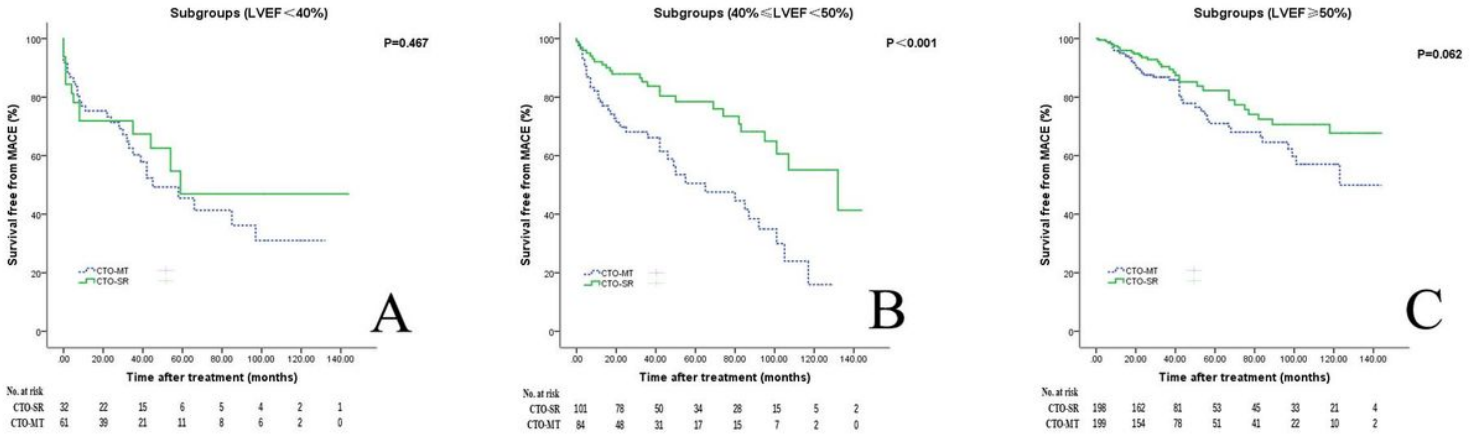

Figure 4

Kaplan-Meier Curves for major adverse cardiac events (MACE) based on LVEF (A), Kaplan-Meier Curves for MACE in patients with LVEF□40% who were treated with CTO-MT versus CTO-SR; (B), Patients with 40%≤LVEF□50%; (C), Patients with LVEF≥50%.

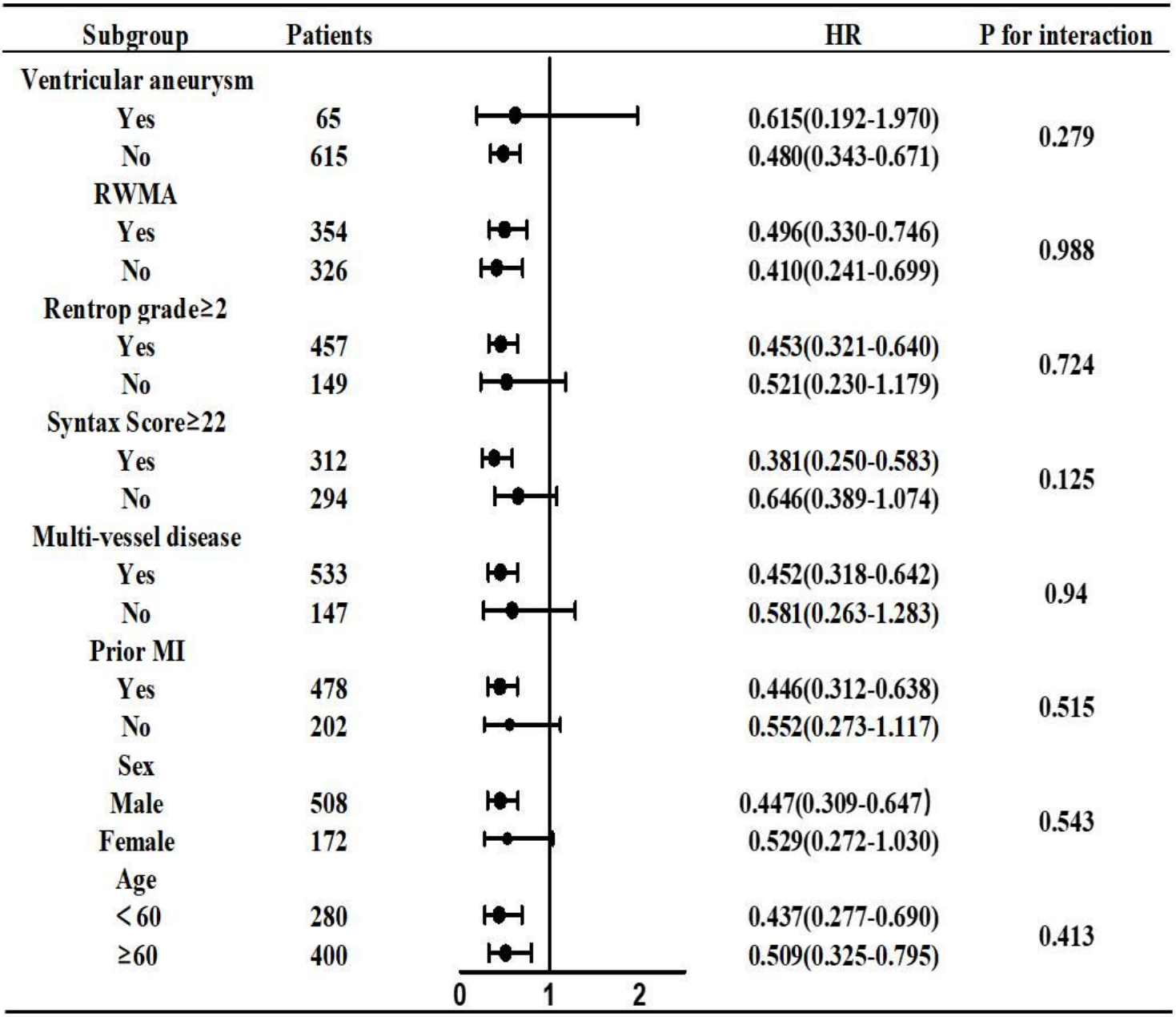

Figure 5

Subgroup Analysis for major adverse cardiac events (MACE)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx