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Biomarker Levels and Benefits of Chronic Total Occlusion Revascularization

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Cardiology

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Abstract

Biomarker Levels and Benefits of Chronic Total Occlusion Revascularization
By Daniel Gold

Background

The survival benefit of revascularization of chronic total occlusion (CTO) of the coronary arteries remains a subject of controversy. We measured high sensitivity troponin-I (hsTn-I) levels and N terminal pro-brain natriuretic peptide (NT pro-BNP) levels in patients with stable coronary artery disease, with the hypothesis that (1) patients with CTO have higher levels of biomarkers than patients without CTO, (2) biomarker levels will predict adverse cardiovascular events in patients with CTO, and (3) patients with elevated biomarker levels will have a survival benefit from CTO revascularization.

Methods

In 428 patients with stable coronary artery disease and CTO undergoing coronary angiography, adverse event rates were investigated. Cox proportional hazards models and Fine and Gray subdistribution hazard models were performed to determine the association between biomarker level and incident event rates in patients with CTO.

Results

HsTn-I levels were higher in patients with compared with those without CTO (median 6.7 versus 5.6 ng/L, P=0.002). NT pro-BNP levels were higher in patients with, compared to those without CTO (median 230.0 vs. 177.7 pg/mL, $p \leq 0.001$). Every doubling of hsTn-I level was associated with a 19% higher adverse event rate and every doubling of NT pro-BNP level was associated with a 25% higher adverse events rate. CTO revascularization was performed in 28.3% of patients. In patients with a high (>median) hsTn-I level, CTO revascularization was associated with substantially lower all-cause mortality (adjusted hazard ratio, 0.26 [95% CI, 0.08–0.88]; P=0.030) compared with those who did not undergo revascularization. In patients with elevated NT pro-BNP levels (> 125 pg/mL), those who underwent CTO revascularization had substantially lower adverse event rates compared to patients without CTO revascularization (adjusted cardiovascular death hazard ratio 0.29, 95% confidence interval (0.09–0.88). In patients with a low biomarker levels, event rates were similar in those with and without CTO revascularization.

Conclusions

Biomarker levels may help identify individuals who benefit from CTO revascularization.

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Introduction

Chronic total occlusion (CTO) of a coronary artery is encountered in 15-30% of patients undergoing diagnostic coronary angiography[1, 2] and is associated with higher mortality than patients with obstructive coronary artery disease (CAD) without a CTO.[3] Although CTO revascularization can improve angina and quality of life, there is lack of data regarding its mortality benefit.[4-6] The American College of Cardiology/American Heart Association percutaneous coronary intervention (PCI) guidelines provide a Class IIb/Level of Evidence B recommendation for PCI for CTOs in patients with refractory angina after performing PCI of non-CTO lesions.[7] Thus, despite its high risk, PCI is attempted in <10% and coronary artery bypass graft (CABG) surgery in <25% of individuals with CTO.[1, 2] Whether specific populations of patients with CTO experience a survival benefit from CTO revascularization remains unknown.

The circulating level of high sensitivity troponin-I (hsTn-I), a biomarker of myocardial ischemia or injury, can be elevated in the absence of an acute coronary syndrome.[8-16] Higher circulating levels of hsTn-I predict incident adverse cardiovascular events and mortality in patients with and without CAD.[17-21] N terminal pro-brain natriuretic peptide (NT Pro-BNP), a hormone secreted by cardiomyocytes in response to cardiac stretch and increased wall stress,[22] can be elevated in the absence of obvious volume overload or left ventricular dysfunction.[23] NT pro-BNP level has also been associated with a higher risk of adverse cardiac events in patients with CAD with and without heart failure.[24-27]

In patients with CTO, those with poorly developed collaterals have a higher level of hsTn-I and NT pro-BNP than those with well-developed collaterals.[28] HsTn-I and NT pro-BNP

levels in patients with CTO compared to patients without CTO have yet to be investigated. Whether these biomarker levels predict adverse outcomes in patients with CTO, and whether those with an elevated level benefit from CTO revascularization remains unknown. In this study of patients with stable CAD and CTO with long-term follow-up, we determined whether (i) these biomarker levels are higher in patients with significant CAD with, compared to those without CTO; (ii) biomarker levels predict incident adverse events in patients with CTO; and (iii) patients with elevated biomarker levels have a survival benefit from revascularization of the CTO. We hypothesized that patients with CTO will have higher levels of hsTn-I and NT pro-BNP than patients without CTO, and higher levels will predict adverse cardiovascular events and survival benefit from revascularization in patients with CTO.

Methods

Patients: We studied participants enrolled in the Emory Cardiovascular Biobank (NCT00378924), a prospective cohort of patients referred for clinically indicated cardiac catheterization at three Emory healthcare sites in Atlanta, GA between May 2004 and March 2018.[29] Exclusion criteria included (1) acute coronary syndrome at presentation, (2) history of cardiac transplantation, and (3) history of CABG. For the outcome analysis, patients without a CTO were excluded.

A CTO was defined as 100% luminal diameter stenosis on angiography with absence of antegrade flow, of known or assumed 3 months duration.[30] Significant CAD was defined as CAD $\geq$ 50% in any major coronary artery. Three-vessel or left main disease was defined as patients with significant CAD in the left anterior descending artery, right coronary artery and left

circumflex artery or in the left main artery.[30] Demographic and clinical data were obtained from medical records and questionnaires and included age, sex, race, body mass index, hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or treatment with anti-hypertensive medications), diabetes mellitus (HbA_{1c}>6.5 or treatment with insulin or oral anti-diabetic medications), dyslipidemia (total cholesterol ≥ 200 mg/dL, low-density lipoprotein > 130 mg/dL, high-density lipoprotein <40 mg/dL or treatment with lipid-lowering medications), left ventricular ejection fraction (LVEF) (defined by most recent transthoracic echocardiography or ventriculography), estimated glomerular filtration rate (eGFR), history of myocardial infarction (MI), smoking, chronic kidney disease, heart failure (HF), use of beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), or statins as previously described.[29] The study was approved by the Emory University Institutional Review Board. All subjects provided written informed consent.

Revascularization: Patients were revascularized as clinically indicated. Revascularization of the CTO was defined as PCI that decreased the stenosis grade by at least 50% and restored Thrombolysis in Myocardial Infarction grade 2 or 3 flow, or CABG that bypassed the CTO lesion within 90 days of enrollment. The non-revascularization group included those who had revascularization of the non-CTO lesions only, or were medically managed without any revascularization.

HsTn-I Assay: Blood samples were collected on the same day as cardiac catheterization, before the procedure, and were stored at −80°C. Measurements were performed using the Architect

analyzer (Abbott Laboratories North Chicago, IL), with a detection limit of 1.2ng/L and an interassay coefficient of variation of <10% at 4.7 ng/L.

NT pro-BNP Assay: Blood samples were collected on the day of catheterization, before the procedure. Samples were stored at −80°C. Plasma NT pro-BNP was measured using NT pro-BNP assay for ARCHITECT (Abbott Diagnostics, Chicago, IL). An NT-pro BNP level of 125 pg/mL was used as a cut-off for elevation based on European Society of Cardiology guidelines.[31]

Follow-Up: Follow-up was conducted for determination of all-cause mortality, cardiovascular death, MI, and HF hospitalization. Follow-up data were collected by personnel blinded to the clinical and biomarker data through chart review, telephone interview, and query of the Social Security Death Index and state records as previously described.[29] Determination of the cause of death was performed by two independent cardiologists, both blinded to the biomarker and clinical data. Cardiovascular death was defined as death attributable to an ischemic cardiovascular cause (ie, fatal MI, stroke or peripheral arterial disease) or sudden death due to an unknown or presumed cardiovascular cause in high-risk patients. Medical records were accessed to validate all self-reported events.

Statistical Analysis: Patient characteristics were summarized using frequency counts, percentages, medians and interquartile ranges as appropriate. Baseline differences between patients, with and without CTO, between patients with CTO and NT pro-BNP levels above and

below 125 pg/mL, hsTn-I levels above and below median and between patients with and without CTO revascularization, were assessed using the chi-squared test for categorical variables and Mann-Whitney U tests for continuous variables.

Outcomes analyses were performed in patients with CTO only. Incident event rates were evaluated based on biomarker levels as a continuous variable, by $\log_2$ transformation (to show the hazard rate ratio for every doubling of biomarker level) and as a binary variable stratified by hsTn-I median (6.7 pg/mL) and a NT pro-BNP level of 125 pg/mL to evaluate cumulative incidence. Cumulative incidence function was used to visualize the differences in survival outcomes across groups coupled with log-rank tests. Incident event rates in patients with and without revascularization of CTO were examined and stratified by hsTn-I median (6.7 pg/mL) and a NT pro-BNP level of 125 pg/mL. Cox proportional hazards models were used to examine the association between groups and time to all-cause death and a composite of all-cause death, MI or HF hospitalization (for hsTn-I). Fine and Gray sub-distribution hazard models[32] were performed for time to cardiovascular death and a composite outcome of major adverse cardiovascular events, (cardiovascular death, MI and HF hospitalizations) (for NT pro-BNP), with non-cardiovascular deaths treated as competing risk events. Model 1 of the analyses was adjusted for age, sex, race (Blacks vs. non-Blacks), body mass index, hypertension, diabetes, dyslipidemia, LVEF, eGFR, history of smoking, history of MI. Model 2 of the analyses included the aforementioned covariates plus disease severity, and non-CTO revascularization. All collected measures had less than 5% missing data. No covariate of interest was missing and therefore there were no sensitivity analyses conducted. All analyses were performed using SPSS software, Stata/BE 17.0. P-values < 0.05 were considered statistically significant.

Results

HsTn-I

Baseline characteristics of the 1912 enrolled patients with hsTn-I data available, 430 with, and 1482 without CTO are shown in **Supplemental Table 1**. The unadjusted median hsTn-I level in patients without CTOs was lower compared to those with CTOs, (median 5.6 vs. 6.7 ng/L, p=0.002).

HsTn-I levels and incident outcomes in patients with a CTO: In the 428 patients with available outcome data, those with higher hsTn-I levels (> median of 6.7 ng/L) were older, more likely to be Black, have lower eGFR, lower LVEF, and a history of MI and HF when compared to those with lower hsTn-I levels (≤ median), **Table 1**. Disease severity was similar between the two groups.

During 3-year follow-up, 14.2% of the patients with CTO had deaths from all causes, 9.3% had cardiovascular death, 7.2% had a MI, and 8.3% were hospitalized with HF exacerbations, **Table 1**. A higher hsTn-I level was associated with a greater risk of all-cause and cardiovascular death and the composite outcome of all-cause death, MI and HF hospitalizations in unadjusted analyses, **Table 2**. In models adjusted for age, sex, race, BMI, smoking history, hypertension, diabetes, dyslipidemia, MI history, eGFR, LVEF, use of ACEi/ARBs, beta-blockers, statins, these differences remained significant, **Table 2.** When compared to patients with a hsTn-I level ≤ median, those with elevated hsTn-I (>median) values had a 5.8-fold higher adjusted rate of cardiovascular mortality, a 5-fold higher adjusted rate of all-cause mortality and

3.8-fold higher adjusted rate of the composite event rate (all-cause mortality, MI, HF hospitalization), all p<0.001, **Figure 1**.

Revascularization and outcomes: Of the total cohort of 428 patients, 121 (28.3%) underwent CTO revascularization (91 with PCI and 30 with CABG), 93 (21.7%) patients received non-CTO revascularization only and 214 (50.0%) patients were medically managed. Patients who received CTO revascularization were younger, more likely to be male, and less likely to have chronic kidney disease or a history of MI compared to patients that did not receive CTO revascularization. HsTn-I levels were similar between the two groups, **Supplemental Table 2**. The proportion of patients with CTO revascularization between the >median and ≤ median hsTn-I groups were similar, **Supplemental Table 3**. During follow up, the unadjusted event rates were significantly higher in the group without, compared to those with CTO revascularization, **Table 3.** After further adjustment for age, sex, race, BMI, smoking history, hypertension, diabetes, dyslipidemia, MI history, eGFR, LVEF, use of ACEi/ARBs, beta-blockers, statins, cardiovascular death remained significant.

HsTn-I levels and outcomes with revascularization: The outcomes of CTO revascularization were further explored based on hsTn-I levels. In patients with elevated hsTn-I (> median) levels, the rates of all-cause mortality, cardiovascular death, and the composite end point were all significantly lower by more than 50% in patients who underwent CTO revascularization, compared to those who did not receive CTO revascularization, a difference that persisted even after adjustment for the aforementioned covariates (all-cause mortality hazard ratio 0.26, 95% confidence interval 0.08 – 0.88 p = 0.030). In contrast, in patients with low hsTnI (≤ median) levels, adverse event rates were similar in those with or without CTO revascularization, even

after adjustment, **Table 3, Figure 2, Supplemental Table 3**. The adjusted interaction term between hsTn-I levels (above/below median) and CTO revascularization on the composite outcome trended to be significant, p = 0.086.

NT pro-BNP

Baseline characteristics of the 1773 enrolled patients with NT pro-BNP data available, 392 with, and 1381 without CTO are shown in **Supplemental Table 4**. NT pro-BNP levels in patients with CTOs were higher compared to those without CTOs, (median 230.0 vs. 177.7 pg/mL, p<0.001).

NT pro-BNP levels and incident outcomes in patients with a CTO: There were 3 patients with CTO that were lost to follow-up. In the 389 patients with CTO and available outcome data, those with higher NT pro-BNP levels (> 125 pg/mL) were older, more likely to be male, have lower body mass index, eGFR, LVEF, have greater disease severity, and a have a history of MI and HF when compared to those with lower NT pro-BNP levels (≤ 125 pg/mL), **Table 4**.

During a median follow-up time of 5.4 years, interquartile range (3.6 – 7.0), there were 123 (31.6%) deaths from all causes, 69 (17.7%) cardiovascular deaths, 48 (12.3%) MIs, and 56 (14.4%) hospitalizations with HF exacerbations, **Table 4**. Each 100% increase in NT pro-BNP level was associated with > 25% risk of incident adverse events, even after adjustment for age, sex, race, body mass index, smoking history, hypertension, diabetes, dyslipidemia, MI history, eGFR, LVEF, disease severity, and any revascularization at enrollment, **Table 5**. Similarly, compared to patients with a NT pro-BNP level ≤ 125 pg/mL, those with elevated NT pro-BNP (>

125 pg/mL) levels had a > 3-fold higher rate all-cause mortality, cardiovascular death and the composite event (all-cause mortality, MI, HF hospitalization), all p<0.001, **Figure 3**.

Revascularization and outcomes: Of the total cohort of 389 patients with CTO, 111 (28.5%) underwent CTO revascularization (82 with PCI and 29 with CABG), 84 (21.6%) patients received non-CTO revascularization only and 194 (49.9%) patients were medically managed. Patients who received CTO revascularization were younger, more likely to be male, have angina and were less likely to have chronic kidney disease or a history of MI than patients that did not receive CTO revascularization, **Supplemental Table 5**. NT pro-BNP levels were higher in the non-revascularized group. During follow up, the unadjusted and adjusted event rates were significantly lower in the group with, compared to those without CTO revascularization, and remained significant after adjusting for age, sex, race, body mass index, smoking history, hypertension, diabetes, dyslipidemia, MI history, eGFR, LVEF, disease severity, and non-CTO revascularization **Table 6.**

NT pro-BNP levels and outcomes with revascularization: The outcomes of CTO revascularization were further investigated based on baseline NT pro-BNP levels. A higher proportion of patients with an NT pro-BNP $\leq$ 125 pg/mL were revascularized compared to patients with an NT pro-BNP level > 125 pg/mL **Supplemental Table 6**.

The interaction terms between NT pro-BNP level (above/below 125 pg/mL) and CTO revascularization on all-cause mortality and cardiovascular death were nearly significant (p = 0.055, p = 0.044, respectively). Thus, in patients with an elevated NT pro-BNP (> 125 pg/mL) level, both the unadjusted and adjusted rates of all-cause mortality, cardiovascular death, and the composite end point were all significantly lower by more than 50% in patients who underwent

revascularization, compared to those who did not receive CTO revascularization (adjusted cardiovascular death hazard ratio 0.24, 95% confidence interval 0.07 – 0.81). In contrast, in patients with a low baseline NT pro-BNP (≤ 125 pg/mL) levels, the unadjusted and adjusted adverse event rates were similar in those with or without CTO revascularization **Table 6, Figure 4, Supplemental Table 6**.

HsTn-I and NT pro-BNP Together

A biomarker score was determined by number of biomarkers elevated. In those with both biomarkers elevated, CTO revascularization was dramatically associated with 3-year decreased all-cause mortality rate [adjusted HR 0.25 95% CI 0.08 – 0.65], **Table 7, Figure 5**. Those with no biomarkers did not have an associated mortality benefit with CTO revascularization.

Discussion

We had several novel findings with our study: Patients with CTO have higher hsTn-I and NT pro-BNP levels than those without a CTO. A higher hsTn-I and NT pro-BNP level was an independent predictor of adverse outcomes in patients with CTO, similar to findings in other individuals with CAD.[24-27] Most importantly, revascularization of the CTO was associated with a dramatic improvement in survival in those with an elevated hsTn-I and NT pro-BNP levels, but not in those with a low biomarker levels. The decision to revascularize a CTO is currently reserved for those with significant symptoms, and presence of ischemia on non-invasive testing.[33] Our findings suggest that the baseline biomarker levels can assist in identifying individuals who are at high risk and may obtain a survival benefit most from revascularization,

which can help inform future trials investigating the effect of CTO revascularization on outcomes.

HsTn-I levels in patients with CTO: In addition to myocardial cell death, reversible ischemia and increased metabolic demand leads to cleavage and release of troponin and its degradation products into in the circulation,[11-16] resulting in higher circulating hsTn levels. Inducible myocardial ischemia has been reported to be greater in the presence of CTO compared to those with obstructed CAD without CTO.[5] One novel finding from our study includes the presence of higher hsTn-I levels in patients with CTO compared to patients without CTO, likely due to greater ischemia in these patients.

Higher circulating levels of hsTn-I predict incident adverse cardiovascular events and mortality in patients with CAD[17-21, 28, 34, 35] as well as elderly individuals.[36] Herein, we demonstrate the independent prognostic value of hsTn-I levels in predicting incident adverse events in patients with a CTO, a population with greater ischemia and overall higher hsTn-I levels, indicating that among this population, patients with greater ischemia are at higher risk of adverse events and vice versa.

NT pro-BNP levels in patients with CTO: Ischemia can lead to myocardial stunning, fibrosis and impairment of left ventricular contractility that can contribute to HF in this population.[37],[38] These alterations increase NT pro-BNP production and release by cardiomyocytes in response.[22] We demonstrate the value of elevated NT pro-BNP levels in predicting incident adverse events in patients with a CTO, a population that is at higher risk than patients with CAD without CTO.[3] Although NT pro-BNP is a known marker of HF severity,[39] higher circulating levels of NT pro-BNP predict incident adverse cardiovascular events and mortality in the general

population[40] and in patients with CAD with and without HF.[24-27] This may be because elevated NT pro-BNP levels are also associated with multiple cardiac pathologies including silent ischemia, inflammation, left ventricular hypertrophy, left atrial dilatation as well as left ventricular systolic dysfunction.[41, 42]

Biomarkers and CTO Revascularization: Patients with CTO and poorly developed collaterals have higher levels of biomarkers than those with well-developed collaterals.[28] We demonstrate that CTO revascularization is associated with improved outcomes in patients with a high biomarker levels, whereas those with a low level of biomarkers, likely had a well-developed collateral circulation, and less change in ischemia, cardiac stretch and thus biomarker levels as a result of CTO revascularization. Although we did not have post-revascularization biomarker measurements in this study, a prior study showed that revascularization in patients with stable CAD decreased biomarkers, independent of left ventricular systolic function, suggesting that lowering of biomarker level after CTO revascularization may be contributing to the mortality benefit in these patients.[43]

Revascularization of CTOs has been shown to improve ischemia on myocardial perfusion imaging.[4, 44-49] Moreover, those with the greatest ischemic burden appear to have the greatest reduction in ischemia after revascularization of the CTO on myocardial perfusion imaging.[50] Importantly, patients undergoing revascularization that had the greatest reduction in ischemia measured by positron emission tomography, had better event-free survival compared to those with less reduction of ischemia.[51] Together, these studies suggest that the decrease in the ischemic burden by revascularization may be driving improved outcomes in patients with CTOs.

Whether there is a survival benefit of CTO revascularization remains unclear. Meta-analyses and observational studies demonstrate reduction in mortality with CTO revascularization,[52-57] but the randomized controlled trial Drug-Eluting Stent Implantation versus Optimal Medical Treatment in Patients with Chronic Total Occlusion (Decision-CTO) found no difference in outcomes with CTO revascularization.[58] This trial, however, was limited by a high cross-over rate and was not powered to assess mortality benefit. Importantly, this trial did not stratify patients by NT pro-BNP level. Additionally, the EURO CTO trial found that there was no difference in major adverse events in patients that undergo CTO PCI compared to medical management alone.[5] This trial, however, was limited by slow patient recruitment and very low event rates, likely due to selection bias of excluding patients with severe symptoms. Most importantly, these trials did not investigate the association of a survival benefit with biomarker levels. Our data, after adjustment for clinical covariates, showed that CTO revascularization was associated with a substantial survival benefit in the subset of patients with high, but not in those with low biomarker levels.

Strengths/Limitations

Strengths of our study include enrollment of a diverse population including women and Black participants with a wide range of LVEF and availability of adjudicated event rates during long-term follow-up. Biomarker measurements were performed at one time to minimize variability. Limitations include a lack of post-revascularization biomarker levels, and thus an assessment of the link between outcomes and the *change* in levels. Additionally, revascularization was performed for clinical reasons and was not randomized. To address differences in the clinical characteristics among patients who did and did not undergo

revascularization, we adjusted for differences in the clinical variables in all our analyses and found that the benefit of revascularization persisted. Nevertheless, our findings demonstrating the value of biomarker levels in identifying a subset of patients with CTO who benefit from revascularization need to be replicated in a randomized trial.

Conclusions

Patients with CTO have higher biomarker levels than those without CTO. In patients with CTO, the elevation of biomarker levels is associated with dramatically higher adverse event rates. Patients with a higher, but not lower biomarker levels experienced a survival benefit from CTO revascularization. Thus, the biomarker levels can identify individuals who may benefit from revascularization of CTOs.

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Supplemental Table 1: Baseline Characteristics of Patients with and without CTO

Variable	**No CTO**	**CTO**	***P* Value**
N	*1482*	*430*	
HsTn-I (pg/mL) (IQR)	5.60 (3.2, 13.5)	6.70 (3.7, 15.0)	**0.002**
Age (IQR)	65.5 (57.7, 73.5)	65.2 (56.9, 71.7)	0.19
Sex: Male	981 (66.3%)	315 (73.3%)	**0.007**
Race: Black	266 (17.9%)	76 (17.7%)	0.90
BMI (IQR)	28.9 (25.7, 32.3)	28.9 (25.5, 33.0)	0.50
History of smoking	976 (65.9%)	298 (69.3%)	0.18
Hypertension	1230 (83.3%)	366 (85.1%)	0.36
Diabetes	562 (38.0%)	156 (36.3%)	0.52
Dyslipidemia	1143 (77.4%)	342 (79.5%)	0.34
Chronic kidney disease	192 (13.0%)	53 (12.3%)	0.73
History of MI	314 (21.3%)	149 (34.8%)	**<0.001**
History of HF	397 (26.8%)	130 (30.2%)	0.16
eGFR (mL/min/1.73m^2) (IQR)	72.7 (56.8, 88.9)	74.5 (58.6, 90.0)	0.23
LVEF (%) (IQR)	60 (50.0, 60.0)	55 (45.0, 60.0)	**<0.001**
Disease Severity			
1 Vessel	835 (56.3%)	151 (35.1%)	**<0.001**
2 Vessel	442 (29.8%)	151 (35.1%)	
3 Vessel	205 (13.8%)	128 (29.8%)	
Medications			
ACEi/ARB	919 (62.0%)	269 (62.6%)	0.84
Beta-blocker	1063 (71.7%)	317 (73.7%)	0.42
Statin	1174 (79.2%)	361 (84.0%)	**0.03**

Values are median (IQR) or n (%). The no CTO group included patients with obstructive CAD $\geq$ 50% in a major coronary artery.

CTO = chronic total occlusion; HsTn-I = high sensitivity troponin-I; BMI = body mass index; MI = myocardial infarction; HF = heart failure; IQR = interquartile range; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker.

Table 1: Characteristics of Patients with CTO Stratified by Median HsTn-I Level

Variable	HsTn-I > 6.7 ng/L (N=212)	HsTn-I ≤ 6.7 ng/L (N=216)	*P* Value
HsTn-I (ng/L)	15.0 (9.2, 30.1)	3.7 (2.8, 5.0)	**<0.001**
Age	66.0 (58.8, 74.5)	63.0 (55.3, 70.0)	**0.004**
Sex: Male	157 (74.1%)	157 (72.7%)	0.75
Race: Black	50 (23.6%)	26 (12.0%)	**0.002**
BMI	28.7 (25.5, 32.8)	29.1 (25.5, 32.7)	0.88
History of smoking	145 (68.4%)	151 (69.9%)	0.74
Hypertension	186 (87.7%)	178 (82.4%)	0.12
Diabetes	83 (39.2%)	72 (33.3%)	0.21
Dyslipidemia	166 (78.3%)	174 (80.6%)	0.56
Chronic kidney disease	34 (16.0%)	18 (8.3%)	**0.015**
History of MI	88 (41.7%)	61 (28.4%)	**0.004**
History of HF	91 (42.9%)	38 (17.6%)	**<0.001**
eGFR (mL/min/1.73m^2)	68.9 (52.2, 83.0)	80.1 (63.9, 93.8)	**<0.001**
LVEF (%)	50.0 (40.0, 55.0)	55.0 (50.0, 60.0)	**<0.001**
Disease Severity			
1 Vessel	64 (30.2%)	86 (39.8%)	0.11
2 Vessel	81 (38.2%)	70 (32.4%)	
3 Vessel	67 (31.6%)	60 (27.8%)	
Medications			
ACEi/ARB	137 (64.6%)	131 (60.6%)	0.40
Beta-blocker	164 (77.4%)	152 (70.4%)	0.10
Statin	175 (82.5%)	185 (85.6%)	0.38
3-year Outcomes			
All-Cause Death	49 (23.1%)	12 (5.6 %)	**<0.001**
Cardiovascular Death	33 (15.6%)	7 (3.2%)	**<0.001**
MI	19 (9.0%)	12 (5.6%)	0.17
HF Hospitalizations	30 (14.2%)	6 (2.8%)	**<0.001**
Composite	50 (23.6%)	15 (7.0%)	**<0.001**

Median (interquartile range) and frequency count (percentage) are shown. Composite events included all-cause death, MI and HF hospitalizations.

CTO = chronic total occlusion; HsTn-I = high sensitivity troponin-I; BMI = body mass index; MI = myocardial infarction; HF = heart failure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker.

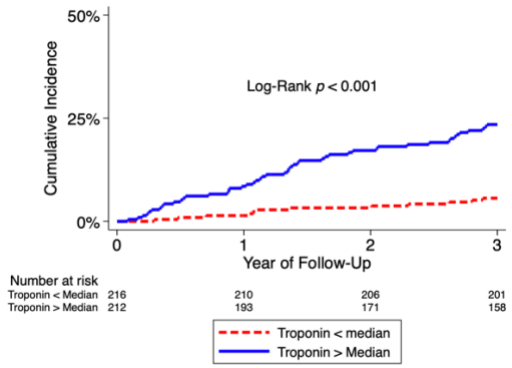
Table 2: Associations between HsTn-I Level and Incident Adverse Events in Patients with CTO

Outcomes	Unadjusted HR (95% CI)	*P* Value	Adjusted Model 1 HR (95% CI)	*P* Value	Adjusted Model 2 HR (95% CI)	*P* Value
For every 100% increase in HsTn-I level						
All-Cause Death	1.21 (1.11 – 1.31)	**<0.001**	1.18 (1.07 – 1.30)	**0.001**	1.19 (1.08 – 1.32)	**0.001**
Cardiovascular Death	1.15 (1.07 – 1.25)	**<0.001**	1.11 (0.99 – 1.25)	0.077	1.11 (0.97 – 1.28)	0.12
All-Cause Death/MI/HF Hospitalization	1.21 (1.12 – 1.31)	**<0.001**	1.19 (1.08 – 1.32)	**0.001**	1.17 (1.07 – 1.29)	**0.001**

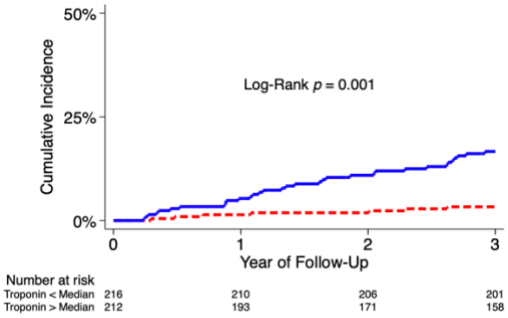
Cox regression was used for all-cause mortality and all-cause death/MI/HF hospitalization. Fine and Gray sub-distribution model was used for cardiovascular death. In adjusted model 1, covariates included age, sex, race (black vs. non-black), BMI, history of smoking, left ventricular ejection fraction, hypertension, diabetes, hyperlipidemia, eGFR, history of MI, use of ACEi/ARB, beta-blockers, and statins. Adjusted model 2 included the covariates in adjusted model 1, with the addition of disease severity and any revascularization at enrollment.
HsTn-I = high sensitivity troponin-I; CTO = chronic total occlusion; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; HF = heart failure; BMI = body mass index; eGFR = estimated glomerular filtration rate; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

Figure 1: Cumulative Incidence of Adverse Events in Patients with a CTO, with or without Elevated (>median 6.7 ng/L) HsTn-I Level

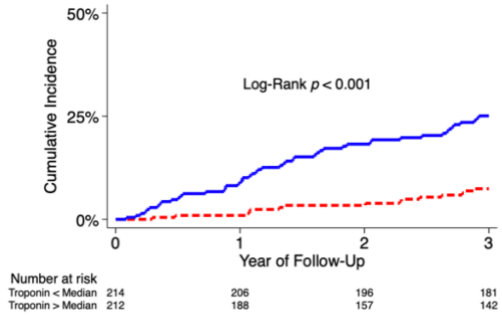
All-Cause Mortality



Cardiovascular Death



Composite Events (All-Cause Death, MI, HF)



Cumulative incidence function as used to visualize differences in outcomes in patients with CTO with above (n=212) and below (n=216) hsTn-I level (6.7 ng/L), coupled with log-rank tests.
CTO = chronic total occlusion; HsTn-I = high sensitivity troponin-I; MI = myocardial infarction; HF = heart failure hospitalization

Supplemental Table 2: Characteristics of Revascularized and Non-Revascularized Patients with CTO

Variable	Non-Revascularized	Revascularized	*P* Value
N	*307*	*121*	
HsTn-I (pg/mL) (IQR)	6.7 (3.8, 14.4)	6.4 (3.2, 15.9)	0.71
Age (IQR)	66.1 (58.1, 73.0)	61.5 (55.2, 67.2)	**<0.001**
Sex: Male	215 (70.0%)	99 (81.8%)	**0.013**
Race: Black	61 (19.9%)	15 (12.4%)	0.07
BMI	28.9 (25.4, 32.5)	28.8 (25.8, 33.6)	0.54
History of smoking	214 (69.7%)	82 (67.8%)	0.70
Hypertension	264 (86.0%)	100 (82.6%)	0.38
Diabetes	106 (34.5%)	49(40.5%)	0.25
Dyslipidemia	248 (80.8%)	92 (76.0%)	0.27
Chronic kidney disease	44 (14.3%)	8 (6.6%)	**0.028**
History of MI	121 (39.7%)	28 (23.1%)	**0.001**
History of HF	95 (30.9%)	34 (28.1%)	0.56
eGFR (mL/min/1.73m^2) (IQR)	71.4 (52.9, 87.4)	80.9 (67.0, 96.1)	**<0.001**
LVEF (%) (IQR)	55.0 (45, 60)	55.0 (50, 60)	0.60
PCI		91 (75.2%)	
CABG		30 (24.8%)	
Non-CTO Revascularization	97 (31.6%)	53 (43.8%)	**0.017**
Disease Severity			
1 Vessel	95 (30.9%)	55 (45.5%)	**0.018**
2 Vessel	115 (37.5%)	36 (29.8%)	
3 Vessel	97 (31.6%)	30 (24.8%)	
Medications			
ACEi/ARB	187 (60.9%)	81 (66.9)	0.25
Beta-blocker	222 (72.3%)	94 (77.7%)	0.25
Statin	251 (81.8%)	109 (90.1%)	**0.034**
3-year Outcomes			
All-Cause Death	53 (17.3%)	8 (6.6 %)	**0.005**
Cardiovascular Death	36 (11.7%)	4 (3.3%)	**0.013**
MI	24 (7.8%)	7 (5.8%)	0.47
HF Hospitalizations	32 (10.4%)	4 (3.3%)	**0.017**
Composite	56 (18.4%)	9 (7.4%)	**0.005**

Values are median or n (%). CABG and PCI were < 90 days after enrollment. Composite events included all-cause death, MI and HF hospitalizations.

CTO = chronic total occlusion; HsTn-I = high sensitivity troponin-I; BMI = body mass index; MI = myocardial infarction; HF = heart failure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker.

Supplemental Table 3: Characteristics of Revascularized and non-revascularized Patients with CTO According to HsTn-I level

	HsTn-I > Median			**HsTn-I ≤ Median**		
Variable	**Revascularized**	**Non-Revascularized**	***P* value**	**Revascularized**	**Non-Revascularized**	***P* Value**
N	*59*	*153*		*62*	*154*	
HsTn-I (pg/mL) (IQR)	16.3 (9.5, 62.7)	14.5 (8.9, 28.3)	0.27	3.3	3.8	0.11
Age (IQR)	64.4 (56.5, 72.8)	66.9 (60.4, 75.1)	0.06	59.6 (53.1, 66.3)	65.0 (57.2, 71.4)	**0.002**
Sex: Male	48 (81.4%)	109 (71.2%)	0.13	51 (82.3%)	106 (68.8%)	**0.045**
Race: Black	13 (22.0%)	37 (24.2%)	0.74	2 (3.2%)	24 (15.6%)	**0.012**
BMI (IQR)	28.7 (25.9, 33.8)	28.7 (25.1, 32.6)	0.62	29.1 (25.8, 33.6)	29.1 (25.4, 32.4)	0.72
History of Smoking	39 (66.1%)	106 (69.3%)	0.66	43 (69.4%)	108 (70.1%)	0.91
Hypertension	47 (79.7%)	139 (90.8%)	**0.026**	53 (85.5%)	125 (81.2%)	0.45
Diabetes	22 (37.3%)	61 (39.9%)	0.73	27 (43.5%)	45 (29.2%)	**0.043**
Dyslipidemia	46 (78.0%)	120 (78.4%)	0.94	46 (74.2%)	128 (83.1%)	0.13
Chronic Kidney Disease	6 (10.2%)	28 (18.3%)	0.15	2 (3.2%)	16 (10.4%)	0.09
History of MI	19 (32.2%)	69 (45.4%)	**0.026**	9 (14.5%)	52 (34.0%)	**0.004**
History of HF	24 (40.7%)	67 (43.8%)	0.68	10 (16.1%)	28 (18.2%)	0.72
eGFR ($mL/min/1.73m^2$) (IQR)	74.4 (60.0, 90.0)	66.5 (50.5, 80.7)	**0.003**	87.9 (73.7, 98.7)	77.6 (60.5, 90.6)	**0.002**
Ejection Fraction (%) (IQR)	50 (44, 55)	52 (35, 60)	0.93	55 (50, 60)	55 (50, 60)	0.41
Non-CTO revascularization	22 (37.3%)	53 (34.6%)	0.72	31 (50.0%)	44 (28.6%)	**0.003**
Type of CTO Revascularization						
PCI	48 (81.4%)			43 (69.4%)		0.13*
CABG	11 (18.6%)			19 (30.6%)		
Disease Severity						
1 Vessel	27 (45.8%)	37 (24.2%)		28 (45.2%)	58 (37.7%)	
2 Vessel	20 (33.9%)	61 (39.9%)	**0.006**	16 (25.8%)	54 (35.1%)	0.40
3 Vessel	12 (20.3%)	55 (35.9%)		18 (29.0%)	42 (27.3%)	
Medications						
ACEi/ARB	44 (74.6%)	93 (60.8%)	0.06	37 (59.7%)	94 (61.0%)	0.85
Beta-Blocker	46 (78.0%)	118 (77.1%)	0.90	48 (77.4%)	104 (67.5%)	0.15
Statin	51 (86.4%)	124 (81.0%)	0.35	58 (93.5%)	127 (82.5%)	**0.036**
3-year Outcomes						
All-Cause Death	5 (8.5%)	44 (28.8%)	**0.002**	3 (4.8%)	9 (5.8%)	0.77
Cardiovascular Death	3 (5.1%)	30 (19.6%)	**0.007**	1 (1.6%)	6 (3.9%)	0.60
MI	5 (8.5%)	14 (9.2%)	0.88	2 (3.2%)	10 (6.5%)	0.34
HF Hospitalization	3 (5.1%)	27 (17.6%)	**0.019**	1 (1.6%)	5 (3.2%)	0.51
Composite	5 (8.5%)	45 (29.4%)	**0.001**	4 (6.5%)	11 (7.2%)	0.84

Values are median or n (%). CABG and PCI were < 90 days after enrollment. HsTn-I median was 6.7. Composite events included all-cause death, MI and HF hospitalizations.

CTO = chronic total occlusion; HsTn-I = high sensitivity troponin-I; BMI = body mass index; MI = myocardial infarction; HF = heart failure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker.

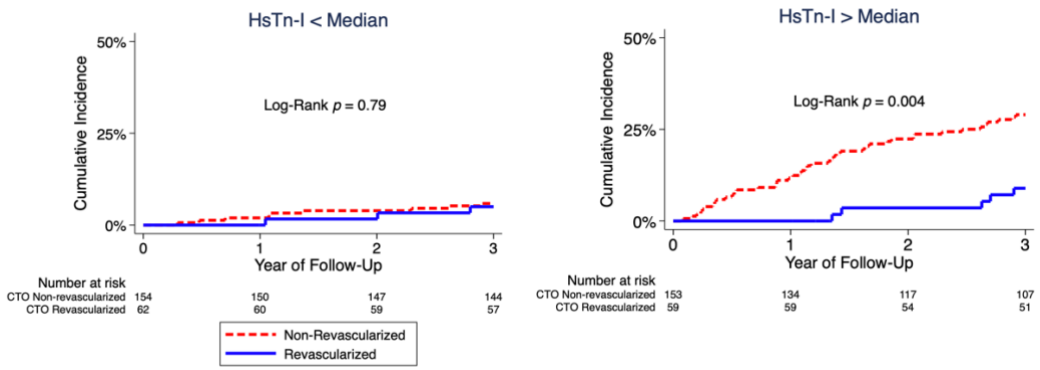
Table 3: Incident Adverse Events in Revascularized compared to Non-Revascularized Patients with CTO

Outcomes	Unadjusted HR (95% CI)	*P* Value	Adjusted Model 1 HR (95% CI)	*P* Value	Adjusted Model 2 HR (95% CI)	*P* Value
Overall						
All-Cause Death	0.36 (0.17 – 0.76)	**0.007**	0.40 (0.16 – 1.05)	0.060	0.43 (0.16 – 1.12)	0.083
Cardiovascular Death	0.27 (0.10 – 0.76)	**0.013**	0.22 (0.05 - 0.92)	**0.039**	0.22 (0.05 – 0.91)	**0.036**
All-Cause Death/MI/HF Hospitalization	0.40 (0.20 – 0.80)	**0.010**	0.57 (0.25 – 1.31)	0.19	0.59 (0.25 – 1.35)	0.21
HsTn-I ≤ 6.7 ng/L						
All-Cause Death	0.83 (0.23 – 3.08)	0.79	1.18 (0.41 – 7.9)	0.86	1.42 (0.18 – 11.32)	0.74
Cardiovascular Death	0.41 (0.05 – 3.40)	0.42	1.13 (0.07 – 18.3)	0.94	0.80 (0.11 – 5.68)	0.83
All-Cause Death/MI/HF Hospitalization	0.95 (0.30 – 3.00)	0.94	1.47 (0.27 – 8.00)	0.66	1.72 (0.30 – 9.92)	0.54
HsTn-I > 6.7 ng/L						
All-Cause Death	0.26 (0.10 – 0.65)	**0.004**	0.25 (0.08 – 0.83)	**0.023**	0.26 (0.08 – 0.88)	**0.030**
Cardiovascular Death	0.24 (0.07 – 0.77)	**0.014**	0.12 (0.02 – 0.94)	**0.043**	0.13 (0.02 – 1.08)	0.059
All-Cause Death/MI/HF Hospitalization	0.26 (0.10 – 0.66)	**0.004**	0.40 (0.14 – 1.10)	0.088	0.41 (0.14 – 1.18)	0.097

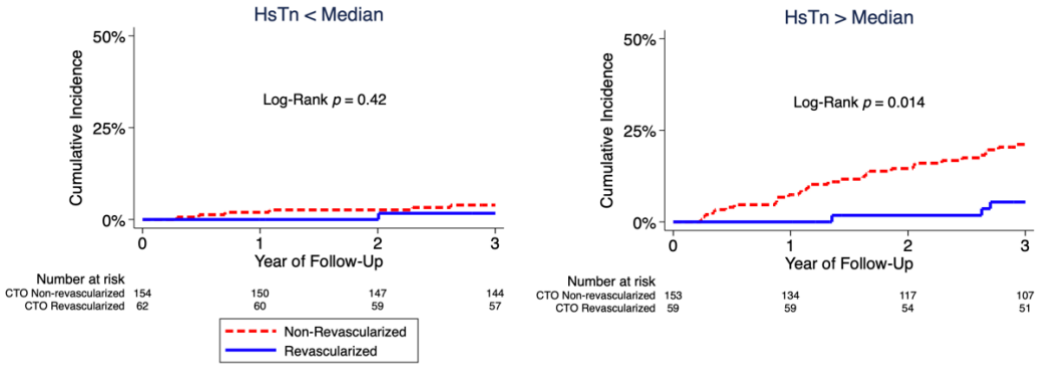
Cox regression model was used for all-cause mortality and all-cause death/MI/HF hospitalization. Fine and Gray subdistribution model was used for cardiovascular death. In adjusted model 1, covariates included age, sex, race (black vs. non-black), BMI, history of smoking, left ventricular ejection fraction, hypertension, diabetes, hyperlipidemia, eGFR, history of MI, use of ACEi/ARB, beta-blockers, and statins. Adjusted model 2 included the covariates in adjusted model 1, with the addition of disease severity and non-CTO revascularization at enrollment.
HsTn-I = high sensitivity troponin-I; CTO = chronic total occlusion; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; HF = heart failure; BMI = body mass index; eGFR = estimated glomerular filtration rate; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker

Figure 2: Cumulative Incidence of Adverse Events in patients with CTO Revascularization Compared to the Non-Revascularized Group in those with Elevated (>median 6.7 ng/L, right), or Low (≤ median 6.7 ng/L, left) HsTn-I levels

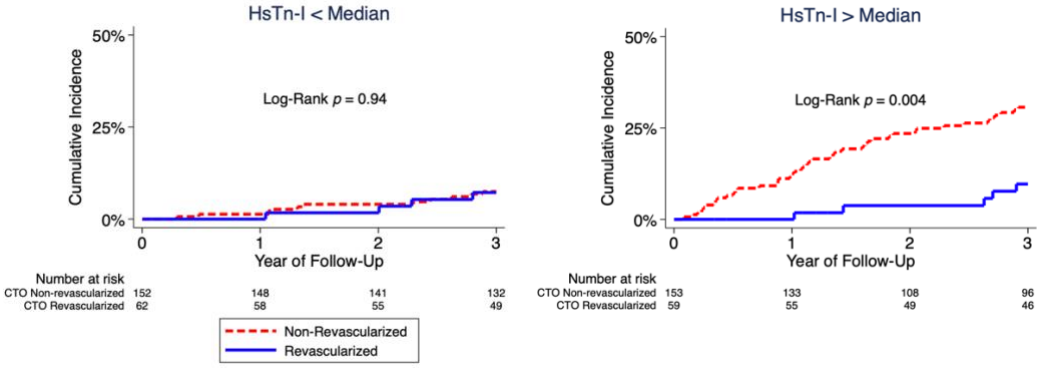
All-Cause Death



Cardiovascular Death



Composite Events (All-Cause Death, MI, HF Hospitalization)



CTO = chronic total occlusion; HsTn-I = high sensitivity troponin-I; MI = myocardial infarction; HF = heart failure

Incident event rates in patients with (n=121) and without (n=307) CTO revascularization were examined and stratified by a hsTn-I level of 6.7 ng/L. Cumulative incidence function was used to visualize the differences in outcomes across groups, coupled with log-rank tests.

Supplemental Table 4: Baseline Characteristics of Patients with and without CTO

Variable	**CTO (n = 392)**	**No CTO (n = 1381)**	***P* Value**
NT pro-BNP (pg/mL) (IQR)	230.0 (103.0, 833.0)	177.7 (78.9, 509.0)	**<0.001**
Age	65.4 (57.1, 71.7)	66.0 (58.2, 74.2)	0.10
Sex: Male	284 (72.4%)	919 (66.7%)	**0.031**
Race: Black	65 (16.6%)	228 (16.5%)	0.97
BMI (IQR)	28.9 (25.5, 33.0)	28.8 (25.7, 33.1)	0.83
History of smoking	270 (68.9%)	911 (66.0%)	0.28
Hypertension	332 (84.9%)	1144 (83.1%)	0.40
Diabetes	139 (35.5%)	514 (37.3%)	0.53
Dyslipidemia	310 (79.3%)	1066 (77.5%)	0.45
History of MI	142 (36.4%)	292 (21.2%)	**<0.001**
History of HF	117 (29.8%)	359 (26.0%)	0.13
Chronic kidney disease	48 (12.2%)	169 (12.2%)	1.00
eGFR (mL/min/1.73m^2) (IQR)	74.6 (58.6, 89.1)	72.5 (57.1, 88.6)	0.26
LVEF (%) (IQR)	55.0 (45.0, 60.0)	60.0 (50.0, 60.0)	**<0.001**
Disease Severity			
1 Vessel	135 (34.4%)	774 (56.0%)	**<0.001**
2 Vessel	139 (35.5%)	421 (30.5%)	
3 Vessel	118 (30.1%)	186 (13.5%)	
Medications			
ACEi/ARB	244 (62.2%)	865 (62.6%)	0.89
Beta-blocker	289 (73.7%)	988 (71.5%)	0.40
Statin	329 (83.9%)	1095 (79.3%)	**0.042**

Values are median (IQR) or n (%). The no CTO group included patients with obstructive CAD $\geq$ 50% in a major coronary artery.

CTO = chronic total occlusion; NT pro-BNP = N terminal pro-brain natriuretic peptide; BMI = body mass index; MI = myocardial infarction; HF = heart failure; IQR = interquartile range; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker.

Table 4: Characteristics of Patients with CTO Stratified by NT-pro-BNP Level

Variable	NT-pro-BNP ≤ 125 pg/mL (n = 125)	NT-pro-BNP > 125 pg/mL (n = 264)	*P* Value
NT pro-BNP (pg/mL) (IQR)	70.8 (48.6, 99.8)	426.9 (224.2,1274.1)	**<0.001**
Age	61.3 (53.1, 67.5)	66.4 (59.7, 74.5)	**<0.001**
Sex: Male	106 (84.8%)	176 (66.7%)	**<0.001**
Race: Black	19 (15.2%)	46 (17.4%)	0.58
BMI	29.4 (26.0, 35.3)	28.6 (24.7, 32.0)	**0.006**
History of smoking	85 (68.0%)	182 (68.9%)	0.85
Hypertension	104 (83.2%)	225 (85.6%)	0.55
Diabetes	37 (29.6%)	101 (38.4%)	0.091
Dyslipidemia	108 (86.4%)	199 (75.7%)	**0.015**
History of MI	32 (25.6%)	110 (42.0%)	**0.002**
History of HF	20 (16.0%)	95 (36.0%)	**<0.001**
Chronic kidney disease	7 (5.6%)	40 (15.2%)	**0.007**
eGFR (mL/min/1.73m^2) (IQR)	78.8 (66.8, 93.7)	70.8 (52.0, 86.9)	**<0.001**
LVEF (%) (IQR)	55.0 (42.0, 60.0)	55.0 (54.0, 60.0)	**<0.001**
Disease Severity			
1 Vessel	58 (46.4%)	76 (28.8%)	**0.002**
2 Vessel	33 (26.4%)	105 (39.8%)	
3 Vessel	34 (27.2%)	83 (31.4%)	
Medications			
ACEi/ARB	88 (70.4%)	155 (58.7%)	**0.026**
Beta-blocker	79 (63.2%)	208 (78.8%)	**0.001**
Statin	112 (89.6%)	215 (81.4%)	**0.040**
5-year Outcomes			
All-Cause Death	10 (8.0%)	67 (25.4 %)	**<0.001**
Cardiovascular Death	16 (4.8%)	45 (17.0%)	**<0.001**
MI	8 (6.4%)	32 (12.1%)	0.083
HF Hospitalizations	2 (1.6%)	43 (16.3%)	**<0.001**
MACE	12 (9.6%)	84 (31.8%)	**<0.001**

Median (interquartile range) and frequency count (percentage) are shown. MACE events included cardiovascular death, MI and HF hospitalizations. CTO = chronic total occlusion; NT pro-BNP = N terminal pro-brain natriuretic peptide; BMI = body mass index; MI = myocardial infarction; HF = heart failure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker; MACE = major adverse cardiac event.

Table 5: Associations between NT pro-BNP Level and Incident Adverse Events in Patients with CTO

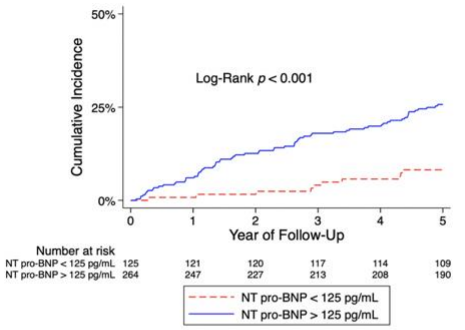
Outcomes	Unadjusted HR (95% CI)	*P* Value	Adjusted Model 1 HR (95% CI)	*P* Value	Adjusted Model 2 HR (95% CI)	*P* Value
For every 100% increase in NT pro-BNP level						
All-Cause Death	1.33 (1.24 – 1.43)	**<0.001**	1.33 (1.17 – 1.50)	**<0.001**	1.33 (1.18 – 1.50)	**<0.001**
CV Death	1.35 (1.24 – 1.47)	**<0.001**	1.39 (1.18 – 1.63)	**< 0.001**	1.39 (1.18 – 1.63)	**<0.001**
CV Death/MI/HF Hospitalization	1.35 (1.24 – 1.46)	**<0.001**	1.27 (1.10 – 1.45)	**0.001**	1.26 (1.10 – 1.45)	**0.001**

Cox regression was used for all-cause mortality. Fine and Gray sub-distribution model was used for cardiovascular death and cardiovascular death/MI/HF hospitalization with non-cardiovascular death as the competing event. In adjusted model 1, covariates included age, sex, race (black vs. non-black), BMI, history of smoking, left ventricular ejection fraction, hypertension, diabetes, hyperlipidemia, eGFR, history of MI, and LVEF. Adjusted model 2 included the covariates in adjusted model 1, with the addition of disease severity and any revascularization at enrollment.

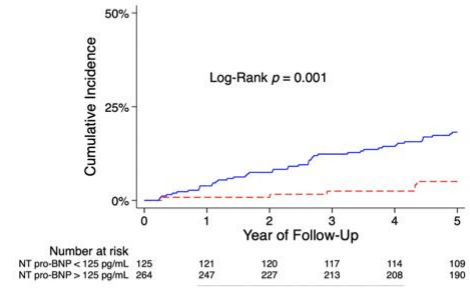
NT pro-BNP = N terminal pro-brain natriuretic peptide; CTO = chronic total occlusion; HR = hazard ratio; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; HF = heart failure; BMI = body mass index; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction

Figure 3: Cumulative Incidence of Adverse Events in Patients with a CTO with or without Elevated NT pro-BNP Level

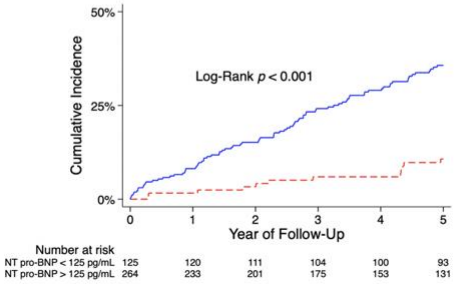
All-Cause Mortality



Cardiovascular Death



Composite Events (Cardiovascular Death, MI, HF)



Unadjusted Cumulative incidence function was used to visualize differences in outcomes in patients with CTO with above (n = 264) and below (n = 125) NT pro-BNP level (125 pg/mL), coupled with log-rank tests. Patients with a NT pro-BNP level > 125 pg/mL had higher rates of all-cause mortality, cardiovascular death, and composite event rate (all-cause mortality, MI, HF hospitalization) compared to patients with a NT pro-BNP level < 125 pg/mL. CTO = chronic total occlusion; NT pro-BNP = N terminal pro-brain natriuretic peptide; MI = myocardial infarction; HF = heart failure hospitalization

Supplemental Table 5: Characteristics of Revascularized and Non-Revascularized Patients with CTO

Variable	No CTO Revascularization (n = 278)	CTO Revascularization (n = 111)	*P* Value
NT pro-BNP (pg/mL) (IQR)	269.4 (117.9, 936.5)	145.3 (69.8, 333.9)	**<0.001**
Age (IQR)	66.1 (58.1, 73.1)	62.0 (55.3, 69.1)	**0.003**
Sex: Male	190 (68.3%)	92 (82.9%)	**0.004**
Race: Black	50 (18.0%)	15 (13.5%)	0.29
BMI	29.0 (25.5, 32.5)	28.7 (25.8, 33.6)	0.90
History of smoking	191 (68.7%)	76 (68.5%)	0.96
Hypertension	237 (85.3%)	92 (83.6%)	0.69
Diabetes	95 (34.2%)	43 (39.1%)	0.36
Dyslipidemia	225 (80.9%)	82 (74.5%)	0.16
History of MI	114 (41.3%)	28 (25.2%)	**0.003**
History of HF	85 (30.6%)	30 (27.0%)	0.49
Chronic kidney disease	39 (14.0%)	8 (7.2%)	0.062
eGFR (mL/min/1.73m^2) (IQR)	71.6 (53.4, 87.0)	78.8 (67.0, 95.7)	**<0.001**
LVEF (%) (IQR)	55.0 (45, 60)	55.0 (50, 60)	0.45
PCI		82 (73.9%)	
CABG		29 (26.1%)	
Non-CTO Revascularization	86 (30.9%)	47 (42.3%)	**0.032**
Disease Severity			
1 Vessel	86 (30.9%)	48 (43.2%)	0.068
2 Vessel	103 (37.1%)	35 (31.5%)	
3 Vessel	89 (32.0%)	28 (25.2%)	
Medications			
ACEi/ARB	171 (61.5%)	72 (64.9)	0.54
Beta-blocker	202 (72.7%)	85 (76.6%)	0.43
Statin	228 (82.0%)	99 (89.2%)	0.081
5-year Outcomes			
All-Cause Death	66 (23.7%)	11 (9.9%)	**0.002**
Cardiovascular Death	45 (16.2%)	6 (5.4%)	**0.004**
MI	30 (10.8%)	10 (9.0%)	0.60
HF Hospitalizations	40 (14.4%)	5 (4.5%)	**0.006**
MACE	83 (29.9%)	13 (11.7%)	**<0.001**

Values are median or n (%). MACE events included cardiovascular death, MI and HF hospitalizations.
CTO = chronic total occlusion; NT pro-BNP = N terminal pro-brain natriuretic peptide; BMI = body mass index; MI = myocardial infarction; HF = heart failure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker; MACE = major adverse cardiac events.

Table 6: Incident Adverse Events in Revascularized compared to Non-Revascularized Patients with CTO

Outcomes	Unadjusted HR (95% CI)	*P* Value	Adjusted Model 1 HR (95% CI)	*P* Value	Adjusted Model 2 HR (95% CI)	*P* Value
Overall (n = 389)						
All-Cause Death	0.49 (0.31 – 0.78)	**0.003**	0.47 (0.26 – 0.85)	**0.012**	0.46 (0.25 – 0.82)	**0.009**
Cardiovascular Death	0.44 (0.24 – 0.84)	**0.012**	0.38 (0.15 -0.94)	**0.035**	0.37 (0.15 – 0.92)	**0.032**
Cardiovascular Death/MI/HF Hospitalization	0.44 (0.28 – 0.71)	**0.001**	0.58 (0.33 – 1.04)	0.069	0.59 (0.33 – 1.05)	0.074
NT Pro-BNP ≤ 125 pg/mL (n = 125)						
All-Cause Death	1.28 (0.50 – 3.23)	0.61	1.29 (0.38 – 4.40)	0.69	1.32 (0.37 – 4.72)	0.66
Cardiovascular Death	1.56 (0.45 – 5.32)	0.48	1.87 (0.36 – 9.81)	0.46	2.46 (0.30 – 20.23)	0.40
Cardiovascular Death/MI/HF Hospitalization	0.71 (0.27 – 1.83)	0.48	0.84 (0.14 – 5.27)	0.86	0.96 (0.17 – 5.35)	0.96
NT Pro-BNP > 125 pg/mL (n = 264)						
All-Cause Death	0.44 (0.25 – 0.77)	**0.004**	0.39 (0.19 – 0.79)	**0.009**	0.38 (0.19 – 0.78)	**0.008**
Cardiovascular Death	0.34 (0.15 – 0.78)	**0.011**	0.24 (0.07 – 0.81)	**0.022**	0.24 (0.07 – 0.81)	**0.022**
Cardiovascular Death/MI/HF Hospitalization	0.45 (0.26 – 0.78)	**0.004**	0.55 (0.29 – 1.06)	0.074	0.54 (0.28 – 1.04)	0.067

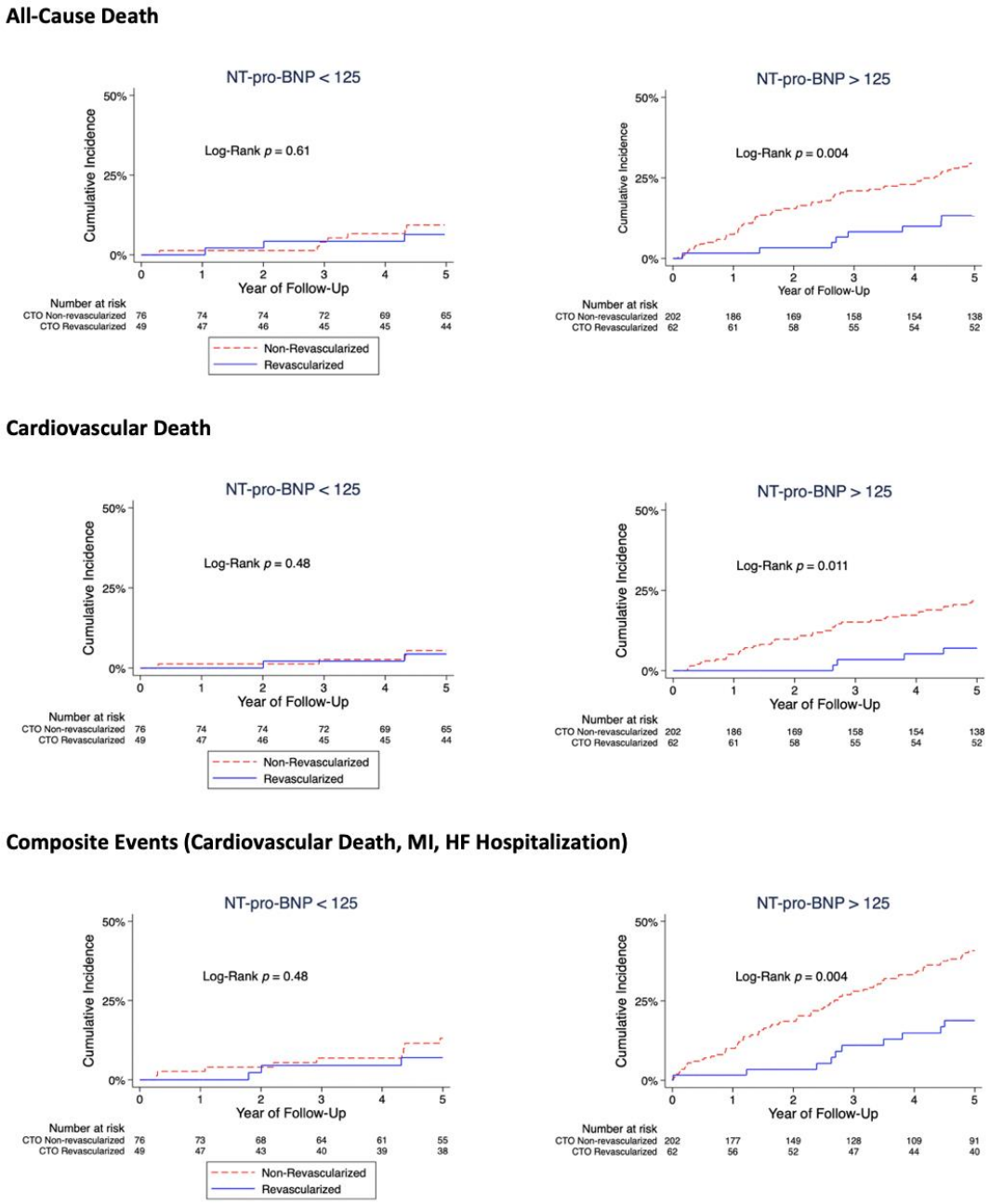
Cox regression model was used for all-cause mortality. Fine and Gray subdistribution model was used for cardiovascular death and cardiovascular death/MI/HF hospitalization with non-cardiovascular death as the competing event. In adjusted model 1, covariates included age, sex, race (black vs. non-black), BMI, history of smoking, hypertension, diabetes, hyperlipidemia, eGFR, history of MI, and LVEF. Adjusted model 2 included the covariates in adjusted model 1, with the addition of disease severity and non-CTO revascularization at enrollment. NT pro-BNP = N terminal pro-natriuretic peptide; CTO = chronic total occlusion; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; HF = heart failure; BMI = body mass index; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction.

Supplemental Table 6: Characteristics of Revascularized and non-revascularized Patients with CTO According to NT pro-BNP level

	NT pro-BNP > 125 pg/mL			**NT pro-BNP ≤ 125 pg/mL**		
Variable	**Revascularized (n = 62)**	**Non-Revascularized (n = 202)**	***P* value**	**Revascularized (n = 49)**	**Non-Revascularized (n = 76)**	***P* Value**
NT pro-BNP (pg/mL) (IQR)	273.4 (188.6, 1036.5)	481.0 (232.9, 1312.1)	**0.013**	64.7 (49.3, 95.2)	76.0 (47.3, 101.7)	0.23
Age (IQR)	64.0 (56.5, 71.6)	67.9 (60.3, 75.1)	**0.005**	58.8 (53.1, 65.7)	61.7 (54.2, 68.4)	0.26
Sex: Male	47 (75.8%)	129 (63.9%)	0.081	45 (91.8%)	61 (80.3%)	0.078
Race: Black	9 (14.5%)	37 (18.3%)	0.49	6 (12.2%)	13 (17.1%)	0.46
BMI (IQR)	28.6 (25.9, 31.7)	28.8 (25.1, 31.9)	0.83	29.1 (26.0, 34.3)	29.3 (26.2, 35.0)	0.79
History of Smoking	43 (69.4%)	139 (68.8%)	0.94	33 (67.3%)	52 (68.4%)	0.90
Hypertension	50 (82.0%)	175 (86.6%)	0.36	42 (85.7%)	62 (81.6%)	0.55
Diabetes	26 (42.6%)	75 (37.1%)	0.44	17 (35.0%)	20 (26.3%)	0.32
Dyslipidemia	42 (68.9%)	157 (77.7%)	0.16	46 (74.2%)	128 (83.1%)	0.13
History of MI	20 (32.3%)	90 (45.0%)	0.076	8 (16.3%)	24 (31.6%)	0.056
History of HF	22 (35.5%)	73 (36.1%)	0.93	8 (16.3%)	12 (15.8%)	0.94
Chronic Kidney Disease	6 (9.7%)	34 (16.8%)	0.17	2 (4.1%)	5 (6.6%)	0.55
eGFR (mL/min/1.73m^2) (IQR)	76.7 (64.1, 93.8)	68.9 (50.5, 83.6)	**0.002**	84.2 (69.9, 98.0)	76.2 (63.9, 91.2)	0.15
Ejection Fraction (%) (IQR)	50 (45, 60)	55 (41, 60)	0.90	55 (55, 60)	55 (50, 60)	0.49
Non-CTO Revascularization	22 (35.5%)	63 (31.2%)	0.53	25 (51.0%)	23 (30.0%)	**0.020**
Type of CTO Revascularization						
PCI	45 (72.6%)			37 (75.5%)		0.73*
CABG	17 (27.4%)			12 (24.5%)		
Disease Severity						
1 Vessel	26 (41.9%)	50 (24.8%)		22 (44.9%)	36 (47.4%)	
2 Vessel	23 (37.1%)	82 (40.6%)	**0.020**	12 (24.5%)	21 (27.6%)	0.78
3 Vessel	13 (21.0%)	70 (34.7%)		15 (30.6%)	19 (25.0%)	
Medications						
ACEi/ARB	41 (66.1%)	114 (56.4%)	0.18	31 (63.3%)	57 (75.0%)	0.16
Beta-Blocker	50 (80.6%)	158 (78.2%)	0.68	35 (71.4%)	44 (57.9%)	0.13
Statin	55 (88.7%)	160 (79.2%)	0.092	44 (89.8%)	68 (89.5%)	0.95
5-year Outcomes						
All-Cause Death	8 (12.9%)	59 (29.2%)	**0.010**	3 (6.1%)	7 (9.2%)	0.53
Cardiovascular Death	4 (6.5%)	41 (20.3%)	**0.011**	2 (4.1%)	4 (5.3%)	0.76
MI	7 (11.3%)	25 (12.4%)	0.82	3 (6.1%)	5 (6.6%)	0.92
HF Hospitalization	4 (6.5%)	39 (19.3%)	**0.016**	1 (2.0%)	1 (1.3%)	0.75
MACE	10 (16.1%)	74 (36.6%)	**0.005**	3 (6.1%)	9 (11.8%)	0.55

Values are median or n (%). MACE events included cardiovascular death, MI and HF hospitalizations.
CTO = chronic total occlusion; NT pro-BNP = N terminal pro-brain natriuretic peptide; BMI = body mass index; MI = myocardial infarction; HF = heart failure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi/ARB = Angiotensin converting enzyme inhibitors/angiotensin-receptor blocker; MACE = major adverse cardiac event
**P* value compares with > and ≤ median NT pro-BNP among patients with CTO that were revascularized

Figure 4: Cumulative Incidence of Adverse Events in patients with Compared to without CTO Revascularization Stratified by NT pro-BNP Level



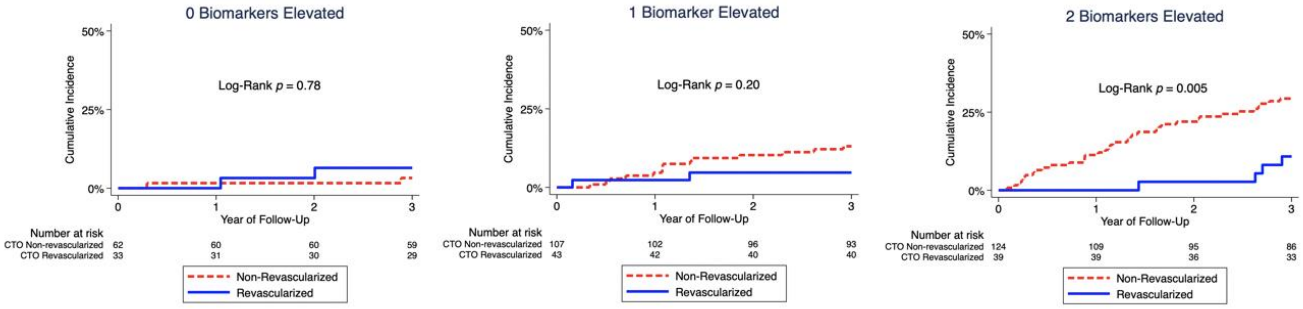
Incident event rates in patients with (n = 111) and without (n = 278) revascularization of CTO were examined and stratified by a NT pro-BNP level of (125 pg/mL). Unadjusted Cumulative incidence function was used to visualize the differences in survival outcomes across groups coupled with log-rank tests. In patients with a high (> 125 pg/mL) baseline NT pro-BNP level, CTO revascularization was associated with lower adverse event rates of all-cause mortality, cardiovascular death and the composite (all-cause mortality, MI, HF hospitalization). In patients with a low (< NT pro-BNP) level, adverse event rates were similar among patients with and without CTO revascularization.

Table 7: Biomarker Score and All-Cause Mortality of CTO Revascularization

Biomarker Score	Adjusted Model HR (95% CI)	*P* Value
0 Biomarkers Elevated (n = 95)	1.28 (0.22 – 7.14)	0.78
1 Biomarkers Elevated (n = 129)	0.49 (0.16 – 1.47)	0.20
2 Biomarkers Elevated (n = 163)	0.25 (0.08 – 0.65)	**0.005**

Cox proportional hazard models were used to measure the association between number of biomarkers elevated (hsTn-I and NT pro-BNP) and all-cause mortality. HsTn-I elevation was defined as over the median (6.7 pg/mL). NT pro-BNP level was defined as over 125 pg/mL.
CTO = chronic total occlusion; HR = hazard ratio; hsTn-I = high sensitivity troponin-I; NT pro-BNP = N terminal pro-Brain natriuretic peptide.

Figure 5: Cumulative Incidence of All-cause Mortality in patients with Compared to Without CTO Revascularization Stratified by Biomarker Score



Incident all-cause mortality in patients with and without revascularization of CTO stratified by number of biomarkers elevated. HsTn-I elevation was defined as over the median (6.7 pg/mL). NT pro-BNP level was defined as over 125 pg/mL. Unadjusted Cumulative incidence function was used to visualize the differences in survival outcomes across groups coupled with log-rank tests. CTO = chronic total occlusion; HR = hazard ratio; hsTn-I = high sensitivity troponin-I; NT pro-BNP = N terminal pro-Brain natriuretic peptide.