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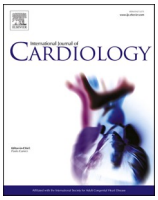

N terminal pro-brain natriuretic peptide level and benefits of chronic total occlusion revascularization☆

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ABSTRACT

Background: The management of revascularization of chronic total occlusions (CTOs) remains controversial. Whether specific patients gain survival benefit from CTO revascularization remains unknown.
Objectives: We investigated whether (i) patients with CTO have higher N terminal pro-brain natriuretic peptide (NT pro-BNP) levels than patients without CTO, (ii) in patients with CTO, NT pro-BNP levels predict adverse events, and (iii) those with elevated levels benefit from revascularization.
Methods: In 392 patients with stable, significant coronary artery disease (CAD) and CTO undergoing coronary angiography, rates of all-cause mortality, cardiovascular death, and a composite (cardiovascular death, myocardial infarction and heart failure hospitalizations) were investigated. Unadjusted and adjusted Cox proportional and Fine and Gray sub-distribution hazard models were performed to determine the association between NT pro-BNP levels and incident event rates in patients with CTO.
Results: 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 NT pro-BNP level in patients with CTO was associated with a > 25% higher rate of adverse events. 111 (28.5%) patients underwent CTO 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). However, in patients with low NT pro-BNP levels (≤ 125 pg/mL), event rates were similar in those with and without CTO revascularization.
Conclusion: NT pro-BNP levels can help identify individuals who may benefit from CTO revascularization.

1. 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

Abbreviations: CTO, Chronic total occlusion; CAD, Coronary artery disease; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass graft; NT pro-BNP, N Terminal pro-Brain natriuretic peptide; LVEF, Left ventricular ejection fraction; eGFR, Estimated glomerular filtration rate; MI, Myocardial Infarction; HF, Heart Failure; ACEi/ARB, Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

☆ Tweet: Patients with CTO have higher NT pro-BNP levels than those without CTO and the elevation is associated with higher adverse event rates. Patients with a higher, but not lower NT pro-BNP level experienced a survival benefit from CTO revascularization.

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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.

N terminal pro-brain natriuretic peptide (NT Pro-BNP), a hormone secreted by cardiomyocytes in response to cardiac stretch and increased wall stress [8], can be elevated in the absence of obvious volume overload or left ventricular dysfunction [9]. In fact, NT pro-BNP level has been associated with a higher risk of adverse cardiac events in patients with CAD with and without heart failure [10–13].

In patients with CTO, those with poorly developed collaterals have a higher level of NT pro-BNP than those with well-developed collaterals [14]. NT pro-BNP levels in patients with CTO compared to patients without CTO have yet to be investigated. Whether NT pro-BNP level predicts adverse outcomes in patients with CTO, and whether those with an elevated level benefit from CTO revascularization remains unknown. In this prospective study of patients with stable, significant CAD and CTO with long-term follow-up, we determined whether (i) NT pro-BNP levels are higher in patients with, compared to those without CTO; (ii) NT pro-BNP levels predict incident adverse events in patients with CTO; and (iii) patients with elevated NT pro-BNP levels have a survival benefit from revascularization of the CTO. We hypothesized that patients with CTO will have higher levels of NT pro-BNP than patients without CTO, and higher NT pro-BNP levels will predict adverse cardiovascular events and survival benefit from revascularization in patients with CTO.

2. Methods

2.1. 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 [15]. 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 [16]. Significant CAD was defined as CAD ≥ 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 [16]. Demographic and clinical data were obtained from medical records and questionnaires, which included age, sex, race, body mass index, hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, 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, and heart failure (HF). use of beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), or statins as previously described [15]. The study was approved by the Emory University Institutional Review Board. All subjects provided written informed consent.

2.2. 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 were medically managed without any revascularization, or who had revascularization of the non-CTO lesions only.

2.3. 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 [17].

2.4. 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 [15]. 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.

2.5. 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, 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 NT pro-BNP levels as a continuous variable by $\log_2$ transformation (to show the hazard rate ratio for every doubling of NT pro-BNP level) and as a binary variable stratified by 125 pg/mL. Incident event rates in patients with and without revascularization of CTO were examined and stratified by a NT pro-BNP level of 125 pg/mL. Cumulative incidence function was used to visualize the differences in survival outcomes across groups coupled with log rank tests. Cox proportional hazards models were used to examine the association between groups and time to all-cause death. Fine and Gray sub-distribution hazard models [18] were performed for time to cardiovascular death and the composite outcome of major adverse cardiovascular events, (cardiovascular death, MI and HF hospitalizations), 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, history of HF, eGFR, history of smoking, history of MI. Model 2 of the analyses included the aforementioned covariates plus disease severity, and non-CTO revascularization. All covariates had <5% missing data. All analyses were performed using SPSS software, Stata/BE 17.0. *P*-values <0.05 were considered statistically significant.

Table 1
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 (224.21274.1)	**Not Applicable**
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 (54.0, 60.0)	55.0 (42.0, 60.0)	**<0.001**
Disease Severity			
1 Vessel	58 (46.4%)	76 (28.8%)	
2 Vessel	33 (26.4%)	105 (39.8%)	**0.002**
3 Vessel	34 (27.2%)	83 (31.4%)	
Indication			
Angina	63 (88.7%)	123 (77.8%)	
Pre-op	6 (8.5%)	11 (7.0%)	0.058
Valvular	0	1 (0.6%)	
HF exacerbation	2 (2.8%)	23 (14.6%)	
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.

3. Results

Baseline characteristics of the 1773 enrolled patients with significant CAD, 392 with, and 1381 without CTO are shown in Supplemental Table 1. NT pro-BNP levels in patients with CTOs were higher compared to those without CTOs, (median 230.0 vs. 177.7 pg/mL, $p < 0.001$), Supplemental Fig. 1.

3.1. 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 female, have lower body mass index, eGFR, LVEF, 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 1. In both groups, angina was the most common indication for coronary angiogram.

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 1. Each 100% increase in NT pro-BNP level was associated with >25% rate of incident adverse events, even after adjustment for age, sex, race, body mass index, smoking history, hypertension, diabetes, dyslipidemia, MI history, eGFR, history of HF, disease severity, and any revascularization at enrollment, Table 2. 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 $p < 0.001$, Fig. 1.

3.2. 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, and were less likely to have chronic kidney disease or a history of MI than patients that did not receive CTO revascularization, Supplemental Table 2. 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, history of HF, disease severity, and non-CTO revascularization, Table 3.

3.3. NT pro-BNP levels and outcomes with revascularization

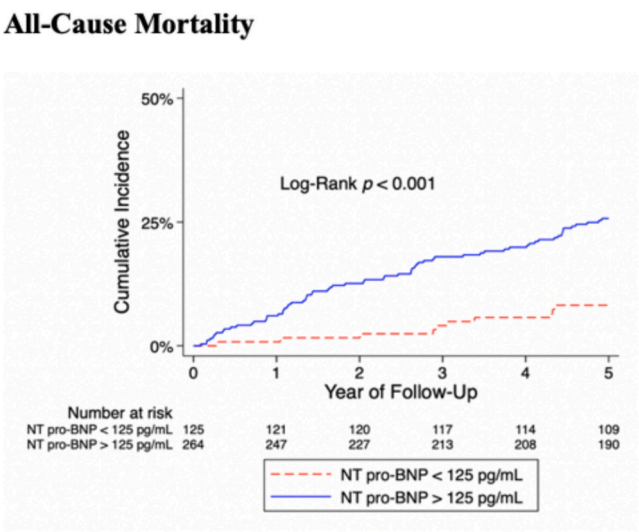
The outcomes of CTO revascularization were further investigated based on baseline NT pro-BNP levels. A higher proportion of patients with an NT pro-BNP ≤ 125 pg/mL were revascularized compared to patients with an NT pro-BNP level > 125 pg/mL Supplemental Table 3.

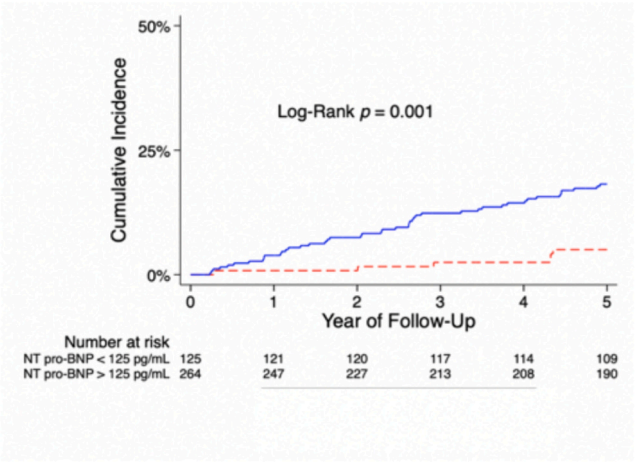
The interaction term between NT pro-BNP level (above/below 125 pg/mL) and CTO revascularization on cardiovascular death was significant in the crude model (hazard ratio (HR) 0.22 95% confidence interval (CI) (0.05–0.96) $p = 0.044$), and nearly significant in the fully

Table 2
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**	1.29 (1.15–1.44)	**<0.001**	1.28 (1.14–1.44)	**<0.001**
CV Death	1.35 (1.24–1.47)	**<0.001**	1.35 (1.16–1.57)	**< 0.001**	1.34 (1.15–1.57)	**<0.001**
CV Death/MI/HF Hospitalization	1.35 (1.24–1.46)	**<0.001**	1.27 (1.12–1.44)	**< 0.001**	1.25 (1.10–1.43)	**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), HF history, BMI, history of smoking, hypertension, diabetes, hyperlipidemia, eGFR, and history of MI. 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.





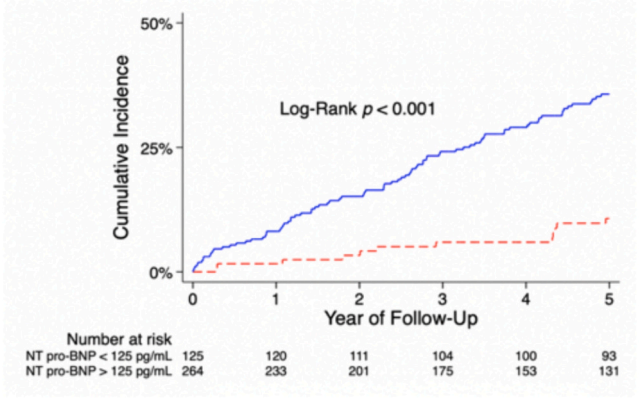


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Fig. 1. Cumulative Incidence of Adverse Events in Patients with a CTO with or without Elevated NT pro-BNP Level.
Unadjusted Cumulative incidence function was used to visualize differences in outcomes in patients with CTO with above ($n = 264$) and 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.

adjusted model (HR 0.22 95% CI (0.04–1.17) $p = 0.076$). For all-cause mortality, this interaction effect was nearly significant in the crude model (HR 0.34 95% CI (0.11–1.02), $p = 0.055$) and not significant in the fully adjusted model (HR 0.40 95% CI (0.12–1.32), $p = 0.13$). The interaction was not significant for the outcome of CV death/MI/HF hospitalization. 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 >50% in patients who underwent revascularization, compared to those who did not receive CTO revascularization (adjusted cardiovascular death HR 0.29, 95% confidence interval 0.09–0.88, $p = 0.029$). 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 3, Fig. 2, Supplemental Table 3. Interestingly, when further adjusting the high and low NT pro-BNP subgroups with NT pro-BNP level, the results remained unchanged. All other covariate interactions were not statistically significant.

4. Discussion

Our study had several novel findings. Patients with CTO have higher NT pro-BNP levels than those with significant CAD, without a CTO. A higher NT pro-BNP level was an independent predictor of adverse outcomes in patients with CTO, similar to findings in other individuals with CAD [10–13]. Most importantly, revascularization of the CTO was associated with a dramatic improvement in survival in those with an elevated NT pro-BNP level, but not in those with a low NT pro-BNP level. These observations were independent of having a history of HF. The decision to revascularize a CTO is currently reserved for those with significant symptoms, or presence of reversible ischemia on non-invasive testing [19]. Our findings suggest that the baseline NT pro-BNP level can assist in identifying individuals who are at high risk and will likely benefit most from revascularization. This can help inform future trials investigating the effect of CTO revascularization on outcomes.

4.1. NT pro-BNP levels in patients with CTO

Patients with CTO have a greater magnitude of ischemia than those without a CTO [20], often leading to myocardial stunning, fibrosis and impairment of left ventricular contractility that can contribute to HF in this population [21]. These alterations increase NT pro-BNP production and release by cardiomyocytes in response [8]. 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 [22], higher circulating levels of NT pro-BNP predict incident adverse cardiovascular events and mortality in the general population [23] and in patients with CAD with and without HF [10–13]. 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 [9,24,25].

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 ($n = 389$)						
All-Cause Death	0.49 (0.31–0.78)	**0.003**	0.50 (0.34–0.74)	**< 0.001**	0.50 (0.29–0.86)	**0.012**
Cardiovascular Death	0.44 (0.24–0.84)	**0.012**	0.38 (0.22–0.67)	**0.001**	0.48 (0.22–1.02)	0.055
Cardiovascular Death/MI/HF Hospitalization	0.44 (0.28–0.71)	**0.001**	0.57 (0.33–0.98)	**0.040**	0.60 (0.35–1.02)	0.058
NT Pro-BNP ≤ 125 pg/mL ($n = 125$)						
All-Cause Death	1.28 (0.50–3.23)	0.61	1.47 (0.50–4.36)	0.49	1.46 (0.47–4.54)	0.51
Cardiovascular Death	1.56 (0.45–5.32)	0.48	2.28 (0.36–9.52)	0.26	2.68 (0.46–15.68)	0.27
Cardiovascular Death/MI/HF Hospitalization	0.71 (0.27–1.83)	0.48	0.98 (0.26–3.72)	0.98	1.02 (0.27–3.85)	0.97
NT Pro-BNP > 125 pg/mL ($n = 264$)						
All-Cause Death	0.44 (0.25–0.77)	**0.004**	0.41 (0.21–0.82)	**0.011**	0.41 (0.21–0.81)	**0.010**
Cardiovascular Death	0.34 (0.15–0.78)	**0.011**	0.29 (0.10–0.85)	**0.025**	0.29 (0.09–0.88)	**0.029**
Cardiovascular Death/MI/HF Hospitalization	0.45 (0.26–0.78)	**0.004**	0.54 (0.28–1.02)	0.059	0.55 (0.29–1.04)	0.066

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), HF history, BMI, history of smoking, hypertension, diabetes, hyperlipidemia, eGFR, and history of MI. 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.

4.2. NT pro-BNP levels and outcomes in patients with CTO

Patients with CTO and poorly developed collaterals have higher levels of NT pro-BNP than those with well-developed collaterals [14]. We demonstrate that CTO revascularization is associated with improved outcomes in patients with a high NT pro-BNP level, whereas those with a low level of NT pro-BNP, likely had a well-developed collateral circulation, and less change in cardiac stretch and NT pro-BNP level as a result of CTO revascularization. Although we did not have post-revascularization NT pro-BNP measurements in this study, a prior study showed that revascularization in patients with stable CAD decreased NT pro-BNP levels, independent of left ventricular systolic function, suggesting that lowering of NT pro-BNP level after CTO revascularization may be contributing to the mortality benefit in these patients [26].

4.3. NT pro-BNP levels and outcomes with CTO revascularization

Whether there is a survival benefit of CTO revascularization remains unclear. Meta-analyses and observational studies demonstrate reduction in mortality with CTO revascularization [27–30], 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 [31]. 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 underwent 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. 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 NT pro-BNP levels.

In patients with CTO, meta analyses have shown that PCI of the CTO improves LVEF compared to medical therapy [32,33], but randomized controlled clinical trials such as the EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) and REVASC (Recovery of Left Ventricular Function After Stent Implantation in Chronic Total Occlusion of Coronary Arteries) did not show improvement in LVEF, except in the subset of patients with left anterior descending artery CTO [34,35]. These trials, nonetheless, did not explore the improvement by NT pro-BNP levels after revascularization. Our data suggests that patients with CTO and a high NT pro-BNP level have lower cardiovascular event rates including cardiovascular death, MI and HF hospitalizations after CTO revascularization.

4.4. Strengths/Limitations

Strengths of our study include enrollment of a diverse population including women and Black participants with a wide range of different clinical characteristics and availability of adjudicated event rates during long-term follow-up. NT pro-BNP measurements were performed at one time to minimize variability. Limitations include a lack of post-revascularization NT pro-BNP levels, and thus an assessment of the link between outcomes and the *change* in NT pro-BNP 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. Although acute coronary syndrome was ruled out in all patients in the study, data for the clinical indications for cardiac catheterization was not available for 40% of the patients. Another limitation was the low numbers of events in the subgroup analyses based on high and low NT pro-BNP levels. Nevertheless, our findings demonstrating the value of NT pro-BNP level in identifying a subset of patients with CTO who benefit from revascularization need to be replicated in a randomized trial.

5. Conclusions

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

5.1. Clinical perspectives

The mortality benefit of CTO revascularization is controversial. If patients have refractory angina from their CTO, revascularization likely will help relieve symptoms. If the benefit of CTO revascularization is unclear, physicians can obtain a baseline NT pro-BNP level to help determine if there may be a mortality benefit with revascularization.

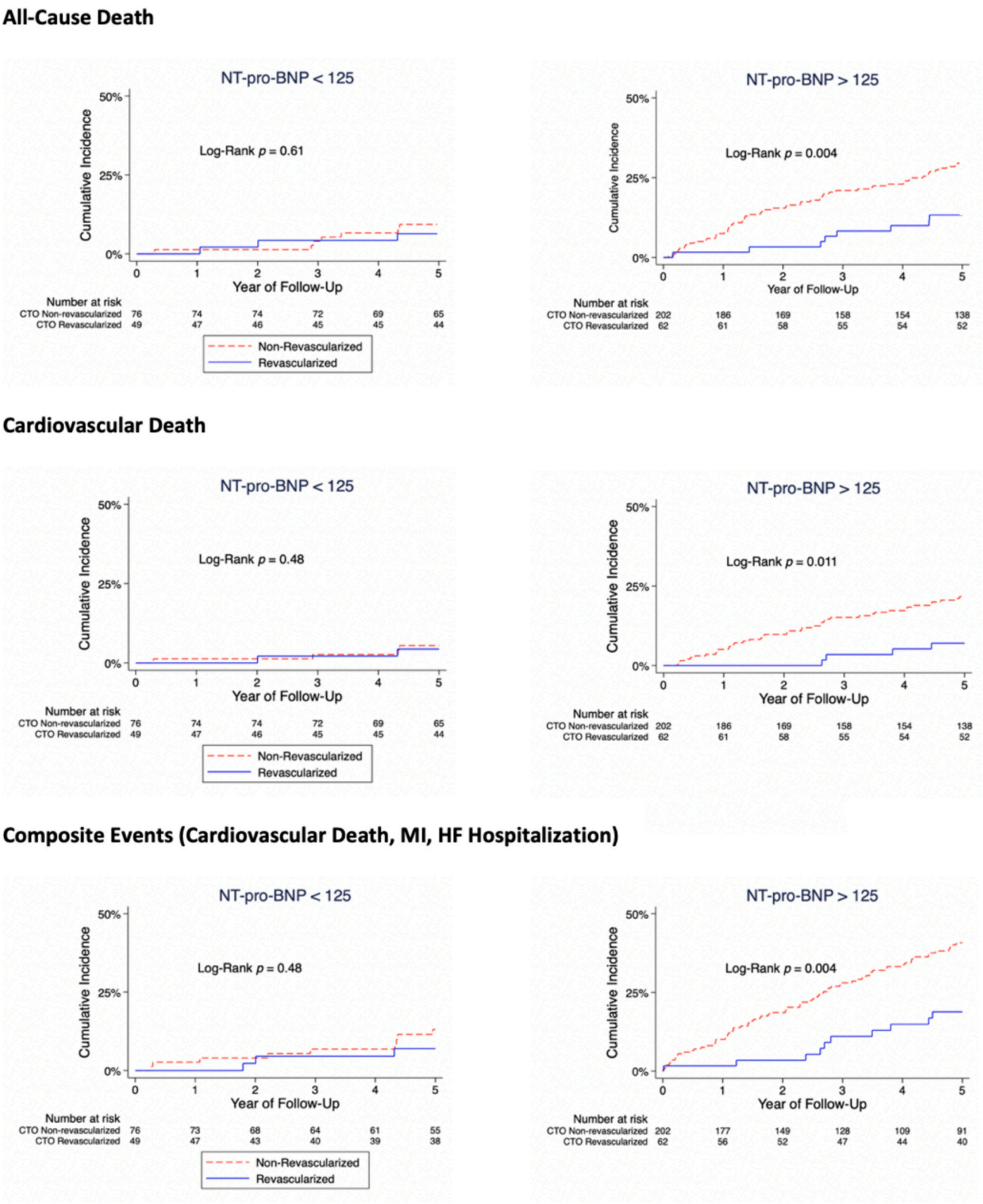

Fig. 2. Cumulative Incidence of Adverse Events in patients with Compared to without CTO Revascularization Stratified by NT pro-BNP Level.
Incident event rates in patients with ($n = 111$) and without ($n = 278$) revascularization of CTO were examined and stratified by a NT pro-BNP level of (125 pg/mL). 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.
CTO = chronic total occlusion; NT pro-BNP = N terminal pro-brain natriuretic peptide; MI = myocardial infarction; HF = heart failure.

CRediT authorship contribution statement

Daniel A. Gold: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Pratik B. Sandesara:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Vardhmaan Jain:** Writing – review & editing, Methodology. **Matthew E. Gold:** Writing – review & editing, Methodology. **Nishant Vatsa:** Writing – review & editing, Methodology. **Shivang R. Desai:** Writing – review & editing, Methodology. **Malika Elhage Hassan:** Writing – review & editing. **Chenyang Yuan:** Formal analysis. **Yi-An Ko:** Methodology, Formal analysis. **Chang Liu:** Methodology, Formal analysis. **Kiran Ejaz:** Data curation. **Zain Alvi:** Data curation. **Ayman Alkhoder:** Data curation. **Alireza Rahbar:** Data curation. **Gillian Murtagh:** Writing – review & editing, Resources. **Christos Varounis:** Writing – review & editing, Resources. **Wissam A. Jaber:** Writing – review & editing, Supervision. **William J. Nicholson:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Arshed A. Quyyumi:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

CV and GM are full-time Abbott employees and shareholders of Abbott.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132196.

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