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Postdischarge prognostic significance of periprocedural myocardial injury after percutaneous intervention of chronic total occlusion

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ABSTRACT

Background The postdischarge prognostic implication of periprocedural myocardial injury in patients undergoing percutaneous coronary intervention (PCI) of a chronic total occlusion (CTO) remains scarcely studied.

Aims The aim of this study is to assess the prognostic value of periprocedural myocardial injury, defined by increased high-sensitive troponin T (hs-TnT) levels according to updated guidelines, after CTO PCI.

Methods Between September 2011 and April 2020, 726 patients undergoing CTO PCI at 2 Belgian referral centres were prospectively included and divided into 4 groups based on postprocedural hs-TnT levels (unelevated; ≥5 times the upper limit of normal (ULN); ≥35 times the ULN; ≥70 times the ULN). Postprocedural hs-TnT levels were subsequently related to patient and procedural characteristics, 1-year major adverse cardiac and cerebrovascular events (MACCE; excluding in-hospital MACCE) as well as 1-year mortality.

Results At 1 year follow-up (FU), elevated hs-TnT≥5 times and ≥35 times the ULN were associated with higher MACCE rates (p=0.001; p=0.007, respectively). In addition, they also resulted in a higher 1-year mortality rate (p=0.009;p=0.021, respectively). Patients with increased hs-TnT≥5 times the ULN (35% of patients) more frequently had signs of more advanced atherosclerotic disease (previous CABG p<0.001; stroke p≤0.001 and peripheral vascular disease p<0.001) and had higher procedural complexity (Japanese CTO Score p=<0.001, stent length>48 mm p<0.001, procedure time p<0.001). Antegrade wire escalation did not result in lower event rate of postdischarge MACCE compared with the other CTO crossing techniques combined (p=0.158).

Conclusion Periprocedural myocardial injury was associated with a significantly higher rate of MACCE and all-cause mortality after 12 months of FU.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Periprocedural myocardial injury is common after percutaneous coronary intervention (PCI).

WHAT THIS STUDY ADDS

⇒ This study shows that periprocedural myocardial injury in PCI of a chronic total occlusion (CTO) is associated with higher rates of major adverse cardiac and cerebrovascular events and all-cause mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients with periprocedural myocardial injury after PCI of a CTO might require a different follow-up (FU) both in-hospital and out-hospital compared with patients without periprocedural myocardial injury to improve prognosis. Further research will have to elucidate what is the best FU for these patients.

INTRODUCTION

Coronary chronic total occlusions (CTOs) are found in 15%–25% of patients with stable coronary artery disease.[1] Percutaneous coronary intervention (PCI) is one of the treatment options in these patients and improves patient symptoms and clinical outcome.[2–5] Advances in materials and techniques have led to an accelerated adoption of CTO PCI and improved success rates in recent years.[2 3] Markers to risk stratify patients undergoing CTO PCI may allow further improvement in clinical outcomes. Multiple studies have shown that periprocedural myocardial injury in patients undergoing PCI is associated with worse long-term cardiovascular outcome.[6–8] Data on the long-term prognostic implications of periprocedural myocardial injury in patients undergoing PCI of a CTO, however, remains scarce. In addition, it is unclear how these patients can be best managed in order to improve their prognosis.

Goliasch *et al* showed that periprocedural myocardial injury (based on troponin T) in CTO PCI was associated with increased mortality.[9] Song *et al*, however, failed to show such an association for postprocedural cardiac Troponin I.[10] Increased incidence of myocardial injury in CTO PCI is likely due

to the increased complexity of procedures in addition to procedure length and amount of balloons and stents used in CTO PCI. More recently, high-sensitive troponin T (hs-TnT) has been introduced as a biomarker to detect even minor myocardial damage, and recently updated consensus documents have defined cut-off values for myocardial injury.[11] However, the long-term clinical impact of these cut-off values remains unclear.

The aim of the current study was to investigate the prognostic value of periprocedural myocardial injury and its association with different CTO PCI approaches, in a cohort of patients undergoing CTO PCI, using the current generation hs-TnT assay and according to the currently accepted cut-off for hs-TnT (≥5 times the 99th percentile of upper limit of normal (ULN) within the first 48 hours after PCI).

METHODS

Study population

A total of 920 patients, who underwent CTO PCI in two CTO PCI centres in Belgium (Oost-Limburg Hospital in Genk and University Hospital Leuven) from September 2011 to April 2020, were prospectively enrolled and eligible for inclusion in this analysis if post-PCI hs-TnT levels were available.

PROCEDURES AND BIOCHEMICAL MEASUREMENTS

CTO PCI procedures were performed using a radial or femoral route with 6–8Fr guiding catheters. All patients received dual antiplatelet therapy before the CTO procedure. During the procedure, anticoagulation therapy in the form of unfractionated heparin was administered with an aimed target of ≥250 s activated clotting time in antegrade procedures and ≥300 s in retrograde procedures.

Baseline and postprocedural blood samples were collected with postprocedural hs-TnT values being obtained 12–16 hours after the procedure. Hs-TnT was measured by a high-sensitivty assay in a cobas 8000 e602 immunoanalyzer using electrochemiluminescence technology (Roche Diagnostics, Switzerland). The lowest concentration that can be reproducibly measured is ≤0.013 mg/L. The 99th percentile ULN is 0.014 mg/L.

Definitions

A CTO was defined as the complete obstruction of a native coronary artery with duration>3 months and Thrombolysis in Myocardial Infarction (TIMI) flow vessel grade 0. CTO complexity was assessed using the Japanese CTO (J-CTO) scoring system.[12]

Technical procedural success was defined as TIMI 3 flow post-PCI and<30% residual stenosis.

Major complications were defined as major adverse cardiac events plus perforation requiring treatment, major bleeding or major vascular complications. Major vascular complications were defined as retroperitoneal haematoma, acute limb ischaemia and vascular bleeding requiring prolonged hospitalisation or transfusion.

Periprocedural myocardial injury was defined as hs-TnT≥5 times the 99th percentile of ULN within the first 48 hours after PCI in accordance with the 2021 consensus paper from the working group of cellular biology of the heart and European Association of Percutaneous Cardiovascular Interventions.[11] In addition, we analysed two subgroups defined as hs-TnT≥35 times the 99th percentile of ULN and hs-TnT≥70 times the 99th percentile of ULN, in accordance with the Academic Research Consortium-2 and Society for Cardiovascular Angiography and Interventions documents.[13 14]

Inclusion and exclusion criteria

All patients who had postprocedural hs-TnT levels available were included. Patients who had elevated baseline levels of hs-TnT (>0.014 mg/L) were excluded from the analysis, as well as patients who were lost to follow-up (FU).

Patients could be included multiple times in the registry, either for a reattempt of the same CTO lesion, a secondary CTO lesion treated at a later stage in time or a second CTO lesion treated during the same procedure. In all cases, treatment of the first CTO lesion was considered as the index procedure. For each patient, the FU period was counted from the index procedure date onwards.

Endpoints

The primary study endpoint was the incidence of major adverse cardiac and cerebrovascular events (MACCE) at 1-year post-PCI, defined as all-cause death, myocardial infarction (MI), target vessel failure (TVF), clinically driven target vessel revascularisation (TVR) (via PCI or bypass graft surgery) and stroke (including transient ischaemic attacks and cerebrovascular accidents). In-hospital adverse events were not included. Bypass graft surgery during FU was defined as TVF and revascularisation. MI at FU was defined according to the fourth universal definition of MI.[15]

The secondary endpoint was all-cause mortality at 1-year FU.

Statistical analysis

Baseline, angiographic and procedural data were analysed using descriptive statistics. Numerical values were expressed as mean±SD or median (IQR) as appropriate. Categorical variables were expressed as percentages. Normality was assessed using the Shapiro-Wilk statistic. Comparisons between groups were performed using Pearson's χ^2 tests for categorical variables and the independent Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. The Kaplan-Meier method was used to construct survival curves, with the log-rank test used for comparison between groups. Statistical significance was always set at a two-tailed probability

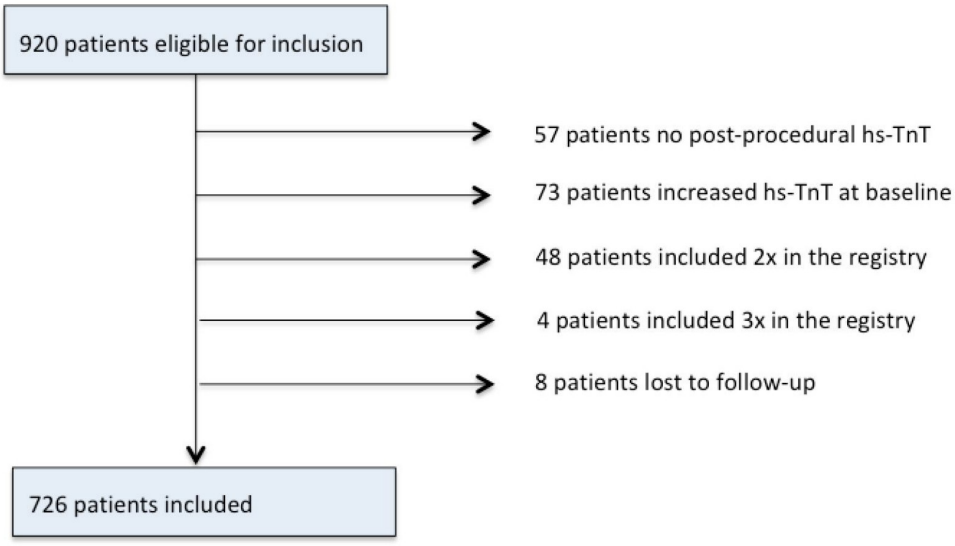

Figure 1 Flowchart inclusions. Hs-TnT, high-sensitive troponin T.

level of <0.05. All statistical analyses were carried out using SPSS Statistics V.28.

RESULTS

A total of 920 patients undergoing a CTO procedure between September 2011 and April 2020 were prospectively screened for inclusion. In total, 194 patients were excluded: 57 patients had no postprocedural hs-TnT available, 73 patients had increased baseline hs-TnT levels, 8 patients had 2 procedures and 4 patients had 3 consecutive procedures. A further 8 patients were lost to FU (figure 1). A total of 726 patients were included in this analysis of whom 471 patients had <5 times the ULN hs-TnT levels, 255 patients were included in the ≥5 times the ULN group, 109 patients in the ≥35 ULN group and 12 patients in the ≥70 times the ULN group. The ≥70 times the ULN group was too small for analysis and subsequent interpretation. These data have been added under online supplementals (online supplemental tables 2 and 3).

Baseline characteristics

The majority of patients included were men (85%). Hs-TnT was elevated a least 5 times the ULN in 35% of our study population. The mean age was 65±8 years in the group without elevation of postprocedural hs-TnT, compared with 69±7 years if hs-TnT was elevated≥5 times the ULN (p<0.001). Patients who had elevated hs-TnT levels≥5 times the ULN more frequently had hypertension (p<0.001) and prior cardiovascular disease including previous coronary artery bypass graft (CABG) (p<0.001), stroke (p<0.001) and peripheral vascular disease (p<0.001).

In this cohort, left ventricular ejection fraction and chronic kidney disease did not affect postprocedural hs-TnT levels (p=0.065 and p=0.746, respectively) (table 1).

Similar results were found for the group with increased hs-TnT≥35 times the ULN (table 2).

MACCE and mortality

The primary composite endpoint of MACCE at 12 months was observed in 8.3% of the study patients. Patients with periprocedural myocardial injury had significantly higher rates of MACCE (p=0.001 for ≥5 times the ULN; p=0.007 for ≥35 times the ULN) (figures 2 and 3).

In the ≥35 times ULN group, the significant difference in MACCE was driven by spontaneous MI (p=0.016). Although there were trends for TVF and target vessel revascularisation (TVR), there was no clear driving force behind MACCE for the ≥5 times the ULN group (figure 2).

The rate of all-cause death was significantly higher in both ≥5 times the ULN and≥35 times the ULN groups (p=0.009; p=0.021, respectively) compared with unelevated hs-TnT (figures 2 and 4).

Patients with failed procedures had more MACCE at 1-year FU compared with those with a successful procedure (p=<0.001) (online supplemental table 1).

Procedural characteristics and biochemical measurements

Treatment of a CTO located in the right coronary artery was associated with higher levels of hs-TnT (p=0.033 when comparing normal hs-TnT levels to ≥5 times the ULN elevated hs-TnT levels) (table 3). In contrast, treatment of a CTO of the circumflex artery more often resulted in lower hs-TnT levels compared with hs-TnT≥5 times the and ≥35 times the ULN groups (p=0.045, p=0.014) (tables 3 and 4).

Patients with increased hs-TnT had more complex lesions (higher J-CTO Score p<0.001; stent length>48 mm, p<0.001 and longer procedure time p<0.001).

CTO technical and procedural success rates were lower in the ≥5 times the ULN group compared with the non-elevated hs-TnT group (p=0.017; p<0.001) (table 1).

Table 1 Baseline characteristics and procedural parameters according to postprocedural high-sensitive troponin T (≥5 times the ULN)

Variable	No elevation (n=471)	Elevated≥5 times the ULN (n=255)	P value
Age (years)	65 (57–73)	69 (61–76)	**<0.001**
Male	405 (86)	214 (84)	0.454
Current smoker	110 (23)	51 (20)	0.299
Hypertension	307 (65)	199 (78)	**<0.001**
Dyslipidaemia	391 (83)	224 (88)	**0.084**
Diabetes mellitus	127 (27)	74 (29)	0.555
Previous myocardial infarction	167 (36)	91 (36)	0.951
Previous coronary artery bypass graft	49 (10)	49 (19)	**<0.001**
Previous percutaneous coronary intervention	203 (43)	124 (49)	0.153
Previous stroke	20 (4)	28 (11)	**<0.001**
Peripheral vascular disease	75 (16)	77 (30)	**<0.001**
Chronic kidney disease	98 (21)	69 (27)	0.065
Stable angina	295 (63)	177 (70)	0.073
Multivessel disease	238 (55)	145 (58)	0.441
Left ventricular ejection fraction			0.746
<35%	34 (7)	19 (8)	
35–59%	143 (31)	71 (28)	
≥60%	282 (61)	160 (64)	
In-stent occlusion	42 (9)	23 (9)	0.970
J-CTO Score	1.72±1.25	2.17±1.10	**<0.001**
J-CTO Score (class)			**<0.001**
Easy (0)	90 (19)	17 (7)	
Intermediate (1)	125 (27)	48 (19)	
Difficult (2)	133 (28)	97 (38)	
Very difficult (≥3)	123 (26)	93 (37)	
CTO length>20 mm	226 (48)	150 (59)	**0.006**

Values expressed as median (IQR), mean (SD) or n (%). P-value <0.05 was considered statitistically significant.
J-CTO, Japanese chronic total occlusion; ULN, upper limit of normal.

Table 2 Baseline characteristics and procedural parameters according to postprocedural high-sensitive troponin T (≥35 times the ULN)

Variable	No elevation (n=471)	Elevated≥35 times the ULN (n=109)	P value
Age (years)	65 (57–73)	70 (62–77)	**<0.001**
Male	405 (86)	90 (83)	0.363
Current smoker	110 (23)	26 (24)	0.912
Hypertension	307 (65)	88 (81)	**0.002**
Dyslipidaemia	391 (83)	88 (81)	0.571
Diabetes mellitus	127 (27)	32 (29)	0.614
Previous myocardial infarction	167 (36)	41 (38)	0.672
Previous coronary artery bypass graft (CABG)	49 (10)	20 (18)	**0.021**
Previous percutaneous coronary intervention	203 (43)	58 (53)	0.056
Previous stroke	20 (4)	13 (12)	**0.002**
Peripheral vascular disease	75 (16)	38 (35)	**<0.001**
Chronic kidney disease	98 (21)	31 (28)	0.102
Stable angina	295 (63)	73 (68)	0.374
Multivessel disease	238 (55)	61 (58)	0.563
Left Ventricular ejection fraction (LVEF)			0.818
<35%	34 (7)	10 (9)	
35–59%	143 (31)	34 (31)	
≥60%	282 (61)	65 (60)	
In-stent occlusion	42 (9)	11 (10)	0.706
J-CTO Score	1.72±1.25	2.17±1.14	**<0.001**
J-CTO Score (class)			**<0.001**
Easy (0)	90 (19)	10 (9)	
Intermediate (1)	125 (27)	16 (15)	
Difficult (2)	133 (28)	44 (40)	
Very difficult (≥3)	123 (26)	39 (36)	
CTO length>20 mm	226 (48)	62 (57)	0.098

Values expressed as median (IQR), mean (SD) or n (%). P-value < 0.05 was considered statitistically significant.
J-CTO, Japanese chronic total occlusion; ULN, upper limit of normal.

Retrograde crossing techniques were more often associated with increased hs-TnT levels, whereas antegrade wire escalation (AWE) was the most frequently used technique in the group with unelevated hs-TnT (71% vs 46%) (online supplemental table 1).

Successful strategy

AWE was the most commonly used crossing technique in our study population (62%) and had similar MACCE rates compared with the other crossing techniques combined (antegrade dissection re-entry, retrograde wire escalation and retrograde dissection re-entry) (p=0.158). In addition, there was no significant difference in survival between AWE and the other techniques combined (p=0.160) (online supplemental table 1).

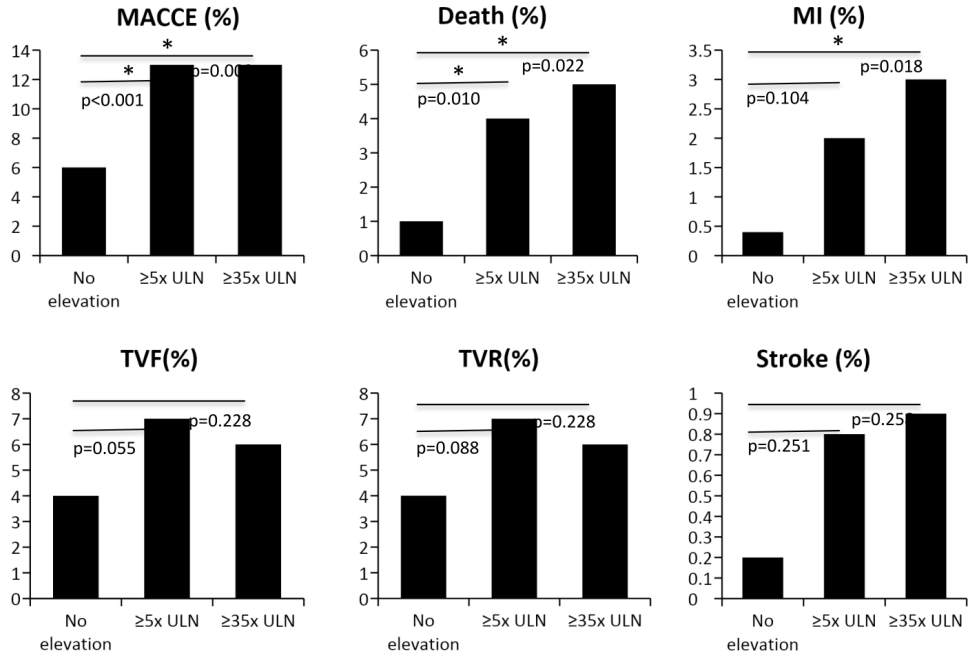

Figure 2 (Central illustration): Clinical outcome at 1-year follow-up according to postprocedural high-sensitive troponin T values. Values expressed as %. MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; TVF, target vessel failure; TVR, target vessel revascularisation; ULN, upper limit of normal.

DISCUSSION

In the current study, we show that in a prospective cohort of patients undergoing CTO PCI, patients with periprocedural myocardial injury were at increased risk of MACCE at FU. Depending on the cut-off levels of hs-TnT, periprocedural myocardial injury was associated with the combined endpoint and all-cause mortality (both ≥5 times the ULN and ≥35 times the ULN group) and spontaneous MI at FU (≥35 times the ULN group only). We excluded patients with increased baseline levels of hs-TnT, as increased levels of hs-TnT levels according to our used cut-off, would not reflect myocardial injury in this patient group.

According to the definition of myocardial injury after CTO PCI used in our study (hs-TnT≥5 times the ULN), the incidence of periprocedural myocardial injury was 35%.[11]

This is slightly higher than in previous studies; however, they did not adhere to the definition of periprocedural myocardial injury used for our current study and

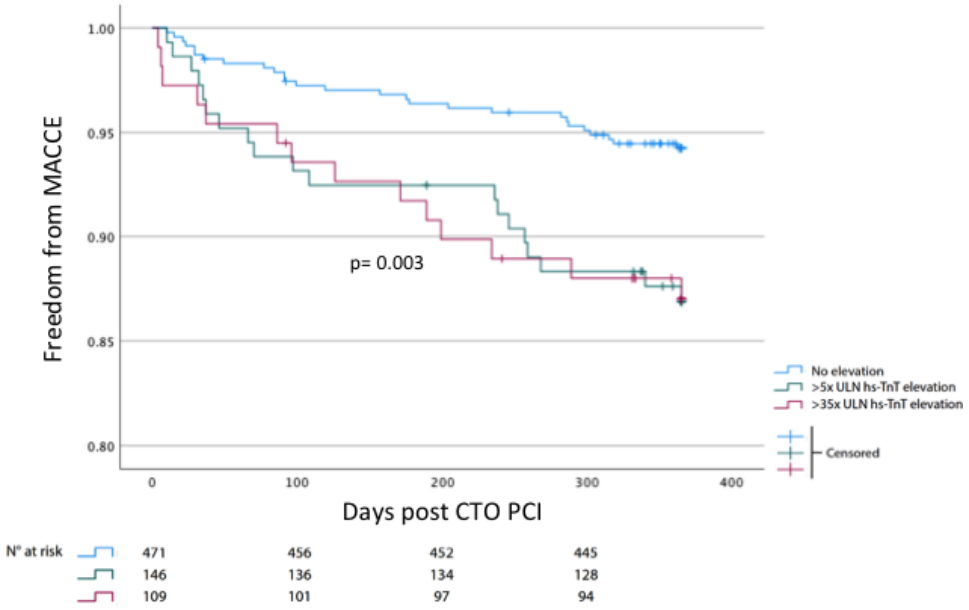

Figure 3 Kaplan-Meier curves for major adverse cardiac and cerebrovascular events (MACCE) according to postprocedural high-sensitive troponin T (hs-TnT) values. No elevation (blue line), hs-TnT≥5 times the upper limit of normal (ULN) (green line) and hs-TnT≥35 times the ULN (red line). CTO, chronic total occlusion; PCI, percutaneous coronary intervention.

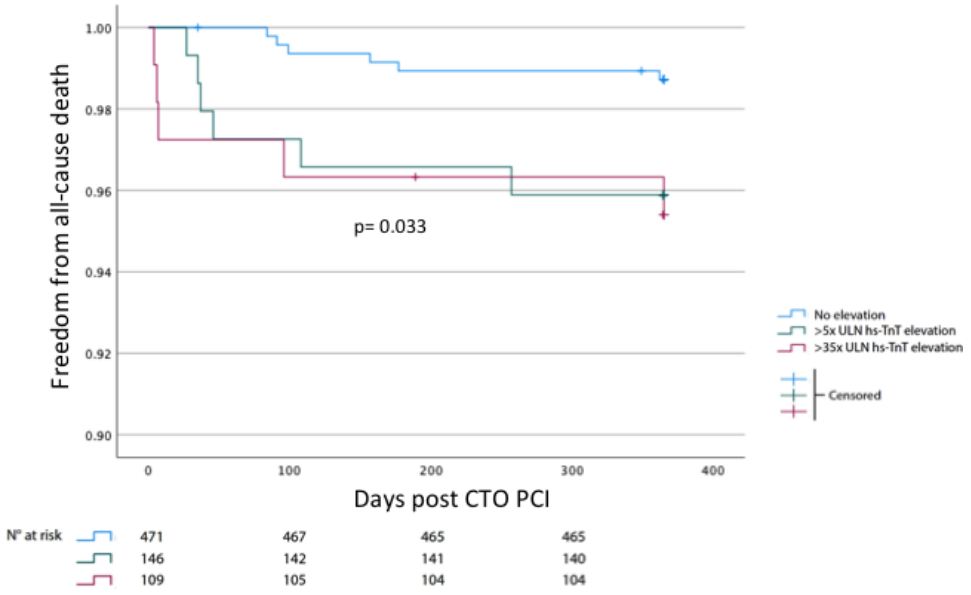

Figure 4 Kaplan-Meier curves for all-cause death according to postprocedural hs-TnT values. No elevation (blue line), hs-TnT≥5 x upper limit of normal (ULN) (green line) and hs-TnT≥35 x ULN (red line).

frequently creatine kinase-MB was used as marker for periprocedural myocardial injury as opposed to hs-TnT, which has a higher sensitivity.[16–19] A previous study from our research group showed a similar event rate of hs-TnT elevation.[20] In order to diagnose MI the addition of supportive criteria including ECG, ultrasound and angiography is needed; however, our data do not allow for the systematic diagnosis of MI in our patient group.[15]

Contrary to some previous reports, we found no significant difference in MACCE between AWE and other crossing techniques combined, which could be explained by technical advances and improvement of material over the previous years and would imply that more complex strategies are safe and do not result in worse outcome.[17 21]

Table 3 Procedural characteristics according to postprocedural high-sensitive troponin T (≥5 times the ULN)

Variable	No elevation (n=471)	Elevated≥5 time the ULN (n=255)	P value
Chronic total occlusion target vessel			
Right coronary artery	255 (54)	159 (62)	**0.033**
Left anterior descending artery	129 (27)	64 (25)	0.505
Circumflex artery	84 (18)	31 (12)	**0.045**
Left main coronary artery	3 (0.6)	1 (0.4)	0.671
Stent length>48 mm	212 (55)	146 (75)	**<0.001**
Procedure time (min)	75 (45–101)	109 (73–134)	**<0.001**
Fluoroscopy time (min)	24 (15–37)	41 (25–60)	**<0.001**
Technical success	383 (81)	188 (74)	**0.017**
Procedural success without major complications	379 (81)	172 (68)	**<0.001**
Major complications	12 (3)	33 (13)	**<0.001**
Major vascular complications	4 (0.8)	5 (2)	0.196

Values expressed as median (IQR) or n (%).P-value < 0.05 was considered statitistically significant.
ULN, upper limit of normal.

Table 4 Procedural characteristics according to postprocedural high-sensitive troponin T (≥35 times the upper limit of normal)

Variable	No elevation (n=471)	Elevated≥35 times the ULN (n=109)	P value
Chronic total occlusion target vessel			
Right coronary artery	255 (54)	68 (62)	0.118
Left anterior descending artery	129 (27)	32 (29)	0.679
Circumflex artery	84 (18)	9 (8)	**0.014**
Left main coronary artery	3 (0.6)	0 (0.0)	0.403
Stenting performed	384 (82)	82 (75)	0.136
Stent length>48 mm	212 (55)	60 (72)	**0.004**
Procedure time (min)	75 (45–101)	111 (83–139)	**<0.001**
Fluoroscopy time (min)	24 (15–37)	44 (27–65)	**<0.001**
Technical success	383 (81)	79 (73)	**0.039**
Procedural success without major complications	379 (81)	65 (60)	**<0.001**
Major complications	12 (3)	24 (22)	**<0.001**
Major vascular complications	4 (0.8)	3 (3)	0.101

Values expressed as median (IQR) or n (%). P-value < 0.05 was considered statitistically significant.

It has recently been shown that procedural success rates indeed improved over time in this study population with the introduction of more contemporary strategies.[22]

MACCE was observed in 8.3% of our study population. This is lower than the 16.7% MACCE at 1-year FU found in the OPEN (Outcomes, Patient Health Status,and Efficiency in Chronic Total Occlusion HybridProcedure)-CTO registry.[21] This discrepancy could be explained by the high percentage of retrograde procedures in the OPEN-CTO registry, as well as inclusion of in-hospital MACCE and mortality in the registry. It is important to note that the MACCE we report here is postdischarge MACCE, suggesting that after discharge the used crossing technique does not determine outcome.

The cause of increased hs-TnT levels and indirectly increased MACCE after CTO PCI is unknown. We show that it is associated with increased prior cardiovascular burden (prior CABG, stroke and peripheral artery disease) but also with perceived anatomical complexity of the CTO lesion (high J-CTO Score). Furthermore, there was no procedural documentation of loss of a side branch, dissection or distal embolisation, though the long-term effects of such periprocedural events on the development of heart failure or arrhythmias remain unknown.

Our posthospital event rate is relatively low, with a comparable rate of TVR to the CONSISTENT (Conventional Antegrade Versus Sub-Intimal Synergy Stenting in Chronic Total Occlusions) CTO Study.[23] It is, however, of note that routine coronary angiography was not performed during FU, potentially missing TVF in asymptomatic patients.

Contrary to the left anterior descending artery, treatment of the right coronary artery was associated with hs-TnT elevation, which has previously been shown in other studies.[24] This association might be caused by the more frequent compromise of the right ventricular branch during the procedure.

It has previously been reported that unsuccessful procedures are associated with higher MACCE rates, which is in accordance with the findings of this study.[25]

The Kaplan-Meier curves for death in relation to hs-TnT level show that most events take place in the first month, after which the curves run mostly in parallel. Since the cause of death was unknown for most cases, it is impossible to elaborate on whether unsuccessful CTO PCI procedures were in any way related to the cause of death.

To our knowledge, this is the first study to show that elevation of postprocedural hs-TnT, as defined by recent guidelines, is associated with increased incidence of MACCE and all-cause death at 12-month FU.

It remains to be discussed how and if this knowledge will influence our daily practice concerning CTO PCI. Further studies are needed to elucidate whether patients with increased postprocedural hsTnT would benefit from a different in-hospital and outpatient FU compared with patients with normal postprocedural hsTnT levels.

STUDY LIMITATIONS

The number of patients in the ≥35 times ULN elevated hs-TnT subgroup is relatively small and therefore might lack in statistic power. The number of patients in the ≥70 times ULN subgroup is too small for analysis, therefore we have included this analysis in the supplements (online supplemental tables 2 and 3).

In 57 patients, there was no postprocedural hsTnT measurement and these patients were excluded from the analysis. This could lead to a selection bias. In addition, patients with elevated hs-TnT levels (>0.014 mg/L) at baseline were excluded from analysis.

Unfortunately, data on the CTO techniques preceding the final strategy was not available.

The inclusion period comprises 8.5 years, during which operator experience increased over time and CTO techniques shifted from antegrade wiring only to more complex antegrade and retrograde techniques.

Our registry did not report on the cause of increased hs-TnT. For instance, loss of side branch, distal embolisation and the reason for an unsuccessful procedure were not documented. In addition, in the case of death during FU, the cause of death was not documented.

The majority of patients in this study were men; however, this is reflected in general CTO PCI populations described elsewhere.

Finally, the FU period was 1 year, potentially missing longer-term events.

CONCLUSION

In patients undergoing CTO PCI, periprocedural myocardial injury, defined by an increase in hs-TnT, was associated with a significantly higher rate of MACCE and all-cause mortality between hospital discharge and 12-month FU.

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Contributors JB and JD conceived and designed the study. EP, MV, DvdB, DC, KA, PL and KM collected, analysed and interpreted the data. EP, MV, DvdB, JB and JD drafted and critically revised the manuscript. JB and JD supervised the study. JD is responsible for the overall content and serves as a guarantor. All authors read and approved the final manuscript.

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Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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