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Impact of Chronic Total Occlusion and Revascularization Strategy in Patients with Infarct-Related Cardiogenic Shock

A Subanalysis of the CULPRIT-SHOCK trial

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Short title: CTO in infarct-related cardiogenic shock

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ABSTRACT

Background The impact of coronary artery chronic total occlusion (CTO) and its management with percutaneous coronary intervention (PCI) in the setting of myocardial infarction (MI) related cardiogenic shock (CS) remains unclear.

Methods This is a pre-specified analysis from the The Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial which randomized patients presenting with MI and multivessel disease complicated by CS to a culprit-lesion-only or immediate multivessel PCI strategy. CTO was defined by central core-laboratory evaluation. The independent associations between the presence of CTO and adverse outcomes at 30 days and one year were assessed using multivariate logistics models.

Results A non-infarct related CTO was present in 157/667 (23.5%) analyzed patients. Patients presenting with CTO had more frequent diabetes mellitus or prior PCI but less frequently presented with ST segment elevation MI as index event. The presence of CTO was associated with higher rate of death at 30 days (adjusted Odds ratio [aOR] 1.63; 95% confidence interval [CI] 1.01-2.60). Rate of death at one year was also increased but did not reach statistical significance (aOR 1.62; 95%CI 0.99-2.66). Compare to immediate multivessel PCI, a strategy of culprit-lesion-only PCI was associated with lower rates of death or renal replacement therapy at 30 days in patients with and without CTO (OR 0.79 95%CI 0.42-1.49 and OR 0.67 95%CI 0.48-0.96, respectively), without significant interaction (p= 0.68).

Conclusion In patients with MI-related CS and multivessel disease, the presence of CTO is associated with adverse outcomes while a strategy of culprit-lesion-only PCI seems beneficial regardless of the presence of CTO.

Key words coronary artery chronic total occlusion; percutaneous coronary intervention; myocardial infarction; cardiogenic shock

INTRODUCTION

Chronic total occlusion (CTO) of a coronary artery is a common finding in patients undergoing coronary angiography for coronary artery disease (1,2). There is a large body of evidence linking the presence of CTO with adverse early and late outcomes, particularly in the setting of an acute myocardial infarction (2–4). Consistently, in the context of the life-threatening situation that is myocardial infarction related cardiogenic shock (CS), the presence of non-infarct related artery CTO may also be burdened with poor prognosis (5–8). The role of percutaneous coronary intervention in the management of CTO remains debated, with only limited data from randomized controlled trials (RCT) (9). Particularly, there is a dearth of data regarding the impact of immediate PCI of non-infarct related CTO in the setting of myocardial infarction complicated by CS. In fact, randomized controlled trials evaluating the role of PCI for the treatment of CTO have excluded patients with either recent acute coronary events (10–13) or sustained hemodynamic instability (14). Non-infarct related CTO PCI could reduce the overall ischemic burden, thus improving the ventricular systolic function and cardiac output. However, CTO PCI may also be associated with increased intervention length, use of greater contrast media volume and procedural complications, even when performed by experienced operators (15). Our aim was to investigate the outcomes associated with the presence of non-infarct related CTO and the performance of culprit-lesion-only or immediate multivessel PCI according to the presence of non-infarct related CTO in patients randomized in the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial.

METHODS

The design and results of the CULPRIT-SHOCK trial have been previously described (16–22). Briefly, the CULPRIT-SHOCK trial was an investigator-initiated, international, multicenter, open-label study where patients presenting with acute myocardial infarction and multivessel coronary artery disease complicated by CS were randomized, in a 1:1 ratio, to a strategy of culprit-lesion-only PCI (with optional staged revascularization) or immediate multivessel PCI. Inclusion and exclusion criteria are detailed in the Online Table 1. Cardiogenic shock was defined by the association of prolonged low systolic blood pressure <90mmHg or need for catecholamine, signs of pulmonary congestion and impaired organ perfusion. In all patients, the culprit lesion was treated first with the use of standard PCI techniques and with the recommended use of drug-eluting stents. In the culprit-lesion-only PCI group, staged revascularization was performed according to the patient clinical status and the presence of residual ischemia (evaluated by means of noninvasive testing or with the use of fractional flow reserve [FFR]), symptoms, and clinical and neurologic status. In the immediate multivessel PCI group any >70% stenosis of major coronary arteries (i.e. ≥2 mm diameter) was recommended to be treated with immediate PCI following the treatment of the culprit lesion with a recommended maximum dose of contrast material of 300 mL. This also included reasonable efforts to recanalize CTO in the acute phase, although operators were advised against excessive revascularization attempts(23). The indication for other therapy, including the use of mechanical circulatory support, was left to the discretion of the local physician, in accordance with generally accepted intensive care guidelines. The investigation was approved by the ethic committee or institutional review board of each participating center and written informed consent was obtained with the use of a prespecified process that varied slightly according to the country (16).

Study populations and objective. CTO was defined as the presence of at least one major non-IRA with complete obstruction with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 for presumably more than 3 months, as blindly evaluated by two experienced readers in the ACTION (Allies in Cardiovascular Trials, Initiatives and Organized Networks) angiographic Core laboratory (Institut de Cardiologie, Pitié-Salpêtrière Hospital). In case of disagreement between readers, a third reader was requested to reach consensus. Our objective was to evaluate the impact of the presence of non-infarct related CTO on early and late outcomes and the respective performance of culprit-lesion-only PCI and immediate multivessel PCI in patients with or without CTO. Outcomes of interest were the composite of all-cause death or severe renal failure leading to renal-replacement therapy and all-cause death within 30 days and within one year of randomization. Events were defined as previously reported and adjudicated by an independent clinical event committee (16,17,23). For the purpose of this prespecified analysis, procedural success in a CTO was defined as the achievement of TIMI flow grade 3 at the end of the procedure. Specific follow-up was performed at 30 days, 6 months and one year by means of structured telephone interviews, with any potential endpoint events verified by review of original records. Death registries were searched to identify or confirm all deaths. The CULPRIT-SHOCK trial was supported by a grant agreement (602202) from the European Union Seventh Framework Program and by the German Heart Research Foundation and the German Cardiac Society. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the papers and its final contents.

Statistical analysis. Categorical variables were described as proportion and compared with Chi-square test or Fisher's exact test. Continuous variables were described as median (Q1; Q3) and compared using Wilcoxon rank-sum test. As previously published, event rates were compared using Chi-square test (16,17). Kaplan-Meier curves were also used to show event

rates over time with classification according to the presence of non-infarct related CTO and compared using log-rank test. Patients without event were censored at 30 days or one year (for renal replacement therapy, deceased patients without event were censored at the date of death). Multivariate logistic regression models were used to evaluate the independent association between the presence of non-infarct related CTO and outcomes. For each outcome, non-infarct related CTO was adjusted on baseline clinical and procedural characteristics possibly associated with the outcome in univariate analysis ($p<0.2$) (**Online Table 2** and **3**). In sensitivity analyses, the independent association of the presence of CTO on outcomes was adjusted on consistent covariates as well as the effective revascularization strategy undergone by the patients to account for crossovers among the groups of randomization. Results are presented as adjusted odd ratios with 95% confidence intervals (CI). A p-value <0.05 was considered significant unless otherwise specified. All statistical analyses were performed with SAS release 9.4 (SAS Institute Inc, Cary, NC) statistical software package.

RESULTS

Baseline and procedural characteristics. Of the 686 randomized patients with available informed consent, a total of 667 (97.2%) patients with available central core laboratory evaluation were included in this analysis, of whom 157 (23.5%; 95%CI 20.5%-26.9%) presented with at least one non-infarct related CTO. More than one CTO was present in 23 (14.6%) of these patients. The right coronary artery was the most frequent localization for CTO (**Online Table 4**). Patients presenting with at least one non-infarct related CTO had more frequent diabetes mellitus or prior PCI, but less frequently presented with ST segment elevation MI (STEMI) in the index event (**Table 1**). Length of the procedure, as estimated by the total duration of fluoroscopy was significantly increased in patients with CTO (**Table 2**). Among patients randomized to the immediate multivessel PCI strategy, an immediate procedural success in all CTO lesions was achieved in 13 of 78 (16.7%; 95%CI 10.0%-26.5%) patients. Staged CTO procedure was performed with 5 patients, with a procedural success in 3/5 (60%) cases.

Association of CTO with outcomes. Early and late outcomes according to the presence of non-infarct related CTO is detailed in **Table 3**. In univariate analysis, the presence of at least one non-infarct related CTO was associated with a significant increase of all-cause mortality or renal replacement therapy and all-cause mortality at 30 days and one year (**Figure 1**). There was no significant difference in the rate of renal replacement therapy at 30 days between patients with or without CTO (17.2% versus 12.7%, p=0.16). There was no significant difference regarding adverse outcomes among patients with only 1 non-infarct related CTO compared to patients with 2 or more non-infarct related CTO (**Online Table 5**). Among patients randomized to an immediate multivessel PCI strategy, procedural success in all CTO lesions was not significantly associated with early or late adverse outcomes (**Online Table 6**). After adjustment on baseline and procedural characteristics, the presence of at least

one non-infarct related CTO remained significantly associated with an increased risk of all-cause death at 30 days. Rates of all-cause death and all-cause death or renal replacement therapy at one year were also numerically increased in the presence of non-infarcted CTO but the difference was not statistically significant. Results remained consistent in a sensitivity analysis adjusted on the effective revascularization strategy performed (**Online Table 7**).

Impact of revascularization strategy in patients with or without CTO. Overall, a strategy of culprit-lesion-only PCI remained associated with lower rates of all-cause death or renal replacement therapy and all-cause death at 30 days and this effect was consistent in patients with and without non-infarct related CTO (p interaction = 0.68 and 0.52, respectively) compared to a strategy of immediate multivessel PCI (**Online Table 8** and **Figure 2**). With respect to one-year outcomes, however, there was no statistically significant difference between the two revascularization strategies in patients presenting with or without non-infarcted CTO.

DISCUSSION

The main results of the present study are as follows: a non-infarct related CTO was present in roughly a quarter of patients with acute myocardial infarction and multivessel coronary disease complicated by CS and was an independent risk factor of early death. Compared to immediate multivessel PCI, a strategy of culprit-lesion-only PCI was associated with lower rates of early all-cause death or renal replacement therapy and all-cause death in patients with and without non-infarct related CTO, without significant interaction.

The prevalence of non-infarct related CTO in this study is consistent to previous reports evaluating the impact of CTO in patients presenting with CS (6–8). This prevalence may be higher to what is more frequently reported in the general population of patients with coronary artery disease (2). In fact, the presence of CTO has been previously described as a strong risk factor for myocardial infarction related CS at admission (7). Patients presenting with both acute myocardial infarction and non-infarct related CTO may be exposed to a so-called "double jeopardy", as the CTO may prevent any collateral blood supply to the acutely infarcted myocardium, while the abrupt coronary occlusion may compromise any previously developed collateral circulation resulting in further myocardial injury (15).

In the current study, the presence of non-infarct related CTO was independently associated with all-cause death at 30 days and a strong trend for 1-year death. There exists only limited data on the impact of the presence of CTO in patients presenting with myocardial infarction related CS, with most from retrospective analyses of observational registries (6,7). To the knowledge of the authors, the only available data from a randomized study came from a post-hoc analysis of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial, which also reported CTO to be an independent risk factor of long-term mortality following

myocardial infarction related CS (24). Of note, this study did not evaluate the impact of the coronary revascularization strategy according to the presence of CTO.

Another interesting finding of the present study is the absence of significant association between non-infarct related CTO and the occurrence of renal replacement therapy. It has been previously hypothesized that CTO PCI may be associated with increased risk of kidney injury, mainly because of higher use of contrast media, which may lead to contrast-induced nephropathy (9,25). Although the amount of contrast media was numerically higher in patients with CTO, the difference did not reach statistical significance, most likely because a limited maximal dose of contrast media was recommended in the protocol. This may partly explain the absence of significant increase of the risk of renal replacement therapy; another explanation may be the relatively low number of patients with CTO. Of note, our results are consistent with prior observational studies which did not report a significant increased risk of contrast induced nephropathy associated with CTO PCI (26).

There are only scarce dedicated RCTs comparing revascularization to conservative management of CTO (27). None has found CTO revascularization to be significantly associated with a reduction of hard clinical endpoints such as mortality or myocardial infarction, albeit a lower rate of repeat revascularization has seldom been reported (10–14). To the knowledge of the authors, the Evaluating Xience and left ventricular function in PCI on occlusiOns after STEMI (EXPLORE) was the only randomized controlled trial evaluating the performance of additional PCI of CTO in patients presenting with STEMI(14). This trial, powered for MRI evaluated parameters, reported also an increased one year rate of freedom from angina but no significant reduction of major adverse cardiac events (28). Moreover, in the EXPLORE trial, CTO PCI were performed within 7 days of the index STEMI, with a superior rate of procedural success compared to the results of immediate CTO PCI in the present study. CTO PCI is a complex intervention with a procedural success rate highly

dependent on operators skills and the availability of dedicated equipment while there exists an increased risk of periprocedural complications such as coronary perforation (29,30). As a consequence, current guidelines do not support systematic invasive management of CTO but rather limit indications to cases of patients with angina resistant to medical therapy or large documented ischemia in the corresponding territory (9,31). Obviously, the recommendations do not deal with emergency chronic CTO revascularization in shock patients. The absence of significant interaction in the present analysis suggests a consistent benefit of the culprit-lesion-only PCI strategy compared to an immediate multivessel PCI strategy in patients with or without non-infarct related CTO. In patients without any non-infarct related CTO the less invasive strategy was associated with a significant reduction of 30-day adverse outcomes. In patients with non-infarct related CTO a culprit-lesion-only PCI was also associated with numerically lower rates of adverse outcomes, although without reaching statistical significance, possibly because of insufficient statistical power in this population.

We acknowledge several limitations. This is a substudy of a randomized trial, and our results should only be considered as hypothesis-generating. Overall, the number of patients presenting with a least one non-infarct related CTO was limited, potentially leading to underpowered analysis and larger studies remain necessary to better comprehend the impact of CTO in patients with cardiogenic shock and multivessel disease. In particular, there is insufficient power to evaluate the impact of successful CTO recanalization on outcomes in the present analysis. The level of expertise of participating operators in the percutaneous management of CTO, the type of dedicated equipment or revascularization strategy (i.e. retrograde or anterograde approach) used in each case were not routinely collected, while specific angiographic risk scores were not prospectively evaluated(29,32). The timing of implantation of mechanical circulatory support compared to CTO procedure was not collected nor was the occurrence of specific complications of CTO procedures such as coronary

perforation or cardiac tamponade. Post-PCI residual stenosis was not evaluated and therefore not included in the definition of procedural success. The management of chronic CTO PCI is not optimal in the context of emergency and shock, and all technical possibilities may have not been used for CTO revascularization in our population, with only limited time likely dedicated for each attempt. This can at least partly explain the low success rate of immediate CTO PCI in this study. Of note, recent consensus statements have advised against performing CTO procedures in acute setting(9,31,33).

CONCLUSION

In patients with myocardial infarction related CS and multivessel disease, the presence of CTO is associated with more adverse outcomes while a strategy of culprit-lesion-only PCI seems beneficial in patients with or without CTO.

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FIGURE TITLE AND LEGENDS

Figure 1. Kaplan Meier curves of early and late outcomes according to the presence of CTO.

CTO: Chronic total occlusion; No: Number

Figure 2. Performance of culprit-lesion-only PCI and immediate multivessel PCI according to the presence of CTO.

PCI: Percutaneous coronary intervention; CTO: Chronic total occlusion; OR: Odds ratio; CI: Confidence interval

Table 1. Baseline characteristics

	Total (n=667)	CTO (n=157)	No CTO (n=510)	p-value
Age, years	70.0 [60.0-78.0]	71.0 [61.0-78.0]	69.0 [60.0-78.0]	0.50
Male sex	510/667 (76.5%)	127/157 (80.9%)	383/ 510 (75.1%)	0.14
Body mass index, kg/m²	26.6 [24.5-29.4]	27.6 [24.7-29.8]	26.4 [24.2-29.4]	0.09
Cardiovascular risk factors				
Current smoking	172/642 (26.8%)	39/153 (25.5%)	133/489 (27.2%)	0.68
Hypertension	394/655 (60.2%)	102/153 (66.7%)	292/502 (58.2%)	0.06
Hypercholesterolemia	222/652 (34.0%)	55/153 (35.9%)	167/499 (33.5%)	0.57
Diabetes mellitus	211/653 (32.3%)	66/154 (42.9%)	145/499 (29.1%)	0.001
Prior myocardial infarction	110/655 (16.8%)	33/154 (21.4%)	77/501 (15.4%)	0.08
Prior stroke	47/658 (7.1%)	16/155 (10.3%)	31/503 (6.2%)	0.08
Prior peripheral artery disease	78/659 (11.8%)	24/155 (15.5%)	54/504 (10.7%)	0.11
Prior chronic kidney disease	46/657 (7.0%)	12/154 (7.8%)	34/503 (6.8%)	0.66
Prior percutaneous coronary intervention	124/655 (18.9%)	39/154 (25.3%)	85/501 (17.0%)	0.02
Prior coronary artery bypass graft	33/659 (5.0%)	23/155 (14.8%)	10/504 (2.0%)	<0.001
Resuscitation before randomization	354/665 (53.2%)	91/156 (58.3%)	263/509 (51.7%)	0.14
Fibrinolysis <24 h before randomization	32/664 (4.8%)	9/156 (5.8%)	23/508 (4.5%)	0.53
ST-segment elevation myocardial infarction	407/647 (62.9%)	79/152 (52.0%)	328/495 (66.3%)	0.001
Anterior ST-segment elevation myocardial infarction	217/403 (53.8%)	42/78 (53.8%)	175/325 (53.8%)	1.00
Left bundle branch block	95/648 (14.7%)	26/153 (17.0%)	69/495 (13.9%)	0.35
Heart rate, beats/min	91.0 (72.0-108.0)	93.0 (75.0-110.0)	90.0 (72.0-107.0)	0.30
Systolic blood pressure, mmHg	100.0 (85.0-125.0)	103.5 (85-125.5)	100.0 (85.0-125.0)	0.81
Diastolic blood pressure, mmHg	61.0 (50.0-80.0)	64.0 (50.0-80.0)	60.0 (50.0-78.0)	0.52
Mean blood pressure, mmHg	76.2 (63.3-93.3)	78.0 (63.3-95.7)	75.7 (63.3-92.3)	0.69
Arterial lactate >2.0 mmol/L	429/647 (66.3%)	105/151 (69.5%)	324/496 (65.3%)	0.34
Number of affected vessels				<0.001
1	5/667 (0.7%)	0	5/510 (1.0%)	

2	238/667 (35.7%)	19/157 (12.1%)	219/510 (42.9%)	
3	424/667 (63.6%)	138/157 (87.9%)	286/510 (56.1%)	
Vessel related to the infarction*				<0.001
Left anterior descending artery	278/667 (41.7%)	67/157 (42.7%)	211/510 (41.4%)	
Left circumflex artery	140/667 (21.0%)	38/157 (24.2%)	102/ 510 (20.0%)	
Right coronary artery	182/667 (27.3%)	29/157 (18.5%)	153/510 (30.0%)	
Left main artery	60/667 (9.0%)	16/157 (10.2%)	44/510 (8.6%)	
Bypass graft	7/167 (1.0%)	7/157 (4.5%)	0	
SYNTAX score*	25.0 (17.5-32.0)	34.5 (27.0-39.5)	22.5 (16.0-29.5)	<0.001
Left ventricular ejection fraction**	30.0 (25.0-40.0)	29.0 (20.0-39.0)	35.0 (25.0-44.0)	0.002

*according to central core-laboratory evaluation; **n=251 (58 patients with CTO and 193 patients without CTO); CTO: chronic total occlusion

Table 2. Procedural characteristics

	Total (n=667)	CTO (n=157)	No CTO (n=510)	p-value
Arterial access				
Femoral	550/667 (82.5%)	130/157 (82.8%)	420/510 (82.4%)	0.90
Radial	123/667 (18.4%)	27/157 (17.2%)	96/510 (18.8%)	0.65
Brachial	3/667 (0.4%)	2/157 (1.3%)	1/510 (0.2%)	0.14
Stent in culprit lesion				
Any	633/667 (94.9%)	146/157 (93.0%)	487/510 (95.5%)	0.21
Bare metal stent	37/633 (5.8%)	8/146 (5.5%)	29/487 (6.0%)	0.83
Drug-eluting stent	596/633 (94.2%)	139/146 (95.2%)	457/487 (93.8%)	0.54
Bioresorbable scaffold in culprit lesion	5/633 (0.8%)	1/146 (0.7%)	4/487 (0.8%)	1.00
Aspiration thrombectomy of culprit lesion	97/667 (14.5%)	22/157 (14.0%)	75/510 (14.7%)	0.83
TIMI grade for blood flow of culprit lesion*				
Before percutaneous coronary intervention				
3	220/663 (33.2%)	61/156 (39.1%)	159/507 (31.4%)	0.073
Other than 3	443/663 (66.8%)	95/156 (60.9%)	348/507 (68.6%)	
After percutaneous coronary intervention				
3	501/641 (78.2%)	116/148 (78.4%)	385/493 (78.1%)	0.941
Other than 3	140/641 (21.8%)	32/148 (21.6%)	108/493 (21.9%)	
Procedural use of glycoprotein IIb/IIIa inhibitors	143/666 (21.5%)	38/157 (24.2%)	105/509 (20.6%)	0.34
Immediate percutaneous coronary intervention of non-culprit lesion	344/667 (51.6%)	83/157 (52.9%)	261/510 (51.2%)	0.71
Total dose of contrast material, mL	220.0 (155.0-300.0)	240 (170.0-310.0)	212.5 (150.0-300.0)	0.08
Total duration fluoroscopy, min	15.7 (9.5-24.5)	18.7 (11.8-26.1)	14.7 (9.0-23.3)	0.002
Staged PCI of non-culprit lesions	62/667 (9.3%)	9/157 (5.7%)	53/510 (10.4%)	0.08
Induced mild hypothermia	220/665 (33.1%)	55/157 (35.0%)	165/508 (32.5%)	0.55
Mechanical circulatory support	191/667 (28.6%)	54/157 (34.3%)	137/510 (26.9%)	0.07
Intraaortic ballon pump	49/191 (25.7%)	15/54 (27.8%)	34/137 (24.8%)	0.67
Impella 2.5	34/191 (17.8%)	9/54 (16.7%)	25/137 (18.2%)	0.80

Impella CP	48/191 (25.1%)	15/54 (27.8%)	33/137 (24.1%)	0.60
TandemHeart	2/191 (1.0%)	2/54 (27.8%)	0/137	0.08
Extracorporeal membrane oxygenation	45/191 (23.6%)	13/157 (24.1%)	32/137 (23.4%)	0.92
Other devices	19/191 (9.9%)	3/54 (5.6%)	16/137 (11.7%)	0.20
Mechanical ventilation	538/664 (81.0%)	135/156 (86.5%)	403/508 (79.3%)	0.05
Duration of mechanical ventilation, days	3.0 (1.0-8.0)	2.0 (1.0-7.0)	3.0 (1.0-8.0)	0.24
Use of catecholamines	598/664 (90.1%)	144/156 (92.3%)	454/508 (89.4%)	0.28
Duration of catecholamines, days	2.0 (1.0-5.0)	2.0 (1.0-5.0)	2.0 (1.0-5.0)	0.31
Time to hemodynamic stabilization, days	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	0.70
Duration of intensive care, days	5.0 (2.0-11.0)	5.0 (2.0-11.0)	5.0 (2.0-11.0)	0.37
Subsequent medications in patients who survived until hospital discharged				
Statin	330/354 (93.2%)	63/69 (91.3%)	267/285 (93.7%)	0.44
Beta-blocker	323/354 (91.2%)	62/69 (89.9%)	261/285 (91.6%)	0.65
ACE or ARB inhibitors	310/354 (87.6%)	64/69 (92.8%)	246/285 (86.3%)	0.15
Aspirin	348/354 (98.3%)	68/69 (98.6%)	280/285 (98.2%)	1.00
Clopidogrel	159/354 (44.9%)	35/69 (50.7%)	124/285 (43.5%)	0.28
Prasugrel	123/354 (34.7%)	23/69 (33.3%)	100/285 (35.1%)	0.78
Ticagrelor	138/354 (39.0%)	27/69 (39.1%)	111/285 (38.9%)	0.98

*according to central core-laboratory; TIMI: Thrombolysis In Myocardial Infarction; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CTO: chronic total occlusion

Table 3. Early and late outcomes according to the presence of chronic total occlusion

	CTO (n=157)	No CTO (n=510)	Unadjusted OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
30-day outcomes						
All-cause death or renal replacement therapy*	92 (58.6%)	243 (47.6%)	1.56 (1.08 – 2.23)	0.016	1.47 (0.92 – 2.35)	0.11
All-cause death*	88 (56.1%)	225 (44.1%)	1.62 (1.13 – 2.32)	0.009	1.63 (1.01 – 2.60)	0.044
1-year outcomes						
All-cause death or renal replacement therapy†	104 (66.2%)	266 (52.2%)	1.80 (1.24 – 2.62)	0.002	1.62 (0.98 – 2.68)	0.061
All-cause death†	100 (63.7%)	254 (49.8%)	1.77 (1.22 – 2.56)	0.002	1.62 (0.99 – 2.66)	0.057

CTO: Chronic total occlusion; OR: Odds Ratio; CI: Confidence interval. Covariates of adjustment are detailed in Online Table 2

*N= 595 for multivariate model. Covariates of adjustment for death or renal replacement therapy at 30 days are : age, male sex, BMI, smoking status, hypercholesterolemia, diabetes mellitus , prior chronic kidney, prior PCI, baseline arterial lactate>2mmol/L, ST segment elevation MI at admission, triple vessel disease, culprit lesion of the LM or LAD, femoral access, stent in culprit lesion, mechanical circulatory support, mild hyperthermia, mechanical ventilation, catecholamine therapy, randomized coronary revascularization strategy; covariables of adjustment for death at 30 days are the same except for mild hypothermia (Online Table 2) † N=597 for multivariate model; covariates of adjustment for death or renal replacement therapy a 1 year are age, BMI, smoking status, hypercholesterolemia, diabetes mellitus ,prior stroke, prior chronic kidney, prior CABG, baseline arterial lactate>2mmol/L, fibrinolysis prior to randomization, ST segment elevation MI at admission, triple vessel disease, culprit lesion of the LM or LAD, femoral access, stent in culprit lesion, mechanical circulatory support, mechanical ventilation, catecholamine therapy, randomized coronary revascularization strategy; Covariates of adjustment for death at 1 year are the same except for prior stroke and fibrinolysis prior to randomization (Online Table 3).

Figure 1

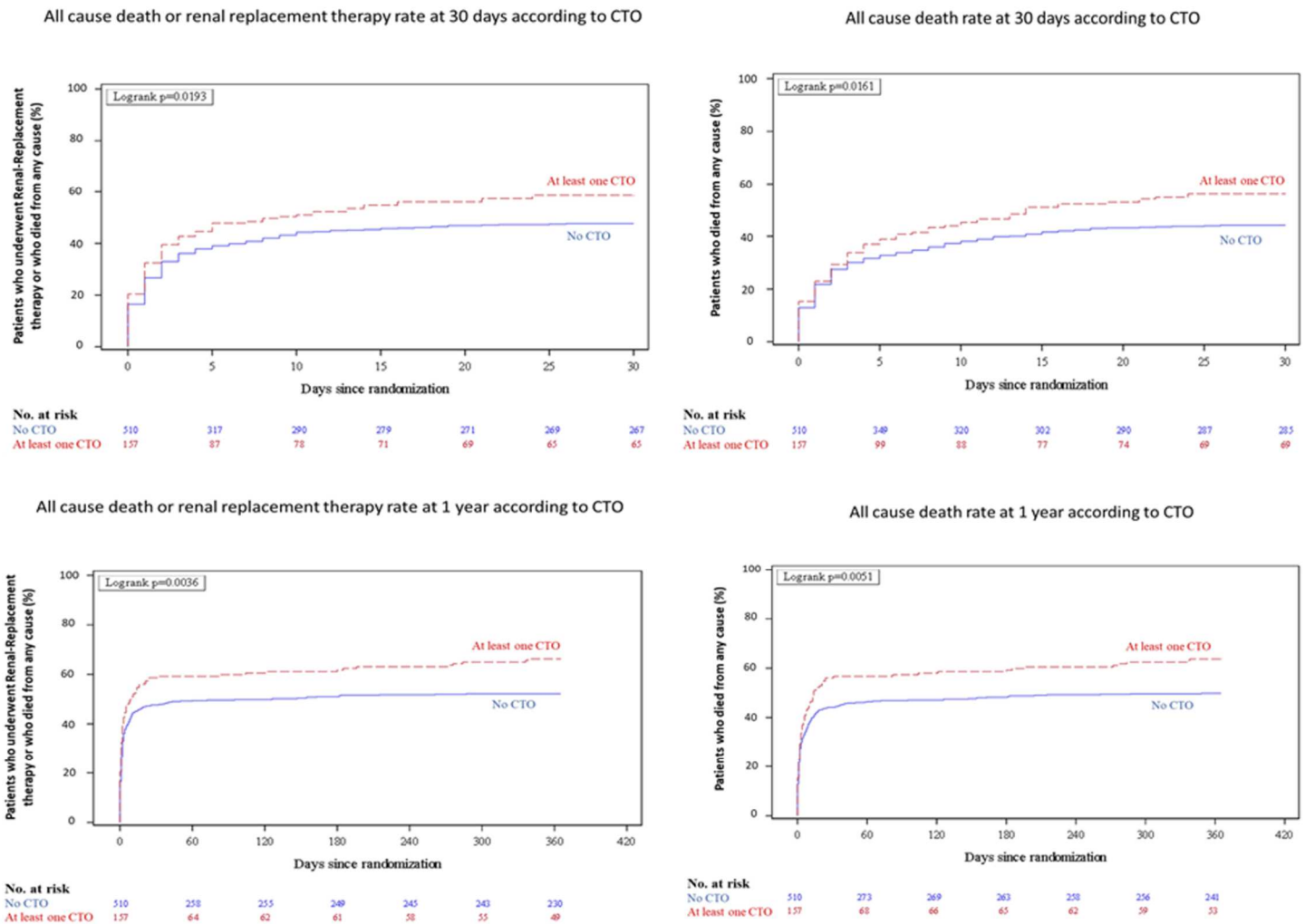
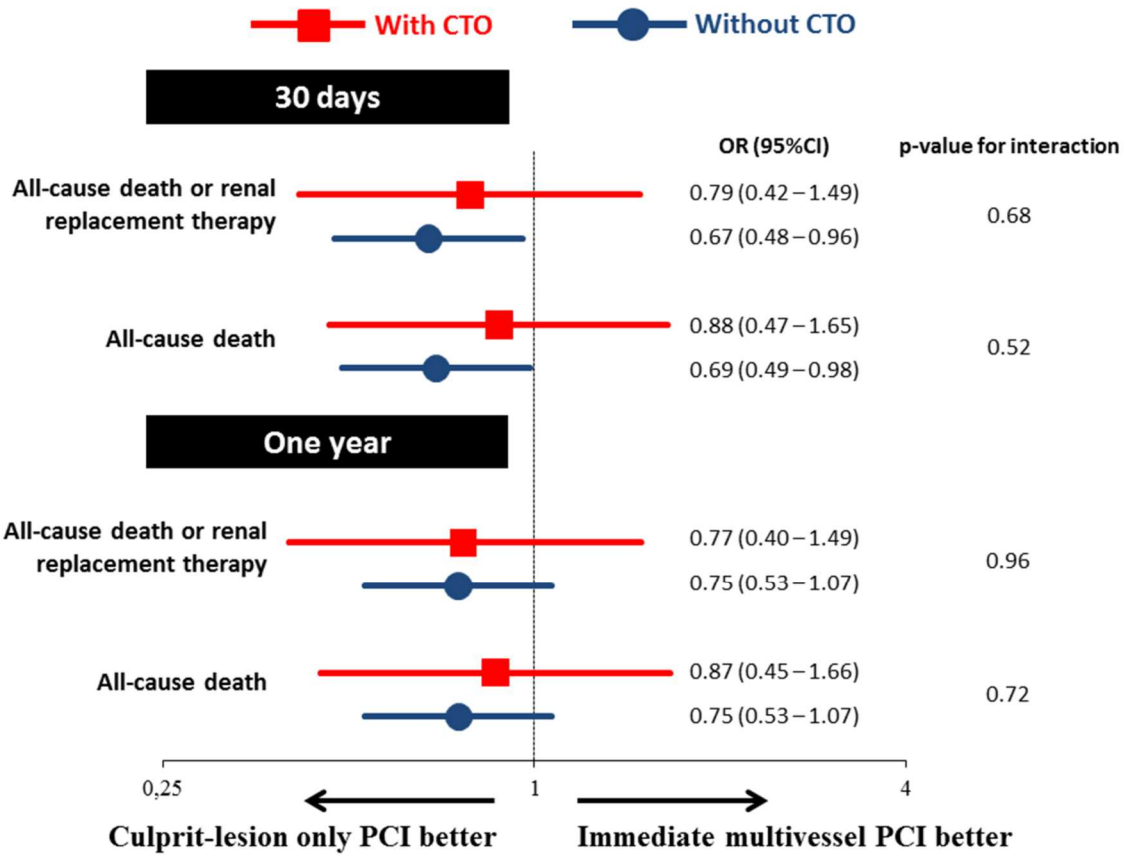

All cause death or renal replacement therapy rate at 30 days according to CTO
Logrank p=0.0193
Patients who underwent Renal-Replacement therapy or who died from any cause (%)
At least one CTO
No CTO
Days since randomization
No. at risk
No CTO 510 317 290 279 271 269 267
At least one CTO 157 87 78 71 69 65 65
All cause death rate at 30 days according to CTO
Logrank p=0.0161
Patients who died from any cause (%)
At least one CTO
No CTO
Days since randomization
No. at risk
No CTO 510 349 320 302 290 287 285
At least one CTO 157 99 88 77 74 69 69
All cause death or renal replacement therapy rate at 1 year according to CTO
Logrank p=0.0036
Patients who underwent Renal-Replacement therapy or who died from any cause (%)
At least one CTO
No CTO
Days since randomization
No. at risk
No CTO 510 258 255 249 245 243 230
At least one CTO 157 64 62 61 58 55 49
All cause death rate at 1 year according to CTO
Logrank p=0.0051
Patients who died from any cause (%)
At least one CTO
No CTO
Days since randomization
No. at risk
No CTO 510 273 269 263 258 256 241
At least one CTO 157 68 66 65 62 59 53

Figure 2


With CTO
Without CTO
30 days
OR (95%CI)
p-value for interaction
All-cause death or renal replacement therapy
0.79 (0.42 – 1.49)
0.67 (0.48 – 0.96)
0.68
All-cause death
0.88 (0.47 – 1.65)
0.69 (0.49 – 0.98)
0.52
One year
All-cause death or renal replacement therapy
0.77 (0.40 – 1.49)
0.75 (0.53 – 1.07)
0.96
All-cause death
0.87 (0.45 – 1.66)
0.75 (0.53 – 1.07)
0.72
0,25
1
4
Culprit-lesion only PCI better
Immediate multivessel PCI better