Medical therapy, percutaneous coronary intervention and prognosis in patients with chronic total occlusions

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Abstract

Objective

There is little published data reporting outcomes for those found to have a chronic total coronary occlusion (CTO) which is electively treated medically versus those treated by PCI. We sought to compare long-term clinical outcomes between patients treated by PCI and elective medical therapy in a consecutive cohort of patients with an identified CTO.

Methods

Patients found to have a CTO on angiography between January 2002 and December 2007 in a single tertiary centre were identified using a dedicated database. Those undergoing CTO PCI and elective medical therapy to the CTO were propensity matched to adjust for baseline clinical and angiographic differences.

Results

In total 1957 patients were identified, a CTO was treated by PCI in 405(20.7%) and medical therapy in 667(34.1%), 885(45.2%) patients underwent CABG. Of those treated by PCI or medical therapy, propensity score matching identified 294 pairs of patients, PCI was successful in 177 patients (60.2%). All-cause mortality at 5 years was 11.6% for CTO PCI and 16.7% for medical therapy HR 0.63(0.40-1.00) p=.052. The composite of 5-year death or MI occurred in 13.9% of the CTO PCI group and 19.6% in the medical therapy group, HR 0.64(0.42 to 0.99), p=.043. Amongst the CTO PCI group, if the CTO was revascularized by any means during the study period, 5 year mortality was 10.6%, compared with 18.3% in those not revascularized in the medical therapy group, HR 0.50(0.28-0.88, p=.016).

Conclusions

Revascularization, but not necessarily PCI of a CTO is associated with improved long-term survival relative to medical therapy alone.

Key messages

What is already known?

A number of studies have demonstrated an associated clinical outcome benefit if patients with a chronic total coronary occlusion (CTO) are treated by successful PCI versus failed PCI. However, there is little data comparing a strategy of PCI versus medical/conservative therapy of the CTO.

What does this study add?

Although we did not identify a statistically significant difference in 5-year all-cause mortality between groups, we demonstrate a significant associated reduction in the composite of death or myocardial infarction at 5 years if a CTO is treated by PCI rather than medical therapy, analysed by intention to treat. The difference appears to be driven by the increased rates of CTO territory revascularisation (including by CABG) during the study period in the CTO PCI group.

How might this impact on clinical practice?

This study adds weight to the suggestion that revascularisation of a CTO is associated with a prognostic benefit, although not necessarily by PCI.

Introduction

A chronic total coronary occlusion(CTO) is present in between one fifth and half of patients who have significant coronary artery disease[1,2]. There is a large body of observational data suggesting an association between successful CTO percutaneous coronary intervention(PCI) and improved clinical outcomes, including survival[3,4]. These findings are contrary to the findings of randomized trials comparing medical therapy with PCI of stable non-occlusive coronary disease, where except for reduced urgent revascularization in the FAME-2 trial[5](which did include a very small proportion of CTOs), no overall outcome benefit has been demonstrated[6–10].

There is little published data reporting outcomes for those found to have a CTO which is electively treated medically versus those treated by PCI; a comparison which is more pertinent to clinical decision making than PCI success versus failure. Practice with respect to revascularization of CTOs varies between clinicians, so it is likely that pre-treatment characteristics overlap. In addition, important confounding variables such as overall angiographic complexity cannot be accounted for if registries from which data is collected do not include them[4].

The aim of this study is to compare long-term clinical outcomes in a consecutive cohort of patients with an identified CTO on angiography between these two treatment groups. Our primary outcome was difference in 5-year all-cause mortality between groups propensity matched for clinical and angiographic pre-treatment characteristics.

Methods

Definitions

A CTO was defined as complete coronary occlusion of ≥3 months duration with TIMI grade 0 flow. Duration of occlusion was estimated as time from symptom onset, MI or from previous angiography (outside the study period) to angiography. CTO PCI success was defined as stenting of the target vessel with <30% residual stenosis and TIMI grade III flow

to the distal vessel. Patients were grouped according to treatment strategy (PCI/CABG/medical therapy) on an intention-to-treat basis. If a patient had multi-vessel disease and was treated by PCI but the CTO was treated medically, they were included in the medical therapy group.

Study population

All patients undergoing coronary angiography or PCI in a single tertiary centre were prospectively entered into a dedicated database including demographic and procedural details; each patient record was validated by a clinical audit officer. Patients with an occluded coronary artery on angiography between 1st January 2002 and 31st December 2007 were identified(n=4457). We excluded those treated for acute MI in the territory of the occluded vessel in the preceding 3 months, with prior CABG, mitral or aortic valve disease of moderate severity or greater, active neoplastic disease and those already included in the study. The final cohort included 1957 patients. Medical records and coronary angiograms were reviewed retrospectively to give additional angiographic, procedural and clinical details not routinely recorded in the database.

Ethics

The study complies with the Declaration of Helsinki. The study protocol was approved by the local research ethics committee (13/YH/0036). As the study was retrospective and we were unable to obtain informed consent from those patients with our primary outcome of mortality, we obtained approval from the National Confidentiality Advisory Group(CAG 3-06(PR3)/2013) to include clinical data and outcome measures without informed consent.

Angiographic assessment

Overall angiographic complexity was quantified by the use of the Syntax Score[11,12]. Complexity of the individual CTO was assessed by the J-CTO score[13]. Left ventricular function was assessed by left ventriculography, and where not available by echocardiography.

Outcome measures

Our primary outcome was 5-year all cause mortality amongst propensity matched groups. Data on patient mortality and international classification of disease cause of death was obtained from Office of National Statistics death certification records.

Secondary outcomes included hospitalization for myocardial infarction (MI), the composite of death and MI, and PCI or coronary artery bypass graft surgery (CABG) at follow-up. Follow-up data was obtained through linkage by The National Institute for Cardiac Outcomes Research, obtained from the Myocardial Infarction National Audit Project, British Cardiovascular Intervention Society Central Cardiac Audit Database and the National Adult Cardiac Surgery Audit respectively.

Statistical analysis

Data is presented as percentages and mean±SD or median(inter-quartile range) as appropriate. Differences in proportions are tested with a chi-squared test or Fisher's exact test, and differences in continuous variables with a Student t-test or Mann-Whitney U-test. Propensity matching was performed to minimize any selection bias due to the differences in clinical characteristics between PCI and elective medical therapy treatment groups. For each patient in the cohort a propensity score indicating the likelihood of a CTO being treated by PCI was calculated by the use of a non-parsimonious multivariable logistic regression model. Co-variates included in the logistic regression model to calculate the propensity score were: age, gender, previous PCI, previous MI, diabetes mellitus, smoking status, peripheral vascular disease(PVD), hypertension, chronic kidney disease(CKD)stage $\geq$3, chronic lung disease, cerebrovascular disease, Canadian Cardiovascular Society(CCS)class, New York Heart Association(NYHA)class, presentation (stable angina, unstable angina(UA)/non-ST elevation myocardial infarction(NSTEMI), ST elevation myocardial infarction (STEMI), arrhythmia or heart failure) estimated CTO duration, left main stem disease, Syntax Score, number of significantly diseased vessels, J-CTO score, proximal LAD CTO, branch vessel

CTO (defined as diagonal, obtuse marginal, posterior descending artery, posterior left ventricular branch or distal circumflex artery in a right dominant circulation), Left ventricular systolic function, confirmed demonstrable ischaemia (confirmed evidence of ischaemia by non-invasive testing, the absence of which does not mean the absence of ischaemia), confirmed myocardial viability in the CTO territory (the absence of a resting left ventricular regional wall motion abnormality or confirmation by non-invasive testing in the presence of a wall motion abnormality, the absence of which does not mean the absence of viability), number of anti-anginal medications, warfarin use and loop diuretic use. The C-statistic for the propensity score model was 0.750 and the Hosmer-Lemeshow test for goodness of fit was 0.778. To identify matched pairs of patients undergoing CTO PCI and elective medical therapy a 1:1 optimal match with a ±0.03 caliper and no replacement was used. Cumulative survival was calculated using the Kaplan–Meier method.Clinical outcomes in the matched population were analysed with Cox proportional hazards regression stratified by matched-pair.

Two sub-group analyses amongst propensity matched patients were performed. We compared outcomes including only propensity matched-pairs in which the CTO PCI patient underwent successful PCI. The second sub-group analysis compared propensity matched patients only if the CTO territory of the CTO PCI patient had been revascularized by any means during the study period and the CTO territory of the medical therapy patient had not been revascularized.

Stata v.12(StataCorp, College Station, Texas) was used for statistical analysis. Probability values were 2-sided, and values of $p<.05$ were considered significant.

Results

Of the 1957 patients identified in the cohort, a CTO was treated by PCI in 405(20.7%) and medical therapy in 667(34.1%), 885(45.2%) patients underwent CABG. In 23 patients, the only CTO identified was a non-dominant right coronary artery; these patients were excluded from analysis, leaving 1934 patients. Of those treated by PCI or medical therapy,

propensity score matching identified 294 pairs of patients. Table 1 lists demographic, clinical and angiographic characteristics by treatment group for the entire cohort and for propensity matched groups. After propensity matching, no significant imbalance was identified in covariates between groups.

Significant multi-variable predictors of 5-year mortality were age, elective medical therapy of the CTO, CKD≥3, peripheral vascular disease, chronic lung disease, NYHA class, and ejection fraction<30% (table 2).

Procedural details

PCI of the CTO was successful in 250(61.7%) of all patients in whom the CTO was attempted and 177(60.2%) of the propensity matched group. In the propensity matched CTO PCI group, 88(29.9%) patients underwent PCI to another vessel other than the CTO vessel as part of their initial revascularization strategy, compared with 62(21.1%) in the group in which the CTO was treated medically. PCI was complicated by wire perforation in 4(1%) of CTO PCI procedures, all of which were included in the propensity matched group (1.4%). Pericardial drainage for tamponade was required in one patient, peri-procedural death occurred in one patient and two patients were managed conservatively. No wire perforations occurred in any patients in the cohort undergoing PCI to non-occlusive disease. In those in the propensity matched CTO PCI group treated by successful PCI, median total length of stented segments was 46mm(31-63mm). In those in the propensity matched medical therapy group in whom PCI to concomitant non-occlusive disease was performed, median total length of stented segment was 24mm(16-35mm). Drug eluting stents were used in 140(79.0%) of patients undergoing successful CTO PCI and 36(58.1%) of patients in the elective medical therapy group who underwent PCI to non-occlusive disease.

5-year outcomes

5-year outcomes for the entire cohort and propensity matched groups are listed in table 3. Mortality at 5 years in the propensity matched CTO PCI group was 11.6%, compared with 16.7% in the medical therapy group but did not quite reach conventional statistical

significance, hazard-ratio 0.63(0.40-1.00, p=.052)(figure 1). However the composite of death or myocardial infarction at 5 years occurred in 13.9% of the CTO PCI group and 19.6% in the elective medical therapy group, hazard-ratio 0.64(0.42 to 0.99), p=.043(figure 2). Repeat revascularization, unplanned in the initial treatment strategy was more common in the CTO PCI group than the elective medical therapy group. The majority of CTO PCI patients (51, 73.9%) who underwent repeat, unplanned revascularization did not undergo successful initial CTO PCI. In the propensity matched CTO PCI group, 54(18.4%) patients underwent CABG within 5 years and 15(5.1%) underwent further PCI unplanned in the initial revascularization strategy. In the medical therapy group, 13(4.4%) underwent CABG within 5 years and 22(7.5%) underwent subsequent PCI.

Sub-group analyses

If only the 177 matched pairs in which CTO PCI was successful were analyzed, there was no statistically significant difference in 5-year mortality or the 5-year composite of death or MI(supplementary figure 1 and table 4). However, the excess of repeat revascularization in the CTO PCI group was no longer evident (Supplementary figure 1).

Of the 117 patients who underwent unsuccessful CTO PCI, 45(38%) underwent revascularization to the CTO territory during the 5 year follow-up period of which 44(98%) were by CABG. Median time to unplanned revascularization in this group was 243 days(183-359). Similarly, 20 of 294 patients treated by medical therapy underwent revascularization to the CTO territory during the 5 year follow-up period, 13(65%) by CABG and 7(35%) by PCI.

There were 208 propensity matched-pairs in whom the CTO territory of the CTO PCI patient had been revascularized by any means during the study period and the CTO territory of the medical therapy patient had not been revascularized. There was a significant difference in mortality at 5 years, the composite of death or MI at 5 years and 5 year cardiac death, favouring the revascularized group(Supplementary figure 2 and table 4).

Drug-eluting stents and target vessel revascularization after successful CTO PCI

Of the 177 patients in the propensity matched group in whom PCI was successful, 18 (10.2%) underwent repeat, unplanned revascularization in the 5-year study period(13 by PCI and 5 by CABG), of which 13(7.4%) patients underwent target vessel revascularization (12 for in-stent restenosis and 1 for very late stent thrombosis). Of the 37(20.9%) patients in whom bare metal stents were used, repeat unplanned revascularization occurred in 5(13.5%) patients during the 5-year study period (4 by PCI and 1 by CABG), 3 of which were due to in-stent restenosis in the CTO vessel and 2 due to de novo disease in another vessel. Amongst the same successful CTO PCI group, 23(12.9%) patients died during the 5-year study period 5(2.8%) of whom had undergone PCI with a bare metal stent. Similarly, 28(15.8%) of these patients suffered the composite of death or myocardial infarction during the study period, 5(2.8%) of whom had undergone PCI with a bare metal stent.

Discussion

We present, in a propensity matched population well balanced for both clinical and angiographic characteristics, 5-year clinical outcomes comparing CTO PCI and elective medical therapy analyzed by intention-to-treat. We are unable to reject our null hypothesis (albeit by a narrow margin) that there is no difference in our primary outcome of 5-year all-cause mortality between propensity matched CTO PCI and elective medical therapy groups. However, we do demonstrate a significant difference in the composite of 5-year death or MI favouring CTO PCI over elective medical therapy. The difference in outcomes appears to be driven by whether the CTO was revascularized, rather than whether it was treated by successful PCI.

Procedural success

The evidence describing long-term outcomes associated with CTO PCI is at present entirely observational and largely involves comparison of successful versus failed procedures[3,4]. A problem peculiar to PCI of CTOs compared to PCI of other coronary lesions is that procedural success rates are much lower. Although success rates as high as 85% have been reported[14], the success rate in the UK between 2005 and 2009 was 70%[4] and a recent

publication using data from The National Cardiovascular Data Registry CathPCI Registry, which included 22,365 attempts at CTO PCI in the USA between 2009 and 2013 reported a success rate of 59%[15] . This has two important implications; firstly, in applying the evidence base we cannot necessarily put our patients in the more favourable successful group. Secondly, in investigating outcomes by the principle of intention-to-treat, a sizeable proportion of patients will not receive the intended treatment because of procedural failure. This may dilute the power of the study, or complicate comparison by including other treatment modalities, in this case CABG. Randomised trials investigating outcomes of CTO PCI are likely to be beset by the same problem.

A survival benefit?

It may be that our failure to demonstrate a difference in all-cause mortality between those treated by CTO PCI and medical therapy(figure 1) is due to insufficient sample size. This is supported by the numerical difference in mortality and by the presence of a statistically significant survival benefit when the composite of death or MI is used(figure 2). In spite of CTO PCI success rates of 60%, 76% of propensity matched CTO PCI patients underwent revascularization to the CTO territory compared with only 7% in the propensity matched medical therapy group. It would appear that the increased rate of repeat revascularization we report in the CTO PCI group(figure 2), absent if only successful cases are analyzed(supplementary figure 1) was related to an intention to revascularize and subsequent referral for CABG on failure of PCI.

If it is revascularization of the CTO territory that is important, it is somewhat surprising that when only propensity matched pairs in which CTO PCI had been successful are analyzed there is a smaller numerical difference in mortality and death/MI(Supplementary figure 1). This could be a true finding, or might be explained by the loss of power as a result of including only 60% of propensity matched patients, and was perhaps contributed to by the comparison with some medical therapy patients who did in fact undergo revascularization of their CTO. In addition, it may be that CABG is associated with a greater survival benefit and

the exclusion of the failed CTO PCI patients who were revascularized by CABG has removed this effect. Although the numbers are small, there was a difference in cardiac death favouring the successful PCI group over medical therapy(table 4). The clear association with improved survival if only propensity matched pairs in which the CTO was revascularized in the CTO PCI patient and not revascularized in the medical therapy patient suggests it is revascularization of the CTO territory that is important in driving the association with improved outcomes (Supplementary figure 2). This is further supported by our multi-variable analysis of the entire cohort, which shows that elective medical therapy (or the lack of revascularization by CABG or PCI) to be independently predictive of 5-year mortality (table 3). This is consistent with the findings of a recently published retrospective cohort study using a similar population[16].

Why should CTOs be any different?

Why would prognostic gain be associated with PCI over medical therapy in the setting of a CTO but not in non-occlusive disease[6–10]? The presence of a CTO in a non-infarct related artery in patients who present with ST-elevation myocardial infarction is associated with inferior outcomes[17,18]. This may be related to a greater myocardial mass at jeopardy in the infarct related artery due to an additional contribution to collateral dependent myocardium. Another possible explanation is that of a reduction in ischaemic myocardium. Unlike some non-occlusive coronary stenoses included in clinical trials, provided the myocardium is viable, CTOs almost invariably result in inducible ischaemia[19]. A larger ischaemic burden is associated with an adverse prognosis[20] and reducing that burden has been associated with improved clinical outcomes[21]. If the effect of PCI on outcome is assessed in patients only if they have demonstrable ischaemia, a clinical benefit associated with PCI seems more likely[5].

Despite the observational evidence, doubt remains as to whether CTO PCI itself confers a prognostic benefit over medical therapy. Ultimately this can only be answered by a randomised trial, two of which are ongoing (ClinicalTrials.gov numbers NCT01760083 and

NCT01078051). Given the low event rates reported here, it seems unlikely that any difference in the harder clinical outcomes of death or MI would become apparent until relatively late in the follow-up period.

Limitations

This study is limited by its observational nature; however the study population was very well balanced for both clinical and angiographic characteristics. Without randomization though, we cannot adjust for any unmeasured differences between groups. It is also limited by including only patients from a single centre. Because data was collected retrospectively, complete records of symptomatic status at follow-up were not collected and therefore control of symptoms and morbidity related to treatment could not be compared across groups. The study benefited from comprehensive national audit data collection resulting in no known censored events and collection of robust hard endpoint data. Migration outside of England or Wales could result in missed events however there is no reason to suppose that this would introduce bias between groups.

Finally, CTO PCI technique has progressed since the period of data collection and the success rates we report are lower than have been reported more recently[4,14]. As a consequence, a proportion of patients in the CTO PCI group were ultimately treated medically or by CABG. However, in an era of rapid development, to achieve 5-year clinical follow up, it is not possible for procedures to be entirely contemporary. Perhaps more importantly, a recent publication reporting over 22,000 attempts at CTO PCI in the USA between 2009-2013 reported success rates of only 59%[15], lower than we report here. Although a proportion of patients underwent PCI with bare-metal stents, rates of repeat revascularization, and more importantly death or myocardial infarction were not sufficiently large in this group to influence our results. It seems unlikely that the use of third generation (rather than first and second generation) drug eluting stents would have greatly altered our results either.

Conclusions

Using an alternative approach to much of the existing literature on the subject[3,4], our findings support the suggestion that the revascularization of a CTO is associated with improved long-term survival. However from this study, we cannot attribute this finding to successful CTO PCI at the index procedure alone.

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Conflicts of interest

None.

Contributorship Statement

All authors have given final approval to the accepted manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Individual contributions:

Andrew Ladwiniec: Study concept and design; data acquisition, analysis and interpretation; drafting and revision of manuscript.

Victoria Allgar: Statistical design and advice, critical revision of manuscript.

Simon Thackray: Study concept and design, critical revision of manuscript.

Farquad Alamgir: Study concept and design, critical revision of manuscript.

Angela Hoye: Study concept and design, interpretation of data, critical revision of manuscript.

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Figure legends

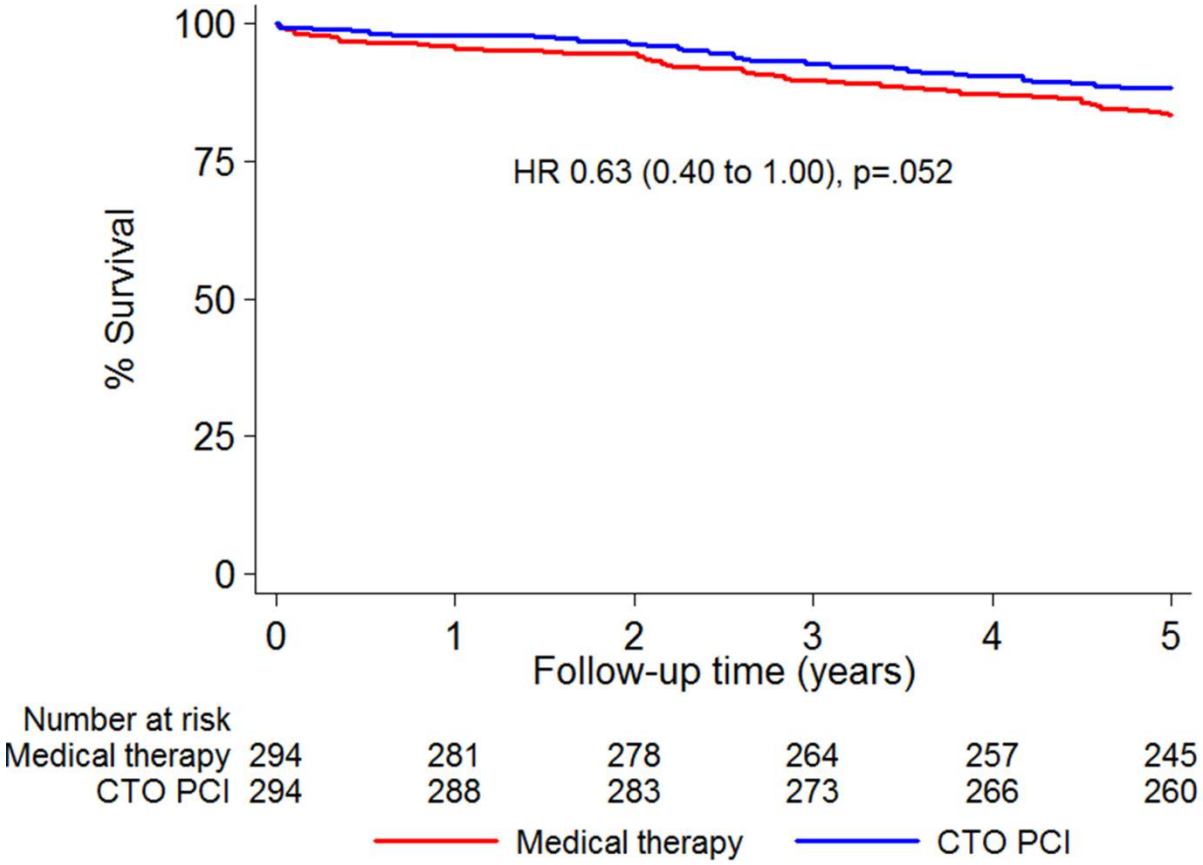


Figure 1. Kaplan-Meier curves showing 5-year survival for propensity matched CTO PCI and medical therapy groups.

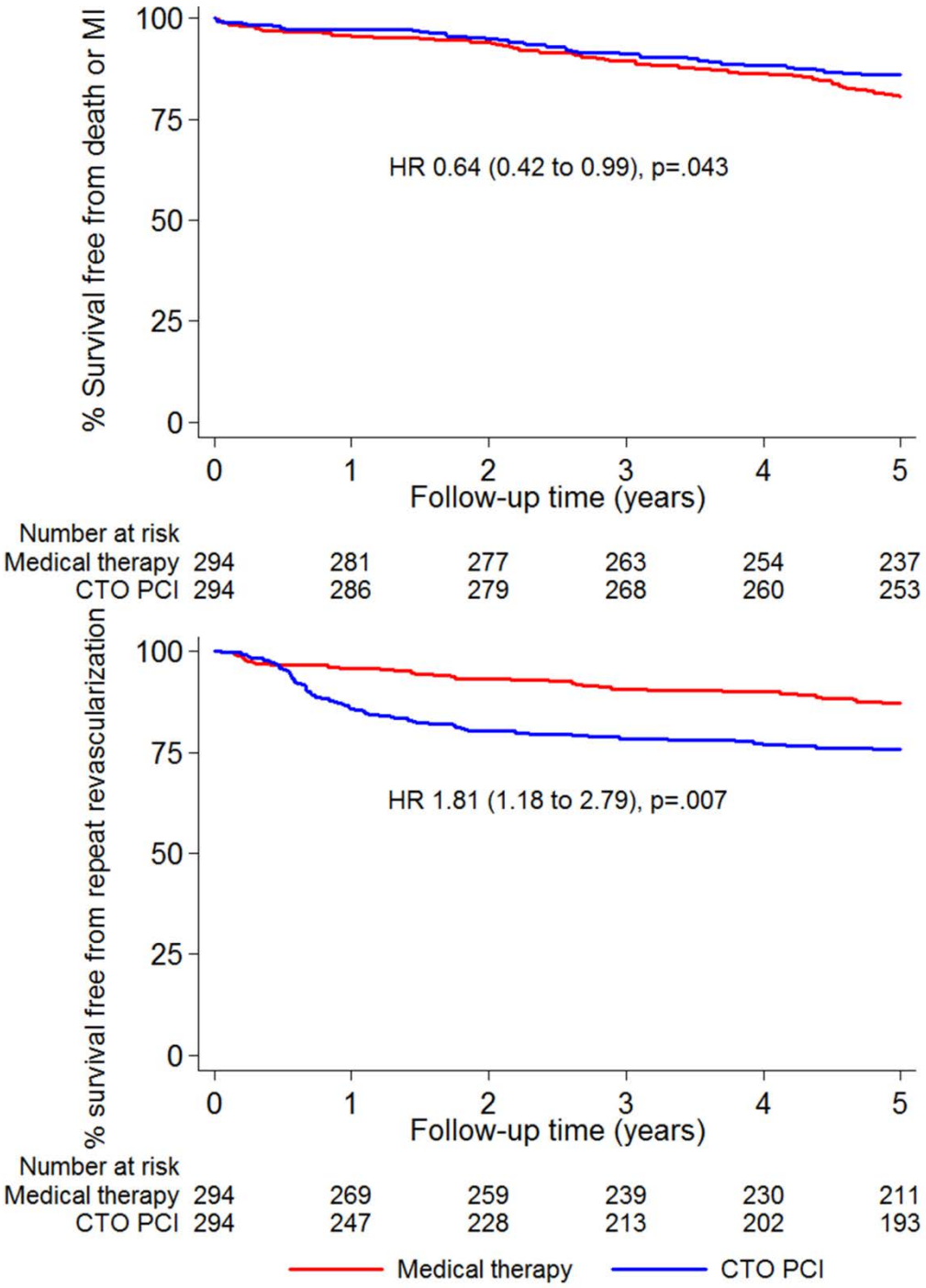
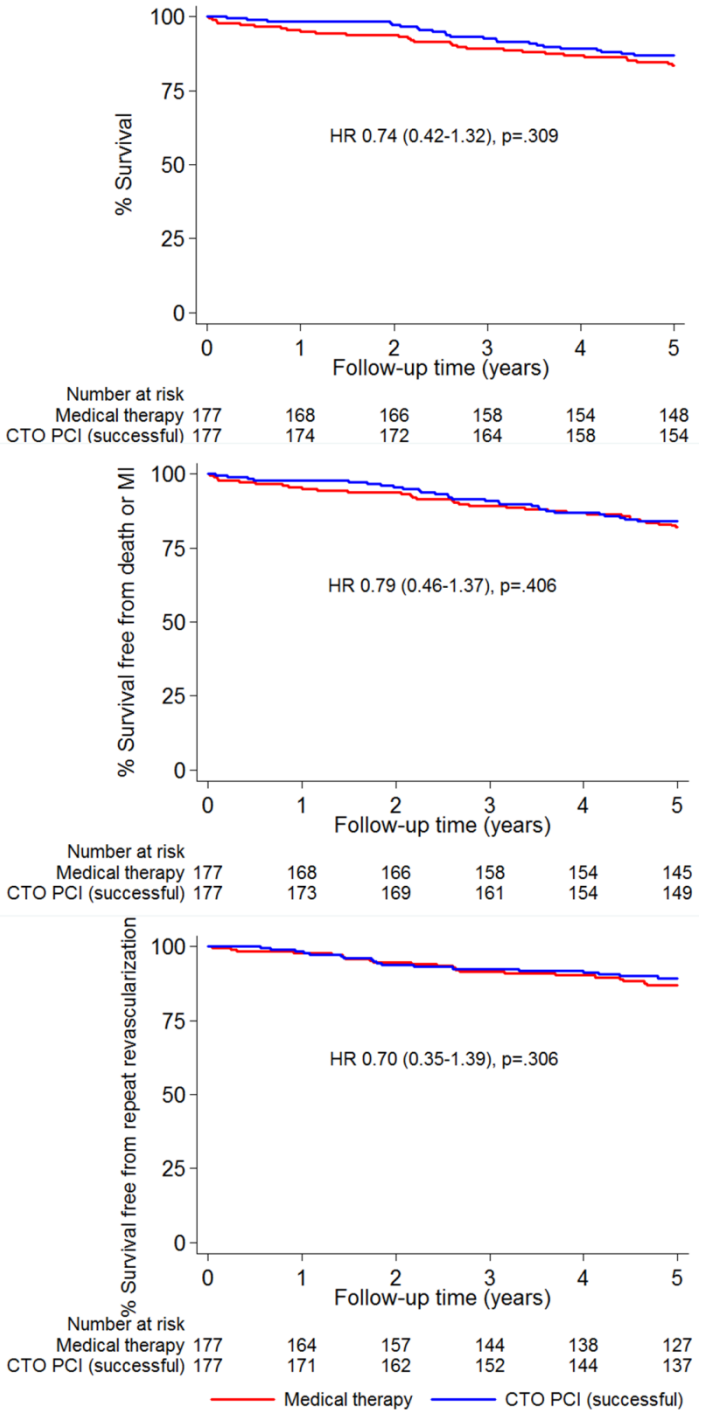
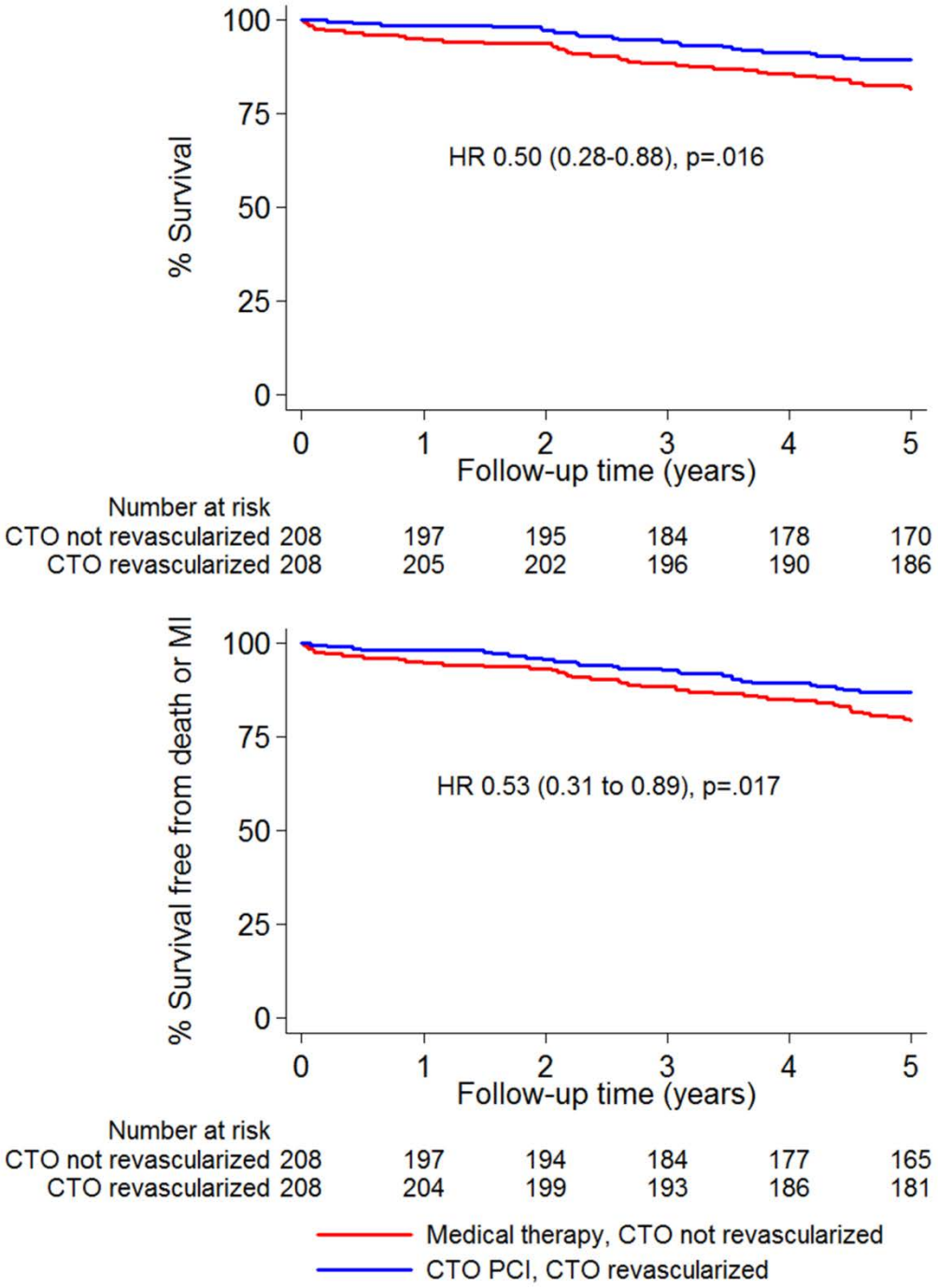


Figure 2. Kaplan-Meier curves showing 5-year composite of death or myocardial infarction(top) and 5-year unplanned repeat revascularization for propensity matched CTO PCI and medical therapy groups.



Supplementary figure 1. Kaplan-Meier curves showing 5-year survival(top), composite of death or MI(middle) and repeat revascularization for propensity matched CTO PCI and medical therapy groups including only matched pairs in which CTO PCI was successful.



Supplementary figure 2. Kaplan-Meier curves showing 5-year survival(top) and composite of death or MI(bottom) for propensity matched CTO PCI and corresponding elective medical therapy groups including only matched pairs in which during the follow-up period, the CTO was revascularized in the CTO PCI patient and the CTO was not revascularized in the medical therapy patient.

Text Tables

Table 1. Baseline characteristics in entire cohort and propensity matched groups.

	Entire cohort (n=1934)					Propensity matched groups (n=588)			
	CABG n=878	**CTO PCI n=405**	**Medical therapy n=651**	**p-value***	**Standardised difference***	**CTO PCI n=294**	**Medical therapy n=294**	**p-value***	**Standardised difference***
Age	66.0±9.3	63.2±10.1	65.8±10.7	p<.001	-0.257	64.3±10.0	63.9±10.2	p=.645	0.038
Male gender	728(82.9)	301(73.1)	506(77.7)	p=.205	-0.080	220(74.8)	220(74.8)	p=1.00	0.000
Previous MI	454(51.7)	202(49.9)	394(60.5)	p=.001	-0.215	151(51.4)	143(48.6)	p=.563	-0.048
Previous PCI	41(4.7)	22(5.4)	64(9.8)	p=.011	-0.166	18(6.1)	24(8.2)	p=.337	-0.079
Diabetes	193(22.0)	78(19.3)	137(21.0)	p=.484	-0.044	62(21.1)	53(18.0)	p=.349	0.077
Smoking				p=.037				p=.802	
Ex	471(53.6)	200(49.4)	306(47.0)		0.048	142(48.3)	141(48.0)		0.007
Current	148(16.9)	73(18.0)	160(24.5)		-0.160	56(19.1)	62(21.1)		-0.051
PVD	115(13.1)	38 (9.4)	103(15.8)	p=.003	-0.195	28(9.5)	31(10.5)	p=.681	-0.034
Hypertension	554(63.1)	225(55.6)	349(53.6)	p=.537	0.039	159(54.1)	157(53.4)	p=.869	0.014
Hypercholestero-laemia	563(64.2)	199(49.1)	293(45.0)	p=.191	0.083	146(49.7)	135(45.9)	p=.364	0.075
Family History	268(30.5)	152(37.5)	198(30.4)	p=.017	0.151	107(36.4)	103(35.0)	p=.731	0.028
CKD ≥3	235(26.8)	82(20.3)	179(27.5)	p=.005	-0.181	59(20.1)	64(21.8)	p=.879	-0.042
Chronic lung disease	52(5.9)	23(5.7)	51(7.8)	p=.182	-0.086	19(6.5)	15(5.1)	p=.480	0.058
Cerebrovascular disease	65(7.4)	22(5.4)	61(9.4)	p=.021	-0.151	17(5.8)	20(6.8)	p=.610	-0.042
CCS class				p<.001				p=.683	
No Angina	24(2.7)	1(0.3)	63(9.7)		-0.445	1(0.3)	0(0)		0.082
I	326(37.1)	192(47.4)	309(47.5)		-0.001	153(52.0)	156(53.1)		-0.020
II	269(30.6)	138(34.1)	181(27.8)		0.136	100(34.0)	92(31.3)		0.058
III	216(24.6)	72(17.8)	92(14.1)		0.100	38(12.9)	45(15.3)		-0.068
IV	43(4.9)	2(0.5)	6(0.9)		-0.051	2(0.7)	1(0.3)		-0.008
NYHA Class				p=.001				p=.970	
I	503(57.3)	298(73.6)	414(63.6)		0.216	217(73.8)	217(73.8)		
II	267(30.4)	95(23.5)	155(23.8)		-0.008	67(22.8)	68(23.1)		-0.008
III	97(11.0)	12(3.0)	74(11.4)		-0.330	10(3.4)	9(3.1)		0.019
IV	11(1.3)	0(0)	8(1.2)		-0.158	0(0)	0(0)		-
Presentation				p<.001				p=.565	
Stable angina	645(73.5)	371(91.6)	491(75.4)		0.446	265(90.1)	268(91.2)		0.012
UA/NSTEMI	194(22.1)	32(7.9)	86(13.2)		-0.173	27(9.2)	26(8.8)		0.082
STEMI	15(1.7)	1(0.3)	11(1.7)		-0.148	1(0.3)	0(0)		0.082
Arrhythmia	11(1.3)	1(0.3)	33(5.1)		-0.303	1(0.3)	0(0)		0.082
Heart Failure	13(1.5)	0(0)	30(4.6)		-0.311	0(0)	0(0)		-
Occlusion duration (months)	16(8-52)	12(6-24)	16(8-56)	p<.001	-0.372	12(7-26)	12(7-29)	p=.551	0.039

LMS disease	184(21.0)	1(0.3)	23(3.5)	p<.001	-0.243	1(0.3)	1(0.3)		0
Syntax score	24(19-29)	14.5(10-19)	14.5(9-21.5)	p=.359	-.197	14.5(10-19)	13.3(9-18.5)	p=.106	0.034
Diseased vessels				p<.001				p=.771	
1	74(8.4)	193(47.7)	293(45.0)		0.053	146(46.3)	144(9.0)		
2	276(31.4)	159(39.3)	223(34.3)		0.104	114(38.8)	106(36.1)		0.056
3	528(60.1)	53(13.1)	135(20.7)		-0.205	44(15.0)	44(15.0)		0.000
J-CTO score				p<.001				p=1.00	
0	210(23.9)	162(40.0)	182(28.0)		0.256	109(37.1)	109(37.1)		0.000
1	355(40.4)	153(37.8)	250(38.4)		-0.013	113(38.4)	114(38.8)		-0.007
2	243(27.7)	76(18.8)	168(25.8)		-0.170	60(20.4)	59(20.1)		0.008
≥3	70(8.0)	14(3.5)	51(7.8)		-0.190	12(4.0)	12(4.0)		0.000
Proximal LAD CTO	138(15.7)	53(13.1)	90(13.8)	p=.733	-0.022	37(12.6)	32(10.9)	p=.522	0.053
Branch vessel CTO	114(13.0)	42(10.4)	115(17.7)	p=.001	-0.211	38(12.9)	43(14.6)	p=.550	-0.049
LV function				p<.001				p=.722	
Good(EF >50%)	527(60.0)	304(75.1)	363(55.8)		0.414	213(72.5)	220(74.8)		-0.054
Mod(EF 30-50%)	246(28.0)	88(21.7)	163(25.0)		-0.078	68(23.1)	60(20.4)		0.066
Poor(EF <30%)	105(12.0)	13(3.2)	125(19.2)		-0.524	13(4.4)	14(4.8)		-0.016
Confirmed ischaemia†	491(55.9)	279(68.9)	356(54.7)	p<.001	0.295	204(69.4)	198(67.4)	p=.595	0.044
Confirmed viability†	551(62.8)	322(79.5)	369(56.7)	p<.001	0.505	222(75.5)	220(74.8)	p=.849	0.016
N anti-anginals				p=.001				p=.991	
0	159(18.1)	85(21.0)	182(28.0)		-0.162	73(24.8)	72(24.5)		
1	332(37.8)	150(37.0)	262(40.3)		-0.066	114(38.8)	113(38.4)		0.007
2	260(29.6)	126(31.1)	130(20.0)		0.257	76(25.9)	77(26.2)		-0.008
3	106(12.1)	38(9.4)	67(10.3)		-0.031	28(9.5)	30(10.2)		-0.023
4	21(2.4)	6(1.5)	10(1.5)		-0.004	3(1.0)	2(0.7)		0.037
Loop diuretic	121(13.8)	30(7.4)	139(21.4)	p<.001	-0.405	26(8.8)	22(7.5)	p=.547	0.050
Warfarin	29(3.3)	13(3.2)	41(6.3)	p=.027	-0.145	3(1.0)	10(3.4)	p=.050	-0.162

***p-values and standardised differences compare CTO PCI and medical therapy groups only. †Confirmed viability/ischaemia only.**

Table 2. Multi-variable predictors of 5 year mortality for the entire cohort (n=1934)

	Multi-variable analysis		
	HR	**95% CI**	**p-value**
Medical therapy*	1.56	1.25-1.94	p<.001
Age(years)	1.05	1.04-1.07	p<.001
Diabetes	1.30	1.04-1.67	p=.023
CKD ≥3	1.42	1.17-1.72	p<.001
PVD	1.63	1.27-2.09	p<.001
Chronic lung disease	1.72	1.26-2.37	p=.001
Presentation with heart failure	1.70	1.09-2.66	p=.019
NYHA class			
II	1.60	1.24-2.06	p<.001
III	1.87	1.34-2.59	p<.001
IV	6.01	3.30-10.95	p<.001
Poor LV function (EF <30%)	2.05	1.56-2.68	p<.001

***Elective medical therapy of the CTO**

Table 3. Outcome comparisons for the entire cohort(left) and propensity matched groups(right).

	Entire Cohort				Propensity matched groups			
	Number of events (%)				Number of events (%)			
Outcome	CTO PCI n=405	Medical Therapy n=667	Hazard-Ratio	p-value	CTO PCI n=294	Medical Therapy n=294	Hazard-Ratio (95% CI)	p-value
5-year mortality	43(10.6)	170(26.1)	0.37(0.26-0.51)	p<.001	34(11.6)	49(16.7)	0.63(0.40-1.00)	p=.052
5-year cardiac death	23(5.7)	71(10.9)	0.47(0.30-0.76)	p=.002	14(4.8)	19(6.5)	0.65(0.30-1.38)	p=.261
5-year death/MI	56(13.8)	187(28.7)	0.44(0.32-0.59)	p<.001	41(13.9)	57(19.6)	0.64(0.42-0.99)	p=.043
5-year unplanned revascularization	96(23.7)	76(11.7)	2.06(1.52-2.78)	p<.001	69((23.5)	35(11.9)	1.81(1.18-2.79)	p=.007

Table 4. Outcome comparisons including only propensity matched pairs in which CTO PCI was successful(left) and including only matched pairs in which during the follow-up period, the CTO was revascularized in the CTO PCI patient and the CTO was not revascularized in the medical therapy patient(right).

	Succesful CTO PCI only				Revascularized CTO vs not revascularized			
	Number of events (%)				Number of events (%)			
Outcome	CTO PCI n=177	Medical Therapy n=177	Hazard-Ratio	p-value	CTO PCI n=208	Medical Therapy n=208	Hazard-Ratio (95% CI)	p-value
5-year mortality	23(13)	29(16.4)	0.74(0.42-1.32)	p=.309	22(10.6)	38(18.3)	0.50(0.28-0.88)	p=.016
5-year cardiac death	5(2.8)	12(6.8)	0.27(0.08-0.98)	p=.046	6(2.8)	15(7.2)	0.21(0.06-0.75)	p=.015
5-year death/MI	28(15.8)	32(18.1)	0.79(0.46-1.37)	p=.406	27(13.0)	43(20.7)	0.53(0.31-0.89)	p=.017
5-year unplanned revascularization	18(10.2)	21(11.9)	0.70(0.35-1.39)	p=.306				