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Myocardial Infarction and All-Cause Mortality Following Percutaneous Coronary Intervention Versus Conservative Treatment of Chronic Total Occlusions: A West Denmark Heart Registry Study

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ABSTRACT

Background: Chronic coronary total occlusions (CTO) represent a therapeutic challenge, and results of randomized clinical trials and observational studies comparing conservative treatment versus percutaneous coronary intervention (PCI) are underpowered.

Aims: To assess myocardial infarction (MI) and all-cause mortality in consecutive patients with CTO lesions.

Methods: Using data from the West Denmark Heart Registry, patients with chronic coronary syndrome and a 100% occluded vessel by invasive coronary angiography (ICA) were identified. Patients were stratified according to PCI within 90 days. Five-year risk of MI and all-cause mortality was calculated using cause-specific Cox-models and g-formula methods. Subsequently, models were stratified on sex, diabetes, estimated glomerular filtration rate above 60 mL/min, procedure before 2012, and history of cardiac surgery. The risk was calculated for patients who did not experience MI or death within 30 days of the initial ICA.

Results: A total of 7675 patients were included in the study, of whom 3129 patients underwent PCI, and 4546 patients were treated conservatively. PCI- and conservatively treated patients had comparable risks of MI (13.1% [95% confidence interval [CI] 12.0%−14.3%] for patients who underwent PCI vs. 13.4% [95% CI 12.4%–13.4%] for patients who received conservative treatment). For all-cause mortality, results were 14.4% (95% CI 13.3%–15.5%) versus 18.9% (95% CI 17.8%–20.0%), respectively. Results were consistent across subgroups. However, CTO-PCI-treated patients with previous heart surgery were at higher risk of MI.

Conclusions: Patients who underwent CTO-PCI had a comparable 5-year risk of MI and lower all-cause mortality as compared to conservatively treated patients.

Abbreviations: CABG, coronary artery bypass grafting; CTO, chronic total coronary occlusions; ICA, invasive coronary angiography; MI, myocardial infarction; PCI, percutaneous coronary interventions; WDHR, West Denmark Heart Registry.

1 | Introduction

Chronic total coronary occlusions (CTOs) are found in about 30% of patients referred for a diagnostic coronary angiography [1, 2]. Recent developments in CTO percutaneous coronary interventions (PCI) have been associated with improved procedural success, reduced risk of complications, and consequently improved outcomes for patients undergoing CTO-PCI [3]. Despite these improvements, the majority of CTO patients have been treated with coronary artery bypass grafting (CABG) or medical therapy [4, 5]. CTO-PCI requires special experience and skills and should be performed by high-volume operators doing more 60 cases per year [6].

There is no randomized clinical trial-derived evidence supporting improved prognostic outcomes following CTO-PCI. Recently, two randomized clinical trials compared CTO-PCI to optimal medical therapy: The DECISION-CTO (Drug-Eluting Stent Implantation vs. Optimal Medical Treatment in Patients With Chronic Total Occlusion) trial and EURO-CTO (A Randomized Multicenter Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Occlusions) [7, 8]. Both trials failed to find significant differences in major cardiac cerebrovascular events up to 3 years [7, 8]. However, the EURO-CTO trial indicated better symptom control and quality of life in PCI-treated patients [8]. Both trials were underpowered to show any difference in myocardial infarction (MI) and had a high number of protocol deviations following randomization, especially there were high rates of primary and secondary crossing over.

The ongoing ISCHEMIA-CTO trial (International randomized trial on the effect of revascularization or optimal medical therapy of CTOs with myocardial ischemia) evaluates the prognostic value of CTO-PCI in patients with CTO lesion and myocardial ischemia $\geq 10\%$ of left ventricular territory, and results are expected by 2029 [9].

Numerous registry studies have described improved patient outcomes, including reduced mortality, of successful CTO-PCI as compared to an unsuccessful intervention. Because of a biased patient selection, comparisons of outcomes in CTO-PCI versus conservatively treated patients are problematic. Another recent comparative analysis of randomized controlled trials and cohort studies found that there are more complex CTOs, comorbidities, and fewer successful CTOs in cohort studies, underlining the importance of assessing real-world data [10]. A recent cohort study demonstrated similar all-cause mortality in CTO-PCI and in chronic coronary syndrome patients but increased all-cause mortality in patients with failed CTO-PCI [11].

In the present study, validated data from the West Denmark Heart Registry (WDHR) comprising all invasive cardiac procedures related to ischemic heart disease were used, and the recordation rate was between 95% and 99% [12]. The primary aim of this study was to evaluate all-cause mortality and MI following CTO-PCI.

2 | Methods

2.1 | Study Population

Using the WDHR, all patients born in Denmark with one or more CTO lesions (defined as a 100% occluded vessel) on a first-time invasive coronary angiography (ICA) with the indication of chronic coronary syndrome (International Classification of Diseases 10-code I20x) between January 2002 and January 2022 were identified. Patients who immigrated or emigrated before their initial ICA were excluded to ensure complete follow-up. Patients with missing information on hypertension, use of lipid-lowering drugs, diabetes, and smoking status were excluded. Patients who underwent CABG within 90 days of their initial ICA were excluded.

Patients were followed from the date of their index ICA until January 1, 2021, emigration or outcome.

The unique civil registration number, assigned to all inhabitants in Denmark at birth or upon immigration, was used to link WDHR with national registries, including the Danish Civil Registration System, for information on vital status, sex, and date of birth [13]. Information on diagnoses assigned at hospitals for outcome assessment was retrieved from the Danish National Patient Registry [14]. Information on comorbidities and patient characteristics were retrieved from WDHR.

During the study period, optimal medical treatment consisted of statins, aspirin, and anti-anginal therapy. The standard period for dual therapy after PCI for chronic coronary disease is 6 months.

2.2 | Exposure

Exposure was based on initial PCI status. Patients were classified into two groups:

1. PCI: Chronic coronary syndrome patients who underwent PCI within 90 days of their index ICA showing a total (100%) occlusion.
2. Conservative treatment: Chronic coronary syndrome patients who did not undergo PCI within 90 days of their index ICA showing a total (100%) occlusion.

2.3 | Study Endpoints

The primary outcome was a 5-year MI with all-cause mortality as a competing risk.

2.4 | Statistical Analysis

Continuous variables were reported using medians and 1st and 3rd quartile. Categorical variables were reported using counts and percentages. Continuous variables were compared using the Kruskal–Wallis test and categorical using the chi-squared test.

Multivariate Cox regression models were used to assess the association between PCI versus conservative treatment with MI as the primary outcome and all-cause mortality as a competing risk. Models were adjusted for age at ICA, sex, diabetes, hypertension, smoking status, and hyperlipidemia. The proportional hazards assumption was tested using Schoenfeld residuals. In addition, models were standardized for the affected vessels.

Using cause-specific Cox models and g-formula methods, 5-year absolute risk were calculated for MI and all-cause

mortality [15, 16]. Absolute risks were presented using bar plots with 95% confidence intervals (CI) and risk differences as forest plots with 95% CIs.

Subsequently, models were stratified on sex, diabetes, estimated glomerular filtration rate (eGFR) above and below 90, procedure before and after 2012, and history of heart surgery. In addition, absolute risks were calculated for patients who did not experience MI or death within 30 days of the initial ICA. Underlying models were not adjusted for variables they were stratified on.

Patients with information on whether their PCI procedure was successful or not was identified, and outcomes were addressed for this group.

A $p < 0.05$ was considered statistically significant.

Statistical analyses were performed with RStudio version 2023.06.1 (PBC, Boston, MA, USA) [17].

2.5 | Missing Data

Sensitivity analyses were conducted using worst-case and best-case scenarios for patients excluded due to missing information on hypertension, hyperlipidemia, diabetes, and smoking status, assuming that the patients either had the given comorbidity or not.

2.6 | Ethical Approval

The present study was approved by the Northern Region Denmark Approval number 2022-019306. Registry-based studies do not require ethical approval or informed consent in Denmark.

3 | Results

3.1 | Study Population

Initially, 180,690 ICAs on the indication chronic coronary syndrome were identified. From this, 26,982 ICAs with a CTO lesion were found. After the selection of only the index procedure showing CTO, 14,399 patients remained. After applying subsequent exclusion criteria, 7675 patients remained in the study (Figure 1). Subsequently, 3628 patients underwent PCI, and 4047 patients did not.

As compared to conservatively treated patients, patients who underwent PCI were younger (69 vs. 71, $p < 0.0001$), less likely to be a current or previous smoker (73.6% vs. 76.5%, $p = 0.005$), less likely to be diabetic (21.5% vs. 24.1%, $p = 0.008$), less likely to be using lipid-lowering drugs (78.4% vs. 81.6%, $p = 0.001$), as likely to be suffering from hypertension (71.1% vs. 70.6%, $p = 0.62$), and having statistically significantly lower body mass index (27.5 [24.9, 30.5] vs. 27.4 [24.7, 30.4], $p < 0.019$) (Table 1). Likewise, they were less likely to have suffered a previous MI (33.5% vs. 40.8%, $p < 0.0001$). The rate of previous PCI was similar (29.8% vs. 28.1%, $p = 0.18$) (Table 1).

Patients undergoing PCI were less likely to have multiple CTO lesions (23.8% vs. 41.0%, $p < 0.0001$) (Table 1).

3.2 | Risks

During the 5-year follow-up, the absolute risk of MI among patients undergoing CTO-PCI compared with those that did not was similar (13.0% vs. 11.8%, $p = 0.20$) in unadjusted results, and a significantly lower risk of all-cause mortality

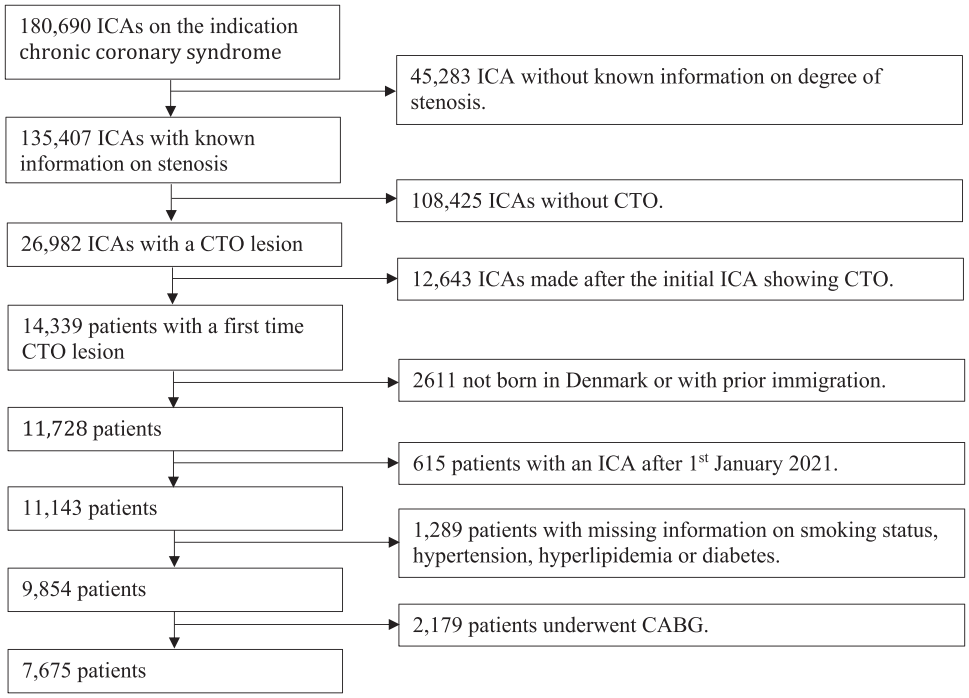

FIGURE 1 | Selection of the study population. Abbreviations: CABG, coronary artery bypass grafting; CTO, chronic total occlusion; ICA, invasive coronary angiography.

TABLE 1 | Baseline characteristics of study population.

Variable	Level	Conservative treatment ($n = 4047$)	PCI ($n = 3628$)	Total ($n = 7675$)	p value
Age	Median [IQR]	71 [65, 77]	69 [63, 76]	70 [64, 77]	< 1e−04
Sex	Males	3141 (77.6)	2821 (77.8)	5962 (77.7)	
Smoking (currently or previously)	Yes	3095 (76.5)	2672 (73.6)	5767 (75.1)	0.005
Diabetes	Yes	974 (24.1)	780 (21.5)	1754 (22.9)	0.008
Lipid lowering drugs	Yes	3301 (81.6)	2845 (78.4)	6146 (80.1)	0.001
Hypertension	Yes	2857 (70.6)	2581 (71.1)	5438 (70.9)	0.62
Previous heart surgery	Yes	506 (12.5)	368 (10.1)	874 (11.4)	0.41
	Missing	3519	3249	6768	
Previous myocardial infarction	Yes	1647 (40.8)	1212 (33.5)	2859 (37.3)	< 1e−04
	Missing	12	8	20	
Previous PCI	Yes	1136 (28.1)	1078 (29.8)	2214 (28.9)	0.18
	Missing	11	7	18	
Left ventricular ejection fraction	Median [IQR]	55 [45, 60]	60 [50, 60]	55 [45, 60]	< 1e−04
	Missing	1648	1235	2883	
Body mass index	Median [IQR]	27.4 [24.7, 30.4]	27.5 [24.9, 30.5]	27.4 [24.8, 30.4]	0.019
	Missing	271	180	451	
CX	Yes	1702 (39.2)	1085 (32.5)	2787 (36.3)	< 1e−04
LAD	Yes	2155 (49.7)	1334 (40.0)	3489 (45.5)	< 1e−04
LM	Yes	111 (2.6)	38 (1.1)	149 (1.9)	< 1e−04
RCA	Yes	2585 (59.6)	1803 (54.0)	4388 (57.2)	< 1e−04
Multiple lesions	Yes	1781 (41.0)	793 (23.8)	2574 (33.5)	< 1e−04

Abbreviations: CX, circumflex artery; IQR, interquartile range; LAD, left anterior descending; LM, left main; PCI, percutaneous coronary intervention; RCA, right coronary artery.

(12.2% vs. 18.2%, $p < 0.0001$) (Figure 2A,B) was observed in the PCI group. Adjusted models showed the same pattern with an absolute risk for MI among patients undergoing PCI at 5 years of 14.2% (95% CI 12.9%–15.6%) for patients who underwent PCI compared with 12.7% (95% CI 11.6%–13.8%) for patients who received conservative treatment ($p = 0.08$) (Figure 3). For all-cause mortality, results were 14.8% (95% CI 13.4%–16.1%) versus 18.8% (95% CI 17.6%–20.0%), respectively ($p < 0.0001$) (Figure 3).

Stratified analyses for MI on sex, diabetes, and procedure before versus after 2012 showed the same pattern, except for males, where a statistically significant lower risk of MI was found among patients who did not undergo PCI (12.2% [95% CI 11.0%–13.3%] vs. 14.3% [95% CI 12.8% vs. 15.8%]) (Figures 3 and 4).

Among patients with a history of prior heart surgery, patients who underwent PCI had a higher risk of MI compared with patients who did not undergo PCI (risk difference 6.02% [95% CI 2.94%−9.11%]) (Figure 5, Figure S1). Risk of MI among patients with a low eGFR, normal eGFR, no prior heart surgery, and including only patients with MI after 30 days, did not change results (Figure 5, Figure S1).

Results for all-cause mortality did not change in stratified analyses, except for patients with a low eGFR, no history of prior heart surgery, and among patients without MI within the first 30 days ($p < 0.05$) (Figures 2, 3, and 5, Figure S1).

3.3 | Missing Data

Sensitivity analyses with worst case and best case for hypertension, hyperlipidemia, diabetes, and smoking status resulted were not materially different from main results (Figures S2, S3, S4, S5).

3.4 | Successful Versus Unsuccessful PCI

Information on PCI outcomes was available in 1968 patients who underwent PCI (59.0%). Of these, 1724 were reported

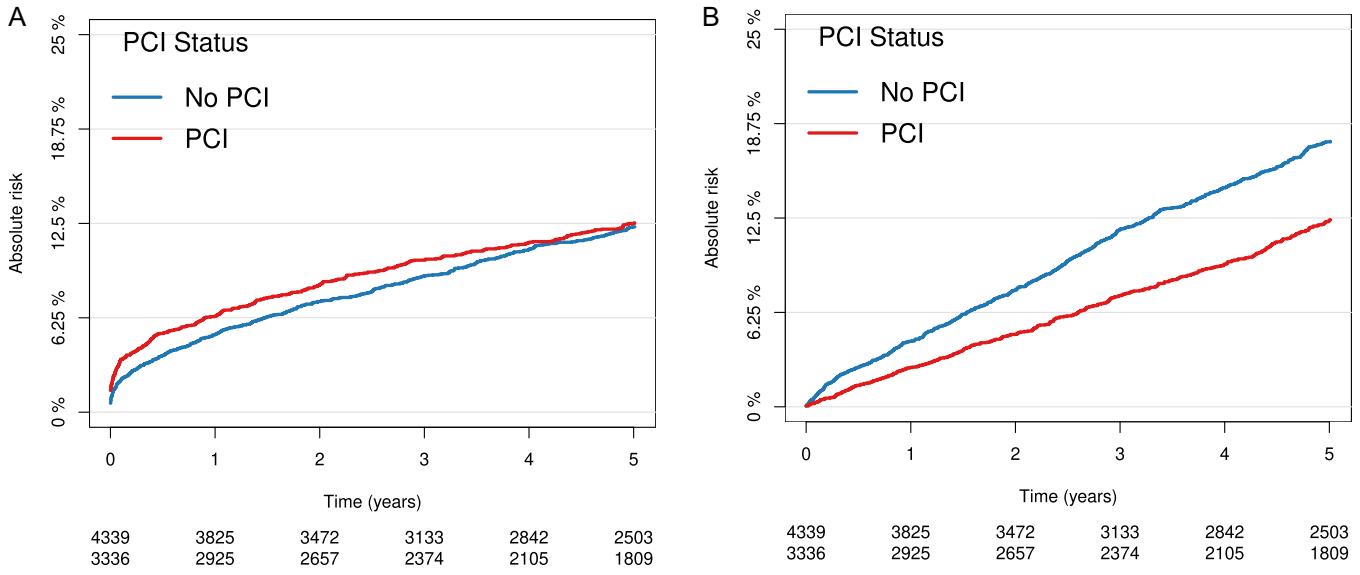

FIGURE 2 | (A, B) Cumulative incidence of myocardial infarction (A) and all-cause mortality (B) according to CTO-PCI status. [Color figure can be viewed at wileyonlinelibrary.com]

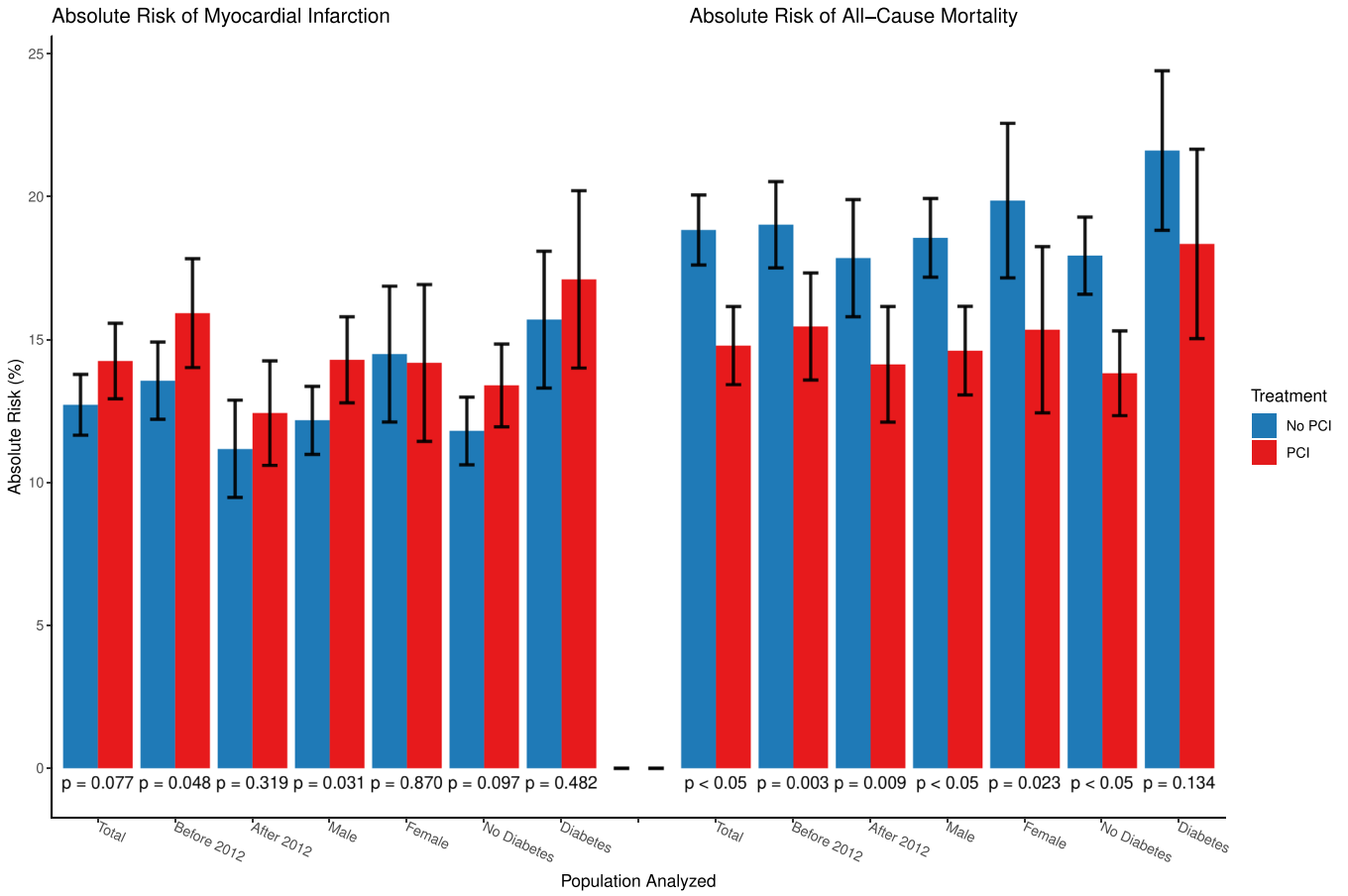

FIGURE 3 | Absolute risks of myocardial infarction and all-cause mortality according to subgroup. [Color figure can be viewed at wileyonlinelibrary.com]

successful, and 244 were unsuccessful. A similar 5-year cumulative incidence of MI (10.37% vs. 9.43%, $p = 0.761$) and all-cause mortality (9.75% vs. 11.69%, $p = 0.305$) was found (Figure S6).

4 | Discussion

The present study compared the 5-year rates of MI and all-cause mortality in PCI versus conservatively treated patients with

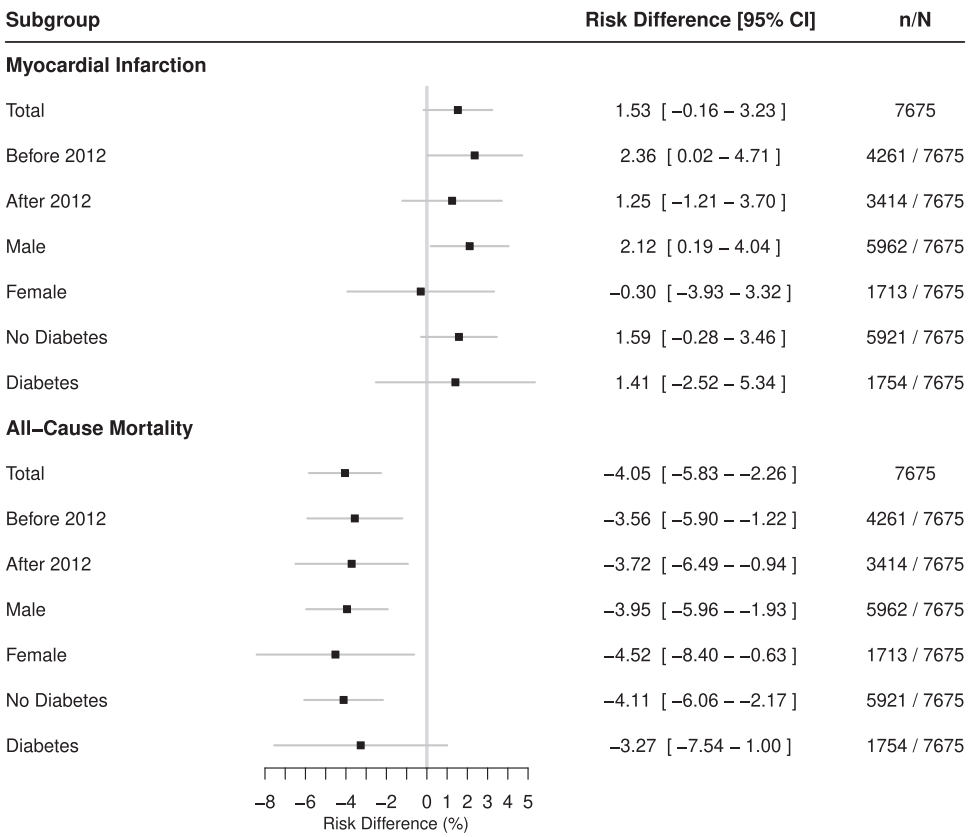

FIGURE 4 | Risk differences (%) of myocardial infarction and all-cause mortality according to subgroup.

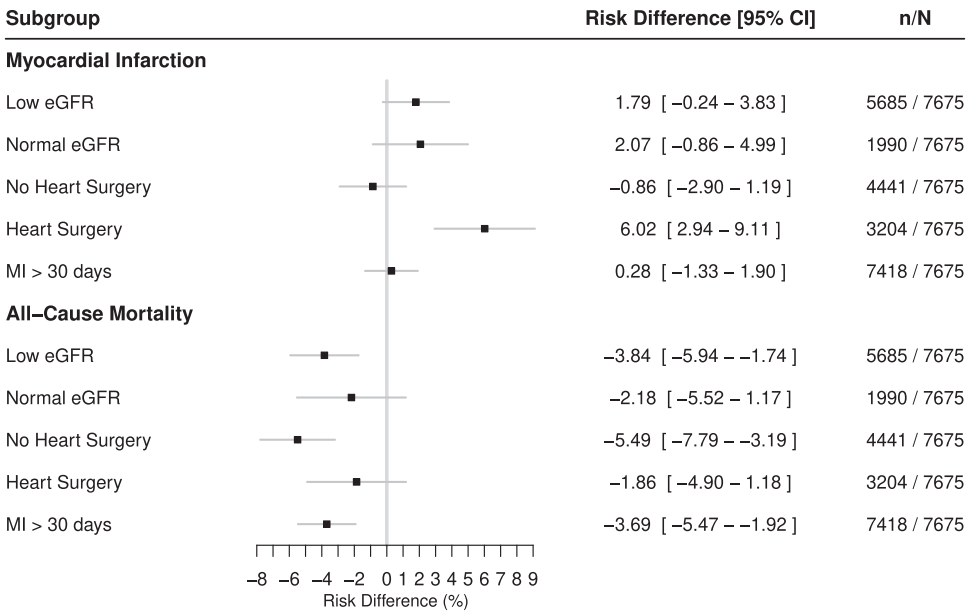

FIGURE 5 | Risk differences (%) of myocardial infarction and all-cause mortality according to subgroup. Abbreviations: eGFR, estimated glomerular filtration; MI, myocardial Infarction.

CTOs. The major findings of the study were: (1) Patients who underwent CTO-PCI had reduced absolute 5-year risk of all-cause mortality, (2) there was no difference in the absolute 5-year risk of MI between the two groups; however, after stratifying the models, there was an increased risk of MI in CTO patients with prior heart surgery who did not receive PCI treatment.

As compared to non-CTO coronary interventions, CTO-PCI is a complex and time-consuming procedure, associated with

increased risk of complications and procedural failure [18]. Therefore, evaluation of short- and long-term symptomatic and prognostic CTO-PCI outcomes is of major clinical interest.

Although the randomized clinical trials on CTO-PCI demonstrated improved angina status, quality of life and physical performance important questions on prognosis have been left unanswered [7, 8]. Instead, difficulties in performing randomized clinical CTO-PCI trials versus conservation treatment have been exposed. As mentioned above, the possible prognostic aspects of CTO-PCI are due after the completions of the ISCHEMIA-CTO trial.

Comparing successful and failed PCI in the evaluation of CTO-PCI provide part of the answer, however, the study cohort is biased, a bias that may not be handled by adjusting for confounding variables. The present study aimed at overcoming the mentioned selection problems by investigating patients with a diagnosis of chronic coronary syndrome and a total (100%) coronary occlusion by ICA. Thus, the bias by procedural success was minimized. However, the current results are still subject to a bias inherent in observational studies. Furthermore, not all the conservatively treated patients may have had a true CTO as defined by treatment guidelines, as there was no data on the duration of the coronary occlusion [18].

Most observational studies comparing successful versus unsuccessful CTO procedures have found increased survival after a successful procedure, although a few studies reported similar mortality after successful and unsuccessful CTO-PCI [19–21]. Park et al. compared 10-year survival in 883 CTO-PCI treated patients and compared the results to 664 medically treated patients with a CTO lesion and found significantly higher survival in the invasively treated group. The patient groups were selected according to their initial treatment of PCI or optimal medical therapy and may not be comparable [22].

Interestingly, a recent study compared mortality in a large cohort of patients with chronic coronary syndrome versus CTO-PCI patients. The investigators found similar mortality in chronic coronary syndrome patients and in patients with successful CTO-PCI. Patients with unsuccessful CTO-PCI had increased mortality [11].

In the present study, there was no significant differences of MI in the CTO-PCI group versus the conservative treatment group. The high number of CTO patients with hyperlipidemia and hypertension in our study suggests that these patients may have a great burden of atherosclerosis, which might contribute to the observed results. The data span of the study was from year 2002 to 2021. Thus, a portion of the patients underwent CTO-PCI with bare metal stents and first generation of drug eluting stents, and early CTO techniques that are inferior to current best practices. However, comparing event rates before and after 2012, no differences were found. The initial increase in MI rate in the PCI group may be procedure-related and consistent with findings of the ISCHEMIA trial [9]. The definition of MI and the use of troponins for MI diagnostics have changed over the study period and may influence MI rates and hamper the interpretation of MI data. However, the results in the present study showed the same pattern when excluding patients who had MI within 30 days of their procedure.

The higher absolute risk of all-cause mortality in the present population with known CTO lesions might be multifactorial. The distribution of comorbidities was similar with comparable prevalence of hypertension and prior PCI, but patients in the CTO-PCI group were more likely to be smokers, whereas patients in the conservative medical treatment group were more likely to be diabetic and suffer from hyperlipidaemia and prior MI. Even though statistical models were adjusted, residual confounding might persist. Patients for whom the clinician recommended a CTO procedure might differ from other patients in ways not assessable in the present study.

4.1 | Limitations

The present study was a retrospective assessment of prospectively collected data from the Western Danish Heart Registry. As an observational study, selection bias was in play, as the patients were selected for CTO-PCI treatment by a clinical assessment. Further, the differences in CTO lesion, number of CTO lesions, or the burden of ischemia, factors which might affect the results, were not assessed.

When assessing successful versus unsuccessful PCI a larger number of missing was found (41.0%) concomitant with relatively few unsuccessful PCIs which could be due to underreporting.

5 | Conclusion

In the present observational study comprising 7675 patients with CTO lesions, a similar 5-year risk of MI and a lower all-cause mortality among patients who underwent PCI for their CTO lesion compared with patients who did not were found. The results persisted across all subgroup analyses. Hence, PCI versus initial conservative treatment of a CTO-vessel is associated with a better long-term outcome.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available after application and approval from relevant Danish authorities.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.