

## Long-term MACCE Rate after Retrograde Compared to Antegrade Recanalization of Chronic Total Coronary Occlusions

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### Abstract

**Background:** The recanalization success rate of chronic total occlusion (CTO) percutaneous coronary interventions (PCI) can be increased by the retrograde approach. However, the long-term outcome of patients undergoing retrograde procedures is unknown.

**Aim:** We aimed to evaluate the long-term MACCE (major adverse cardiac and cerebrovascular event) rate (death, myocardial infarction, coronary artery bypass surgery and stroke) in patients after retrograde versus antegrade CTO-PCI.

**Methods and results:** In a prospective single center study from January 2008 to June 2012, 396 consecutive patients with CTO's ( $\geq 3$  months old) were enrolled. Mean age was  $63.4 \pm 10.3$  years, 86.4% were male. The recanalization success rate of the total patient cohort was 88.6%. The retrograde PCI, only attempted after a failed antegrade intervention, was performed in 18% ( $n = 71$ ) of patients. Long-term MACCE rate (mean follow up  $2.3 \pm 1.6$  years) was significantly higher in the unsuccessful compared to the successful CTO-PCI group (23.1% versus 9.4%,  $p = 0.01$ ) and this was also the case in the subgroup of antegrade CTO-PCI. In the retrograde subgroup, however, procedural success had no impact on outcome. As a possible explanation for this surprising finding, patients with unsuccessful retrograde CTO-PCI had a significantly better collateral connection compared to patients with an unsuccessful antegrade approach.

**Conclusions:** Long-term MACCE rate after unsuccessful recanalization was significantly higher which was driven by a higher MACCE rate after unsuccessful versus successful antegrade approach. In contrast, procedural success in the retrograde group had no impact on outcome.

**Keywords:** Chronic total occlusion; Retrograde; Long term follow-up

### Introduction

Successful CTO-PCI has been shown to relieve symptoms, reduce the rate of myocardial infarction and coronary artery bypass surgery and may improve long term survival compared to unsuccessful CTO-PCI [1-6]. There are several suggested mechanisms by which revascularisation of occluded coronary arteries could contribute to a benefit including reduction in ischemic burden [7] or in future arrhythmic events [8], improvement in left ventricular function [9], better tolerance of future myocardial infarctions in a non-CTO artery [10] and less referral to bypass surgery [4].

The standard antegrade approach aims to penetrate the CTO from proximal to reach the occlusion. Success rates, however, have been limited to 60% to 70% [4]. Knowledge and expertise in the retrograde techniques have become an essential adjunct to improve success of CTOs. The retrograde technique consists of cannulating both the contralateral and the ipsilateral coronary artery and advancing a guidewire from the contralateral artery to the distal end of the occlusion via collateral channels [11]. Retrograde guidewire advancement may increase the chances of success as histopathological

studies have shown that the distal cap of the occlusion tends to be less rigid than the proximal one [12,13].

Compared to the antegrade approach the retrograde procedure is associated with a significantly higher in-hospital MACE rate, longer procedure time, higher radiation exposure and contrast volume [14].

Data on long-term outcome after retrograde CTO-PCI are not available. The aim of the present study was to analyze the long-term MACCE rate of patients with retrograde versus antegrade CTO-PCI.

### Methods

#### Study design and patients

In this prospective single center registry, from January 2008 to December 2012 a total of 396 consecutive patients with CTOs were included who met the following criteria.

#### Inclusion criteria

CTO defined as thrombolysis in myocardial infarction (TIMI) flow grade 0 with an estimated duration of at least 3 months. The duration of occlusion was determined by the interval from the last episode of acute coronary syndrome, or from the first episode of effort angina

consistent with the location of the occlusion, or by a previous coronary angiography. No angiographic CTO characteristic was considered an absolute contraindication for an attempt to recanalization.

Angina symptoms or evidence of ischemic myocardium related to the occluded coronary artery, as judged by an abnormal bicycle exercise test, stress-echocardiography, stress-magnetic resonance imaging or stress-single photon emission tomography.

### Exclusion criteria were

Acute ST-segment elevation myocardial infarction. Severe renal failure (creatinine > 3mg/dl). Primary Endpoint of the study was the long-term MACCE rate, defined as death, myocardial infarction, coronary bypass surgery and stroke in patients with successful versus unsuccessful antegrade and retrograde CTO-PCI.

### Complexity classification of the CTO procedures

To classify the CTO procedures according to their complexity, we used the J-CTO Classification scheme [15].

For each of the following characteristics one point was assigned:

- Blunt morphology of occlusion entry point.
- Any visible calcification within the occluded segment.
- Tortuosity exceeding 45° within the occluded segment determined by angiography.
- Occlusion length ≥ 20 mm.
- Previous failed attempts at recanalization.

The lesions were classified as easy, intermediate, difficult and very difficult if the total J-CTO score was 0, 1, 2, or ≥ 3, respectively.

### Angiographic collateral assessment

For collateral connections (CC) the angiographic grading system described by Werner et al. was used [16].

CC 0: No continuous connection,

CC 1: Threadlike continuous connection,

CC 2: Side branch-like connection.

### Definitions

Arterial hypertension was defined as a repeatedly elevated blood pressure exceeding 140/90 mmHg or treatment with antihypertensive drugs.

Dyslipidemia was defined as either an elevated LDL (>100 mg/dl) or the use of lipid-lowering therapy.

The presence of diabetes was based on the use of insulin or oral hypoglycemic agents.

Myocardial infarction was defined according to the “Third universal definition of myocardial infarction” [17].

Procedural success was defined as reopening of the coronary artery with a TIMI III flow and a residual stenosis <30%.

Stroke was defined as a neurological deficit attributed to an acute focal injury of the central nervous system.

### Procedure

All procedures were performed via the femoral artery. Patients received un-fractionated heparin (100 IU/kg) to maintain an activated clotting time >250 sec. The antegrade technique was used as the first approach in all patients. A retrograde procedure was only performed after antegrade failure.

The antiplatelet agent regimens consisted of aspirin 100 mg daily and clopidogrel 75 mg daily at least 5 days before or 600 mg loading dose immediately before the procedure followed by 75 mg daily for 12 months in case of a drug eluting stent or for at least 1 months in case of a bare-metal-stent implantation.

### Follow up

Patient’s follow up was performed either by a clinical visit or by a standardized telephone interview.

### Statistical analysis

Continuous variables were presented as mean ± SD or median. Discrete variables were expressed as percentages. Chi-square test or Fisher’s exact test were used for categorical variables, and unpaired Student t-test for continuous variables. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with Prism 3.0 (GraphPad Software, San Diego, CA).

### Results

#### Patient and procedure characteristics

Mean age of the patients was 63.4 ± 10.3 years, 86.4% were male. The retrograde CTO-PCI, which was used only after a failed antegrade intervention, was performed in 17.9% (n = 71) of patients (Table 1).

Patients with retrograde CTO-PCI had significantly more previous bypass surgery (32.4% versus 19.4%, p = 0.02), RCA as the target vessel (81.7% vs. 56.9%), significantly longer lesions (46.5 vs. 25 mm, p<0.01), longer procedure duration (107.7 vs. 62.5 min, p<0.01), higher contrast volume (421.2 vs. 264.2 ml, p<0.01), longer fluoroscopy time (60.6 versus 29.6 min, p<0.01) and higher radiation exposure (288.0 vs. 144.7 Gy·cm<sup>2</sup> p<0.01) (Tables 1-3).

Target vessel in patients who had a successful antegrade CTO procedure was the right coronary artery (RCA) in 78.6%, the left anterior descending (LAD) in 14.3% and the circumflex artery (CX) in 7% of cases. There was no statistical difference compared to patients with antegrade failed CTO-PCI (RCA 63.2%, LAD 13.2%, CX 21%) (p = 0.62).

Compared to the antegrade group more patients with a RCA occlusion underwent a retrograde procedure (56.9% vs. 81%, p = 0.0001). No difference was found between the retrograde successful compared to the retrograde failed CTO-PCI (successful group: RCA 82.5%, LAD 12.3% versus unsuccessful group: RCA 78.6% and LAD 14.3%, p = 0.9%).

#### In-hospital MACCE

The in-hospital MACCE (death, myocardial infarction, coronary artery bypass graft (CABG), stroke) rate was 0.76% (n = 3), comprising of 2 patients with myocardial infarction and one patient with emergent bypass surgery due to acute left main stent thrombosis. The MACCE

rate did not differ between patients with the antegrade and the retrograde approach.

	All patients (n = 396)	Antegrade (n = 325)	retrograde (n = 71)	p-value ante vs. reto
Age	63.4 ± 10.3	63.7 ± 10.3	61.8 ± 10.2	0.15
Male	86.40%	86.20%	87.30%	0.79
CCS class II-III	77.30%	78.20%	73.20%	0.8
EF%	67.90%	71.9% (n = 226)	57.9% (n = 40)	0.08
>55	25.20%	22.3% (n = 70)	36.2% (n = 25)	
40-55	5.60%	4.1% (n = 13)	2.9% (n = 2)	
30-40	1.30%	1.6% (n = 5)	2.9% (n = 2)	
≤ 30				
Hypokinesia in CTO related segment	39.60%	40.5% (n = 126)	49.3% (n = 34)	0.16
Previous myocardial infarction	27.80%	27.1% (n = 88)	30.9% (n = 22)	0.51
Previous CABG	22.50%	19.4% (n = 63)	32.4% (n = 23)	0.02
Previous PCI	85.60%	84.3% (n = 274)	92.9% (n = 66)	0.06
Coronary artery disease				0.1
1 vessel disease	41.2% (n = 163)	38.8% (n = 126)	52.1% (n = 37)	
2 vessel disease	29.3% (n = 116)	29.8% (n = 97)	26.7% (n = 19)	
3 vessel disease	29.0% (n = 115)	31.8% (n = 100)	21.1% (n = 15)	
Hypertension	98.90%	99.1% (n = 322)	98.6% (n = 70)	0.71
Dyslipidemia	88.60%	87.1% (n = 283)	95.8% (n = 68)	0.036
Diabetes mellitus	25.30%	26.8% (n = 87)	18.3% (n = 13)	0.14
Peripheral artery disease	21.50%	20.0% (n = 65)	28.2% (n = 20)	0.13

**Table 1:** Baseline characteristics.

	All procedures(n = 396)	Antegrade (n = 325)	Retrograde (n = 57)	P-value antegrade vs retrograde
Success rate%	88.6	88	80.3	0.07
Target vessel RCA%	61.4 (n = 243)	56.9 (n = 185)	81.7 (n = 58)	0.0006
LAD%	16.2 (n = 64)	16.9 (n = 55)	12.6 (n = 9)	
CX%	21.5 (n = 86)	25.2 (n = 82)	5.6 (n = 4)	
other%	0.8 (n = 3)	0.9 (n = 3)	0 (n = 0)	
Duration of procedure (min)	70.6 ± 36.4	62.5 ± 30.9	107.7 ± 36.9	<0.0001
Contrast volume	292.4 ± 148.3	264.2 ± 134.2	421.2 ± 142.7	<0.0001
Fluroscopy time	35.2 ± 25.8	29.6 ± 22.8	60.6 ± 23.1	<0.0001
Radiation exposure (Gycm2)	170 ± 145.1	144.7 ± 115.8	288.0 ± 198.4	<0.0001

**Table 2:** Procedural characteristics.

Pericardial effusions were found in 4.0% (n = 13) of patients, significantly more often in the retrograde compared to the antegrade CTO-PCI group (9.8 versus 1.8%, p = 0.006). No patient needed a pericardiocentesis.

Vascular and bleeding complications occurred in 1.5% (n = 5) of patients (1 retroperitoneal hematoma, 4 minor access side bleedings). There was no need for vascular surgery or blood transfusions.

### Long-term MACCE

Follow up data were available in 76.7% of the patients, the mean follow up time was 2.3 ± 1.6 years. The overall long-term MACCE rate was 11.2% (death 5.9%, myocardial infarction 1.6%, CABG 3.6%, stroke 2%). No difference was found in the overall long-term MACCE rate between antegrade versus retrograde CTO-PCI (11.4% vs. 10.3%) and for the components of MACCE. The MACCE rate in patients with unsuccessful CTO-PCI was significantly higher compared to successful CTO-PCI (23.1% versus 9.4%, p=0.01) (Figure 1A).

A significant difference was also found in the subgroup of patients with the antegrade approach (Figure 1B). In more detail, patients with unsuccessful CTO-PCI had a significantly higher rate of CABG, stroke and a trend for higher death rate.

In contrast to the antegrade group, in patients, who underwent the retrograde approach (Figure 1C), the long-term MACCE rate of unsuccessful CTO-PCI was not significantly different to successful PCI (9.1 vs. 10.6%).

The target vessel in patients who experienced a MACCE did not significantly differ in the antegrade successful compared to the antegrade failed CTO-PCI group (RCA 50%, LAD 25%, CX 25% vs. RCA 75%, LAD 0%, CX 25%, p = 0.27). The same was true for patient with MACCE in retrograde successful versus retrograde failed patients where all patients had the RCA as target vessel.

	All procedures (n = 396)	Antegrade (n = 325)	Retrograde (n = 71)	P value
Lesion morphology				
blunt stump	64.10%	60.0% (n = 195)	83.1% (n = 59)	0.027*
calcification	43.20%	43.4% (n = 141)	42.3% (n = 30)	
tortuosity	48.20%	44.6% (n = 145)	64.8% (n = 46)	
lesions length >20 mm	63.90%	58.8% (n = 191)	87.3% (n = 62)	
Previous failed attempt	56.60%	47.1% (n = 153)	100% (n = 71)	
J-CTO score mean	2.8 ± 1.4	2.6 ± 1.3	3.9 ± 0.89	<0.0001*
Lesion complexity				
classification (J-CTO score)				
Easy (score = 0)	4.6% (n = 18)	5.6% (n = 18)	0% (n = 0)	<0.0001*
Intermediate (score = 1)	15.7% (n = 61)	18.8% (n = 60)	1.4% (n = 1)	
Difficult (score = 2)	19.1% (n = 74)	21.9% (n = 70)	5.8% (n = 4)	
Very difficult (score ≥ 3)	60.6% (n = 35)	53.6% (n = 171)	92.8% (n = 64)	
Lesion length (mm) Median (25th, 75th percentile)	25 (18, 45)	25 (18, 45)	46.5 (29, 65)	<0.0001*

**Table 3:** Lesion characteristics.

During follow-up no patient after an unsuccessful retrograde CTO died whereas 3 patients (6.3%) died in the successful retrograde group which did not reach statistical significance. The components of MACCE (death, myocardial infarction, CABG, stroke) were not different between the antegrade and the retrograde group.

Of the total cohort of successfully recanalized patients (n = 344) 10.2% (n = 35) of patients received a 1<sup>st</sup> generation drug eluting stent.

Six out of 35 patients (17.1%) with a 1st generation compared to 19 out of 309 patients with a 2nd generation drug eluting stent (6.2%) experienced a MACCE (p = 0.02).

### Patient characteristics in unsuccessful CTO-PCI

Patient characteristics including age, sex, left ventricular function, previous myocardial infarction, CABG, PCI, extent of coronary artery disease, and cardiovascular risk factors did not differ between patients

with unsuccessful antegrade versus unsuccessful retrograde CTO-PCI (data not shown).

Patients with unsuccessful retrograde CTO-PCI, however, had a significantly better collateral connections compared to patients with unsuccessful antegrade CTO-PCI, CC 2: 89% and 32%, CC 1: 11% and 44%, CC 0: 0% and 24% in unsuccessful retrograde and antegrade CTO-PCI, respectively (p = 0.009) (Figure 2).

## Discussion

### Major findings

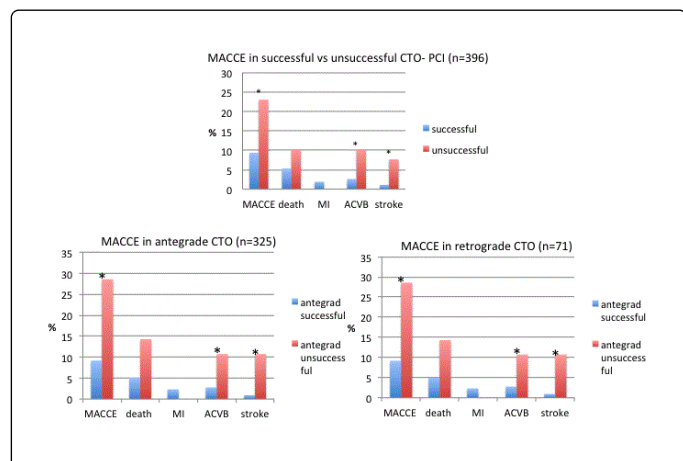
The major findings of the present study are:

- Comparable overall long-term MACCE rate (10.3% vs. 11.4%) and their components (death, myocardial infarction, CABG, stroke) after antegrade versus retrograde CTO-PCI.

- A significantly higher long-term MACCE rate in unsuccessful versus successful CTO-PCI patients (23.1% vs. 9.4%) driven by a higher MACCE rate in unsuccessful versus successful antegrade CTO-PCI (28.6 vs. 11.4%).
- No difference in the long-term MACCE rate of unsuccessful retrograde versus successful retrograde CTO-PCI (9.1 vs. 10.6%).
- A superior collateral connection in patients with unsuccessful retrograde compared to unsuccessful antegrade CTO-PCI.

### Long-term MACCE rate of antegrade versus retrograde CTO-PCI

Long-term data on patients with retrograde CTO-PCI have not been published so far. Gallassi reported a 2 year MACE rate of 13.1% in 172 consecutive CTO-PCI patients. Although 27.5% of patients underwent a retrograde procedure the authors did not provide the outcome of this subgroup [19].



**Figure 1:** A. Total long-term MACCE rate and the components of MACCE. \*p<0.05. MACCE (death, MI, CABG, stroke). MI myocardial infarction. CABG coronary artery bypasses graft. B. Long-term MACCE rate after antegrade CTO-PCI and the components of MACCE. \*p<0.05. C. Long-term MACCE rate after retrograde CTO-PCI and the components of MACCE.

### Long-term MACCE rate of successful versus unsuccessful CTO-PCI

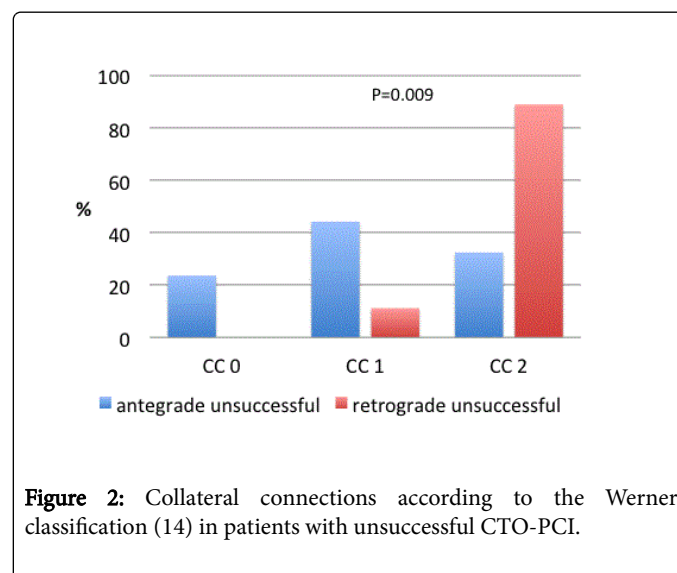
A recently published meta-analysis comprising almost 13,000 patients revealed an improved all-cause mortality, lower MACE rate and reduced need for subsequent bypass surgery after successful versus failed CTO-PCI at a mean follow up time of 3.7 years [18].

In another analysis of 13 observational studies encompassing more than 7,000 patients with a 6-year follow-up, successful CTO-PCI was associated with a 44% reduction in mortality, 78% reduction in the rate of CABG and a significant improvement in symptoms [4]. In the present study we also found a significantly higher MACCE rate in patients with unsuccessful versus successful CTO-PCI. For mortality, however, only a trend in favour of successful PCI was seen. Whereas others [6] found an all-cause mortality for unsuccessful CTO recanalization of 17.2% after a median follow up time of 3.8 years, the mortality in the present study was 14.3% after a mean follow up of 2.3 years. Most probably, the survival curves further diverge over time and after a longer follow up the difference in mortality may have become

significant in our study. In accordance with previous studies [5,6], the rate of bypass surgery was significantly higher in patients with failed recanalization.

In the present study we also considered the long term stroke rate, which has not been analysed previously. There was a surprisingly unfavourable stroke rate in patients with failed antegrade (10.7%) compared to successful antegrade recanalization (0.9%) with no difference in the baseline demographics between both groups. We do not have information on the incidence of atrial fibrillation and oral anticoagulation regime of patients which might have an impact on the stroke rate. Another explanation might be that patients with failed complex CTO have a more advanced general atherosclerosis associated in a higher risk for cerebrovascular events.

However, based on these findings we believe that future follow up studies should include the stroke rate.



**Figure 2:** Collateral connections according to the Werner classification (14) in patients with unsuccessful CTO-PCI.

In the present study, we found no difference in the overall MACCE rate between the antegrade and the retrograde group of patients, although patients in the retrograde group had a higher incidence of previous CABG and dyslipidemia, a trend for a lower ejection fraction and a higher rate of previous PCI, a higher lesion complexity and a more complex recanalization procedure, all of which could impact long-term outcome.

Whereas the MACCE rate between the unsuccessful and the successful antegrade CTO-PCI was significantly different, it did not differ between unsuccessful and successful retrograde CTO-PCI.

The target vessel in patients who experienced a MACCE did not significantly differ in the antegrade successful compared to the antegrade failed CTO-PCI group (RCA 50%, LAD 25%, CX 25% vs. RCA 75%, LAD 0%, CX 25%, (p = 0.27)). The same was true for patient with MACCE in retrograde successful versus retrograde failed patients where all patient had the RCA as target vessel.

The baseline demographics of both groups with failed interventions did not show any significant difference. The selection of patients for a retrograde procedure is based on the suitability to cross collateral vessels.

Indeed we found a significantly better collateral connection in unsuccessful retrograde compared to unsuccessful antegrade patients

which might protect the retrograde patients from future events and at least in part explain their more favourable outcome.

The death rate in patients after successful retrograde during follow up was 6.3% (n = 3), whereas no patient after unsuccessful retrograde CTO-PCI died which did not reach statistical significance. The death rate in patients after successful retrograde CTO-PCI during follow up was 6.3% (n = 3) whereas no patient after unsuccessful retrograde CTO-PCI died which did not reach statistical significance.

### Study limitations

This study has some limitations. First, this is a non-randomized single center study which may have a selection bias that could influence the results.

Second, the follow-up rate was 77%, the mean follow-up time was 2.3 years, and the events were not core lab adjudicated.

Third, the number of patients who underwent a retrograde procedure was limited.

It remains to be shown whether similar results will be found with a more liberal use of the retrograde approach.

### Clinical implications

The study confirms previous findings of a better outcome of patients with successful versus failed CTO-PCI. The new observation is a similar outcome of patients with unsuccessful versus successful retrograde interventions.

This raises the question, whether a selected group of patients with failed antegrade attempts and good collaterals may not benefit from a retrograde procedure in terms of hard endpoints. Further studies have to confirm these preliminary data.

### Conclusions

Compared to successful CTO-PCI, long-term MACCE rate after unsuccessful recanalization was significantly higher which was driven by a higher MACCE rate after unsuccessful versus successful antegrade approach, whereas patients with unsuccessful retrograde CTO-PCI had similar outcome compared to patients with successful retrograde interventions.

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