Impact of clinical characteristics on treatment strategies: the Zurich chronic total occlusion registry

Treatment of patients with chronically occluded coronary arteries

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Summary

Background: Chronic total occlusions (CTOs) are a common finding in patients with coronary artery disease; however, their best management is currently debated.

Objectives: The aim of this study was to assess treatment strategies in patients with CTOs and their interaction with clinical factors.

Methods: From January 2010 to December 2015, all patients in our coronary angiography database with at least one CTO were included. Patients with a history of coronary artery bypass graft (CABG) surgery or heart transplantation and patients with acute occlusions were excluded. Clinical, angiographic and treatment information was collected by review of hospital records and coronary angiograms.

Results: Of 15 869 patients undergoing coronary angiography from 2010–2015, 1004 (6.3%) had at least one CTO (mean age 67.4 ± 11.7 years, 20.0% female). Of these, 899 (89.5%) were symptomatic at the time of presentation. Mean left ventricular ejection fraction (LVEF) was 49.3% ± 14.5%. The initial treatment strategy was medical therapy in 500 patients (49.8%), percutaneous coronary intervention (PCI) in 322 (32.1%), and CABG in 182 (18.1%). Clinical factors associated with medical therapy were advanced age, female gender, congestive heart failure and reduced LVEF. The presence of multivessel coronary artery disease, two or more CTOs in a single patient and a CTO in a main branch (as opposed to side branches) were associated with revascularisation (either PCI or CABG).

Conclusion: CTOs are common findings in patients undergoing invasive coronary angiography. Despite significant improvements in revascularisation techniques, medical treatment remains the most common treatment. Clinical factors significantly influence the choice of the most appropriate treatment strategy.

Key words: chronic total occlusion; medical therapy; percutaneous coronary intervention; coronary artery bypass grafting

Introduction

Chronic total occlusions (CTOs) are a common finding in patients undergoing coronary arteriography, with a reported prevalence in the range of 10–20% [1–4]. The appropriate management of CTOs is a matter of debate, as these lesions are often associated with symptoms (particularly angina pectoris) and myocardial ischaemia, despite well-developed collaterals [5]. Left ventricular ejection fraction (LVEF) is often preserved, indicating residual viability in the territory subtended by the occluded artery [2]. The presence of a CTO is associated with poorer outcomes: in survivors of acute myocardial infarction, a CTO in a noninfarct-related artery was associated with higher long-term mortality than in patients with multivessel disease but without any CTO [6]. Treatment strategies include medical therapy (consisting of optimal anti-ischaemic and antianginal treatment) [3] and/or revascularisation by either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Despite the proven benefits of revascularisation (particularly in the presence of myocardial ischaemia [7]), medical therapy is often contemplated because of concerns about the feasibility and safety of revascularisation. CABG may offer complete revascularisation and is preferred in patients with multivessel disease or left main disease [8]. However, many patients are denied surgery owing to advanced age or comorbidities. The recent two decades have witnessed enormous advances in PCI techniques for revascularisation of CTOs, including improved materials (wires, microcatheters, low-profile balloons, drug-eluting stents) and techniques (retrograde, dissection-re-entry techniques). Thereby, current success rates of PCI have improved to 80–90% with an acceptable safety margin of 1–3% for serious complications (e.g., myocardial infarction, pericardial tamponade, stroke, death) [9]. However, the most appropriate treatment of patients with CTOs remains unclear and is often debated among experts in heart teams.

The purpose of the present study was to assess current treatment strategies and utilisation of resources in patients with CTOs and to evaluate factors associated with treatment decisions.

Methods

Study design

We searched our clinical database of coronary angiographies performed in patients with CTOs between

January 2010 and December 2015 at the University Heart Centre Zurich in Switzerland. The University Hospital Zurich is a tertiary referral centre for PCIs, with an average of 2500–3000 coronary angiographies per year. The study protocol was approved by the local institutional review board (KEK-ZH-Nr. 2015-0041). Consent of patients whose coronary angiography was before 1 January 2015 was waived by the ethics committee because of the retrospective nature of the study. For patients included after that date, informed consent was retrospectively obtained, in accordance with the new Swiss human research rights declaration.

Patient population

All patients with at least one CTO were retrospectively included in our registry. A CTO was defined as an occlusive lesion with TIMI (thrombolysis in myocardial infarction) flow of zero in the occluded segment and an occlusion duration >3 months. If the duration of the CTO was unknown, a CTO was assumed if there was no clinical sign of an acute or subacute occlusion (based on clinical history, electrocardiogram [ECG] and/or biomarkers) and/or the interventional cardiologist was unable to cross a wire after a short antegrade attempt. Exclusion criteria were prior CABG, prior heart transplantation or any acute coronary occlusion. Baseline clinical characteristics were collected from the in-house clinical information system and included age, gender, cardiovascular risk factors, clinical presentation (stable coronary artery disease versus acute coronary syndrome), symptoms, LVEF, and prior ischaemia testing.

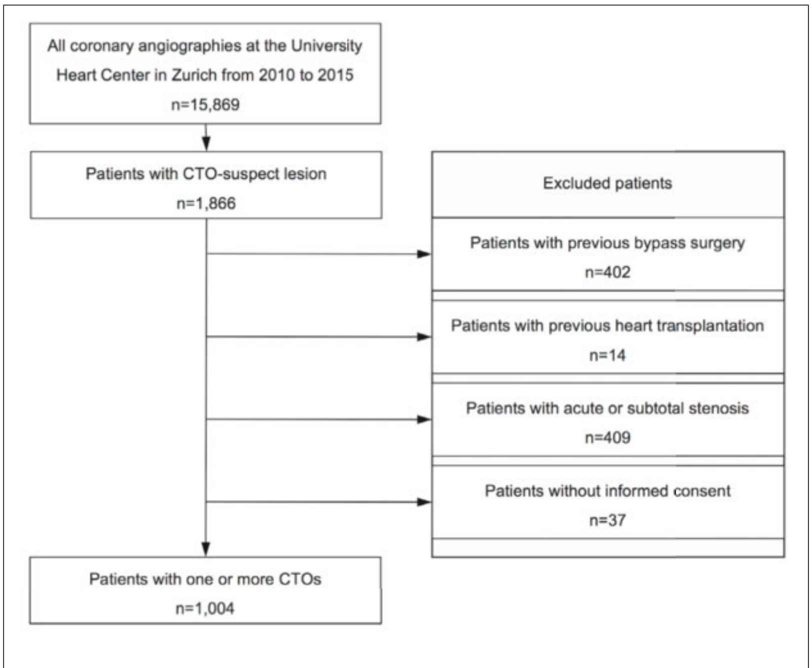

Figure 1: Study recruitment. CTO = chronic total occlusion.

Coronary angiography

All coronary angiograms were stored in a digital database. The location of the CTO was determined using the coronary segmentation model suggested by the American Heart Association, which consists of 15 coronary artery segments [10]. CTOs in the segments 1, 2, 3, 5, 6, 7, 8, 11 or 13 were defined as main-branch CTOs, whereas occlusions in segments 4, 9, 10, 12, 14 or 15 were considered as side-branch CTOs. The severity of coronary artery disease (number of stenosed coronary arteries) was determined from the angiograms. Coronary artery stenosis was defined as luminal narrowing of ≥50%.

Treatment strategies

Patients were categorised into three treatment groups according to their initial treatment strategy: medical therapy, PCI and CABG. The medical therapy group included all patients who did not undergo revascularisation. If there was any attempt to revascularise the CTO by means of PCI, the patient was included in the PCI group regardless of the outcome or the further treatment of the CTO. In patients treated primarily with CABG, the number and location of the bypass grafts did not influence inclusion into this group.

Statistical analysis

All statistical analyses were performed using SPSS statistics 24.0 (SPSS Inc., SPSS, Chicago, USA). Continuous values are presented as mean ± standard deviation (SD) and were compared using the Kruskal-Wallis test. Categorical data are presented as counts and percentages and were compared with the chi-squared test. Logistic regression was used to evaluate differences between the medically treated group and the revascularisation group (PCI and CABG). The results of logistic regression analysis are given as odds ratios (ORs) with their respective 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant for all tests.

Results

Study population

From 2010 to 2015, a total of 15 869 patients underwent coronary angiography at the University Heart Centre Zurich. Of these patients, 1004 (6.3%) showed at least one CTO on coronary angiography (figs 1 and 2). The patients' baseline characteristics are summarised in table 1. The majority of CTO patients were male (80.0%) and the mean age was 67.4 ± 11.7 years. Dyslipidaemia,

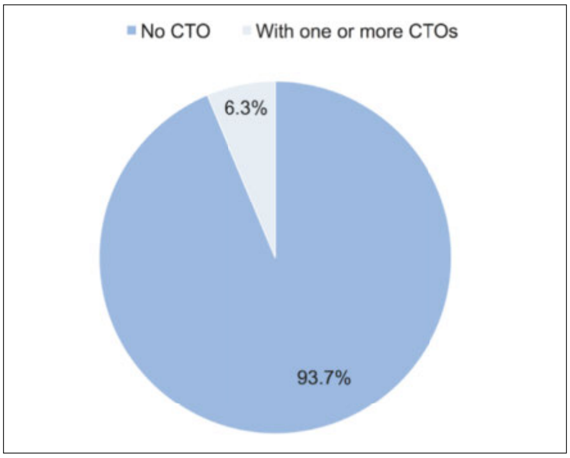

Figure 2: Total coronary angiographies at the University Heart Centre Zurich from 2010 to 2015. CTO: chronic total occlusion.

hypertension and smoking were present in about two thirds of all patients.

Approximately half of the patients (52.8%) presented in an unstable condition (e.g., acute coronary syndrome, congestive heart failure, out-of-hospital resuscitation or cardiogenic shock). The other half of the patients presented for elective coronary angiography. Ischaemia testing was performed in less than half of the patients (46.2%), with a majority of these having either a stress ECG or myocardial perfusion imaging with SPECT (single photon emission computed tomography). The mean LVEF was 49.3 ± 14.5% and 18.4% of all patients had a LVEF lower than 35%.

Patients in the medical therapy group were older and more often female compared with the other groups. There were few differences in clinical presentation be-

Table 1: Baseline characteristics.

	All patients (n = 1004)	MT (n = 500)	PCI (n = 322)	CABG (n = 182)	p-value
Age (years) (mean ± SD)	67.4 ± 11.7	69.2 ± 11.9	64.1 ± 12.0[¶,§]	68.1 ± 9.7	<0.001
Female (%)	201 (20.0)	115 (23.0)	59 (18.3)	27 (14.8)[#]	0.041
Cardiovascular risk factors (%)					
Obesity (BMI >30 kg/m²)	269 (26.8)	125 (25.0)	89 (27.6)	55 (30.2)	0.576
Diabetes mellitus	312 (31.1)	147 (29.4)	98 (30.4)	67 (36.8)	0.175
Hypertension	736 (73.3)	369 (73.8)	225 (69.9)[Δ]	142 (78.0)	0.112
Dyslipidaemia	696 (69.3)	341 (68.2)	228 (70.8)	127 (69.8)	0.655
Current or previous smoker	683 (68.0)	329 (65.8)	228 (70.8)	126 (69.2)	0.293
Clinical presentation (%)					
Stable patients	474 (47.2)	234 (46.8)	146 (45.3)	94 (51.6)	0.382
Typical angina	171 (17.0)	70 (14.0)	63 (19.6)*	38 (20.9)	0.020
Atypical angina	11 (1.1)	5 (1.0)	4 (1.2)	2 (1.1)	0.922
Dyspnoea	135 (13.4)	79 (15.8)	33 (10.2)*	23 (12.6)	0.040
Asymptomatic patients	105 (10.5)	55 (11.0)	30 (9.3)	20 (11.0)	0.776
Others	52 (5.2)	25 (5.0)	16 (5.0)	11 (6.0)	0.965
Unstable patients	530 (52.8)	266 (53.2)	176 (54.7)	88 (48.4)	0.382
Unstable angina / NSTEMI	297 (29.6)	136 (27.2)	101 (31.4)	60 (33.0)	0.240
STEMI	76 (7.6)	39 (7.8)	27 (8.4)	10 (5.5)	0.481
Congestive heart failure	57 (5.7)	43 (8.6)	6 (1.9)[¶]	8 (4.4)	<0.001
Cardiogenic shock	35 (3.5)	19 (3.8)	12 (3.7)	4 (2.2)	0.577
Out-of-hospital resuscitation	65 (6.5)	29 (5.8)	30 (9.3)[Δ]	6 (3.3)	0.021
Ischaemia testing (%)	464 (46.2)	204 (40.8)	170 (52.8)[¶]	90 (49.5)[#]	0.002
Exercise ECG	147 (14.6)	56 (11.2)	50 (15.5)[Δ]	41 (22.5)[#]	0.006
Stress echocardiography	19 (1.9)	8 (1.6)	7 (2.2)	4 (2.2)	0.978
SPECT	161 (16.0)	74 (14.8)	64 (19.9)	23 (12.6)	0.123
Stress CMR	95 (9.5)	44 (8.8)	34 (10.6)	17 (9.3)	0.855
PET	43 (4.3)	22 (4.4)	16 (5.0)	5 (2.7)	0.361
LVEF (%) (mean ± SD)	49.3 ± 14.5	47.2 ± 15.3	51.3 ± 13.7[¶]	51.4 ± 12.9[#]	<0.001
LVEF ≤35% (%)	185 (18.4)	114 (22.8)	46 (14.3)*	25 (13.7)[#]	0.001

MT: medical therapy; PCI: percutaneous coronary angiography; CABG: coronary artery bypass grafting; BMI: body mass index; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; ECG: electrocardiogram; SPECT: single photon emission computed tomography; CMR: computer magnetic resonance; PET: positron emission tomography; LVEF: left ventricular ejection fraction; * MT vs PCI, p <0.05; ¶ MT vs PCI, p ≤0.001; # MT vs CABG, p <0.05; Δ PCI vs CABG, p <0.05; § PCI vs CABG, p ≤0.001.

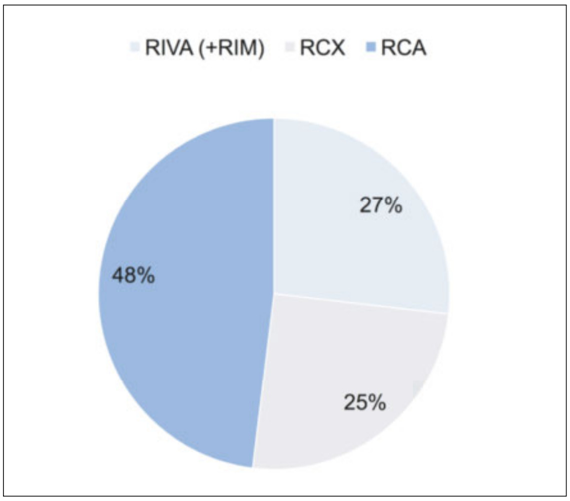

Figure 3: CTO distribution in main vessel territories. RIVA: ramus interventricularis anterior; RIM: ramus intermedius; RCX: ramus circumflexus; RCA: right coronary artery

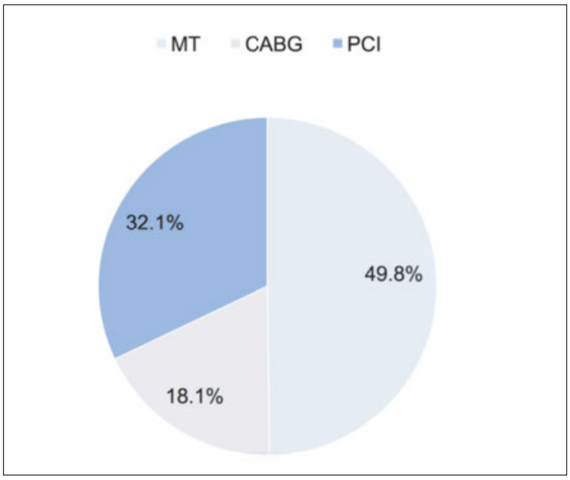

Figure 4: CTO treatment strategies. MT: medical treatment, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention.

tween the three treatment groups. There was a higher prevalence of congestive heart failure and dyspnoea in the medical therapy group than the revascularisation groups. Moreover, patients presenting with typical angina or after out-of-hospital resuscitation were more likely to undergo PCI. Ischaemia testing was more common and LVEF was higher in patients undergoing revascularisation (PCI or CABG) compared with the medical therapy group.

Angiographic characteristics

Table 2 shows the angiographic characteristics of the entire study population. In 1004 patients, 1159 single CTOs were counted of which 557 affected the RCA (right coronary artery) territory, 291 the RCX (ramus circumflexus) territory and 311 the RIVA (ramus interventricularis anterior) territory (fig. 3). The majority of patients (84.8%) had only one CTO; the remainder had two or more. Approximately half of all patients had triple-vessel disease. In the CABG group, the proportion of triple-vessel disease patients was almost 80%. Single-vessel disease patients were more likely to receive medical therapy or undergo PCI, with only a minority referred for CABG.

Treatment strategies

The distribution of treatment strategies is illustrated in figure 4. Half of all patients received medical therapy only. In 32.1%, PCI was the initial treatment strategy, but recanalisation of the CTO was successful in only 55.6% of these patients. Hence, essentially 34.2% crossed over from the PCI group to the medical therapy group since the CTO remained occluded. CABG was the treatment strategy in 18.1% of all patients. Table 3 shows a logistic regression analysis of different patient

Table 2: Angiographic findings.

	All patients (n = 1004)	MT (n = 500)	PCI (n = 322)	CABG (n = 182)	p-value
Single-vessel disease (%)	144 (14.3)	79 (15.8)	61 (18.9)§	4 (2.2)$^{\Sigma}$	<0.001
Double-vessel disease (%)	345 (34.4)	178 (35.6)	134 (41.6)§	33 (18.1)$^{\Sigma}$	<0.001
Triple-vessel disease (%)	515 (51.3)	243 (48.6)	127 (39.4)*§	145 (79.7)$^{\Sigma}$	<0.001
CTO in main artery (%)	850 (84.7)	398 (79.6)	281 (87.3)$^{*\Delta}$	171 (94.0)$^{\Sigma}$	<0.001
Number of CTOs (%)					
1	851 (84.8)	447 (89.4)	261 (81.1)¶	143 (78.6)$^{\Sigma}$	<0.001
2	121 (12.1)	41 (8.2)	48 (14.9)*	32 (17.6)$^{\Sigma}$	0.001
≥3	32 (3.2)	12 (2.4)	13 (4.0)	7 (3.8)	0.365
CTO vessel (%) (segments)					
RIVA (6, 7, 8, 9, 10)	311 (31.0)	142 (28.4)	114 (35.4)	55 (30.2)	0.103
RCX (11, 12, 13, 14, 15)	291 (29.0)	133 (26.6)	105 (32.6)	53 (29.1)	0.179
RCA (1, 2, 3, 4)	557 (55.5)	281 (56.2)	160 (49.7)$^{\Delta}$	116 (63.7)	0.009
In-stent CTOs (%)	35 (3.5)	14 (2.8)	19 (5.9)$^{*\Delta}$	2 (1.1)	0.009

CTO: chronic total occlusion; RIVA: ramus interventricularis anterior; RIM: ramus intermedius; RCX: ramus circumflexus; RCA: right coronary artery; MT: medical treatment; PCI: percutaneous coronary intervention; CABG: coronary atery bypass graft. * MT vs. PCI, $p < 0.05$; ¶ MT vs. PCI, $p \leq 0.001$; $^{\Sigma}$ MT vs. CABG, $p \leq 0.001$; $^{\Delta}$ PCI vs. CABG, $p < 0.05$; § PCI vs. CABG, $p \leq 0.001$

Table 3: Uni- and multivariate logistic regression analysis – predictors of revascularisation.

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex	0.69 (0.50–0.94)	0.019	0.85 (0.58–1.25)	0.415
Age	0.97 (0.96–0.98)	<0.001	0.98 (0.97–0.99)	0.003
Obesity	1.15 (0.87–1.53)	0.326	1.17 (0.85–1.63)	0.341
Diabetes	1.17 (0.90–1.53)	0.244	1.17 (0.85–1.61)	0.345
Hypertension	0.94 (0.71–1.25)	0.675	0.92 (0.65–1.29)	0.612
Dyslipidaemia	1.10 (0.83–1.46)	0.519	0.89 (0.64–1.24)	0.490
Smoking status	1.20 (0.91–1.58)	0.191	1.01 (0.73–1.39)	0.958
Stable clinical presentation	1.03 (0.81–1.32)	0.795	0.80 (0.59–1.10)	0.167
Unstable clinical presentation	0.97 (0.76–1.24)	0.795	0.80 (0.59–1.10)	0.167
Ischaemia testing	1.55 (1.21–1.99)	0.001	1.37 (1.01–1.87)	0.045
Ejection fraction	1.02 (1.01–1.03)	<0.001	1.03 (1.02–1.04)	<0.001
Three-vessel-disease	1.24 (0.97–1.59)	0.089	1.42 (1.05–1.91)	0.024
CTO in main artery	0.45 (0.31–0.64)	<0.001	0.45 (0.30–0.67)	<0.001
Number of CTOs	1.69 (1.23–2.33)	0.001	1.87 (1.28–2.75)	0.001

OR: odds ratio; CI: confidence interval; CI: confidence interval; CTO: chronic total occlusion

characteristics, comparing medical treatment with revascularisation (either PCI or CABG). Predictors for revascularisation were younger age, a preserved LVEF, three-vessel disease, two or more CTOs in a single patient or location of the occlusion in a main artery.

Discussion

In our study, patient characteristics and treatment strategies were assessed in more than 1000 consecutive patients with CTOs undergoing coronary angiography in a large tertiary referral centre over a period of 6 years. We found a 6.3% prevalence of CTOs among all diagnostic coronary angiographies. Although this is a sizable number, it is lower than in previously published literature. The Canadian Multicenter Chronic Total Occlusions Registry reported a CTO prevalence of 18.4% [2]. Råmunddal et al. found a prevalence of 10.9% [4] and Tomasello et al., 13.3% [11]. The lower prevalence in our registry may be explained by centre or referral bias: as a tertiary referral centre for many structural heart disease interventions and operations, we have a considerable number of referrals for preoperative diagnostic angiography (e.g., prior to valvular surgery, transcatheter aortic valve implantation or percutaneous mitral valve repair). This lowers the proportion of patients referred for suspected coronary artery disease, and thereby the CTO prevalence. Nonetheless, the reported CTO prevalence amounts to an average of almost four patients with at least one CTO per week.

Clinical characteristics

In line with previous studies [2, 4, 11, 12], our CTO population showed a high prevalence of cardiovascular risk factors. The vast majority were symptomatic at the time of presentation (only 10.5% were asymptomatic), emphasising the need for appropriate treatment strategies to reduce symptomatic burden. Moreover, half of the patients presented with unstable symptomatology, either acute coronary syndrome or congestive heart failure. Several studies indicate improvement of symptoms after successful revascularisation of CTOs [11, 13, 14]. The presence of angina, dyspnoea or other related symptoms is one of the main reasons for interventions in patients with CTO lesions. Werner et al. demonstrated, by measuring fractional flow reserve across the CTO lesions and assessing collateral flow reserve (using a Doppler ultrasound catheter), that even in the presence of well-developed collaterals the vast majority of patients with CTOs suffer ischaemia in the territory of the occluded artery [5]. Safley and colleagues showed that CTO PCI was effective in reducing myocardial ischaemia in the territory subtended by the occluded artery and that patient outcome was improved in those with the most significant reduction in ischaemic burden after PCI [7].

LVEF was well preserved in the majority of the patients, indicating significant myocardial viability. Tomasello et al. found that a low LVEF is an independent predictor for medical treatment [11]. In our study, we obtained similar results, with significantly more patients in the medical therapy group with an LVEF below 35%. However, a low LVEF may not necessarily indicate lack of myocardial viability. Assessment of myocardial viability with imaging techniques may be warranted in patients with a low LVEF, as those with significant myocardial viability may improve their LVEF upon successful CTO recanalisation.

Like the findings of Tomasello et al. in the Italian CTO registry, more than half of our patients had triple-vessel disease [11]. This confirms that CTOs often coexist with advanced coronary disease. These patients were significantly more often treated with CABG than with PCI or medical treatment, as recommended by ESC guidelines for myocardial revascularisation [8]. Of patients with single-vessel disease (only one CTO without any further remote stenosis), only a minority were referred for CABG, with medical therapy and PCI being the preferred treatment strategies.

Ischaemia testing

Ischaemia testing can be used as a tool for decision making and follow up in patients with CTOs [15–17]. Several studies have shown that successful PCI for a

CTO reduces inducible myocardial ischaemia and improves regional wall motion [17, 18]. Moreover, findings of ischaemia in a collateral-supplied area may favour revascularisation over medical treatment, as there is evidence that even well-developed collaterals do not prevent myocardial ischaemia during cardiac stress [19, 20]. However, the amount of myocardial ischaemia is an important predictor of outcome [21]. Furthermore, patients with small ischaemic territories have less ischaemic relief and worse outcomes after revascularisation [7]. In our study population, less than half of all patients were tested for ischaemia. Although there were significantly more ischaemia tests in the PCI and CABG groups than in the medical therapy group, the overall rate of examinations was between 40 to 50% in all three treatment groups, emphasising the need for more extensive ischaemia testing prior to CTO revascularisation procedures.

Patient management

Fefer et al. found that 44% of their study population received medical treatment only, 26% had bypass surgery and 30% underwent a PCI procedure, but only 10% of the CTOs as such were approached via PCI [2]. In the report from the Swedish Coronary Angiography and Angioplasty Registry, Råmunddal et al. analysed data of 16 818 CTO patients; 56% of them received medical therapy, 21.7% had surgical revascularisation and 22.3% PCI [4]. In contrast to these studies, 32.1% of our patients were treated with PCI. Tomasello et al. had an even higher rate of patients undergoing PCI (43.7%) and only 9.8% had CABG [11]. These results may be explained by differences in study populations, the individual benefit assessment by cardiologists in single institutions and progress in the field of interventional cardiology driven by better equipment, new techniques and more experienced operators. As in previous studies [2, 4, 11, 12], angiographic characteristics that favoured the decision to revascularise the CTO were the presence of three-vessel disease, number of CTOs, and a CTO in a main vessel (as opposed to a side branch).

Limitations

A number of limitations should be acknowledged. Because of the single-centre nature of the study, our report is based on a limited sample size. Furthermore, we did not have a non-CTO control group to compare the distribution of baseline characteristics and treatment strategies between CTO and non-CTO patients. Moreover, we did not obtain clinical follow-up to assess the effects of treatment strategies on patient outcomes and symptoms. Finally, the adequacy of revascularisation with CABG was not systematically assessed. In the SYNTAX trial, only 68.1% of patients with at least one CTO had adequate grafting of the occluded artery; therefore complete revascularisation was not achieved in some of our patients undergoing CABG [22].

Conclusion

CTOs are common findings in patients undergoing invasive coronary angiography. Despite significant improvements in revascularisation techniques (particularly in the field of PCI), medical therapy remains the most common treatment of CTO patients. Advanced age and reduced ejection fraction are factors that predispose patients to medical treatment. On the other hand, multivessel disease, the presence of a CTO in a main coronary artery and more than one CTO in a patient favour revascularisation with either PCI or CABG.

Disclosure statement
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The full list of references is included in the online version of the article at www.cardiovascmed.ch

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