Clin Res Cardiol (2017) 106:428–435
DOI 10.1007/s00392-016-1072-z

ORIGINAL PAPER

Impact of multi-vessel versus single-vessel disease on outcomes after percutaneous coronary interventions for chronic total occlusions

Aurel Toma[1] · Barbara E. Stähli[2] · Michael Gick[1] · Cathérine Gebhard[1] · Thomas Nührenberg[1] · Kambis Mashayekhi[1] · Miroslaw Ferenc[1] · Franz-Josef Neumann[1] · Heinz Joachim Buettner[1]

Received: 8 November 2016 / Accepted: 21 December 2016 / Published online: 24 February 2017

Abstract
Background Successful chronic total occlusion (CTO) revascularization has been associated with prognostic benefits. Whether the extent of coronary artery disease interferes with these benefits has not been investigated yet.
Aims We sought to compare the survival after percutaneous coronary intervention (PCI) for CTO between patients with multi- (MVD) and single-vessel disease (SVD).
Methods A total of 2002 consecutive patients undergoing CTO PCI between 01/2005 and 12/2013 were identified and stratified according to the presence/absence of MVD. The primary endpoint was all-cause mortality. Median follow-up was 2.6 (interquartile range 1.1–3.1) years.
Results A total of 1634 (81.6%) patients had MVD. Procedural success rates were 81.5 and 89.7% in the MVD and SVD groups ($p<0.001$). All-cause mortality during entire follow-up was higher in MVD as compared to SVD patients (13.5 versus 5.7%, $p<0.001$), and differences were attenuated after multivariable adjustment for baseline characteristics [adjusted hazard ratio (HR) 1.51, 95% CI 0.98–2.33, $p=0.06$]. The effect of successful CTO PCI on all-cause mortality was consistent among patients with MVD [11.0 versus 24.5%; adjusted HR 0.60, 95% CI 0.45–0.80, $p<0.001$] and SVD [5.2 versus 10.5%; adjusted HR 0.74, 95% CI 0.24–2.26, $p=0.59$, $P_{int}=0.65$]. However, due to the greater baseline risk in the former group, the absolute survival benefit after successful CTO PCI was higher.
Conclusions Successful recanalization of a CTO is a strong independent predictor for reduced long-term mortality. Due a higher baseline risk, the absolute benefit in patients with MVD is substantially larger than in patients with SVD.

Keywords Coronary artery disease · Chronic total occlusion · Percutaneous coronary intervention · Multi-vessel disease · Single-vessel disease

Introduction

Chronic total occlusions (CTO) are frequently encountered in patients evaluated for coronary artery disease [1, 2], and percutaneous coronary intervention (PCI) for CTO is increasingly performed in contemporary angioplasty practice given the survival benefit associated with successful CTO recanalization that was found in various registries [3–8]. Albeit impressive advancements in device technology and interventional techniques were achieved over the last decades [9–11], along with a growing operator experience in this field, recanalization of CTO lesions continues to be particularly challenging and associated with lower procedural success rates as compared with PCI for non-occlusive coronary artery disease [12, 13]. Given the comorbidities and complex lesion characteristics frequently encountered in these high-risk patients, along with the associated increased procedural risk, selection of patients that are likely to benefit most from percutaneous coronary revascularization is paramount. Besides patient-related factors, lesion characteristics, such as calcification severity, tortuosity, stump morphology, and occlusion length, along

A. Toma and B. E. Stähli have contributed equally.

✉ Aurel Toma
toma.aurel@gmail.com

[1] Division of Cardiology and Angiology II, University Heart Center Freiburg-Bad Krozingen, Bad Krozingen Suedring 15, 79189 Bad Krozingen, Germany

[2] Department of Cardiology, Campus Benjamin Franklin, Charité-University Medicine Berlin, Berlin, Germany

with the disease extent, need to be taken into account when attempting CTO PCI [14, 15]. Although complex coronary artery disease as reflected by a high SYNTAX score has recently been associated with reduced procedural success rates and worse clinical outcomes in patients undergoing CTO PCI [16, 17], a more pronounced survival benefit of CTO recanalization in patients with multi-vessel disease (MVD) has been suggested in a cohort of 486 patients [6]. However, evidence that prognostic benefits of successful CTO recanalization may depend on the extent of coronary artery disease is scarce, and direct comparisons of outcomes between patients with and without MVD undergoing CTO PCI are lacking.

The aim of this analysis was therefore to assess procedural characteristics and long-term clinical outcomes of patients with MVD and single-vessel disease (SVD) undergoing CTO PCI, and further, to elucidate survival benefits of successful CTO recanalization according to the disease extent.

Methods

Patients

As part of the quality management program the clinical database of our institution comprises comprehensive demographic, clinical and angiographic data, as well as in-hospital and long-term outcomes of all patients undergoing elective PCI [18]. Outpatient visits and/or telephone calls were prospectively performed at 30 days, at 1 year, and at 3 years after PCI. A total of 2002 patients who underwent elective PCI for at least 1 CTO between January 2005 and December 2013 were identified and included in the CTO registry [19, 20]. All operators performing CTO PCI procedures had significant expertise in this field. Indications for CTO PCI were based on angina symptoms and/or proven ischemia (presence of viable myocardium with perfusion defect on cardiac magnetic resonance imaging, inducible ischemia on stress echocardiography, or inducible ischemia on myocardial perfusion scintigraphy).

Definitions

Coronary CTO was defined as a totally occluded coronary artery with complete interruption of antegrade blood flow (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0) of an estimated duration of ≥3 months [21]. Duration was estimated based on previous angiography findings, onset of anginal symptoms, and prior myocardial infarction in the CTO vessel territory. Procedural success was defined based on coronary angiography findings. CTO revascularization was considered successful when both a <30% residual diameter stenosis by visual assessment within the target segment and complete restoration of antegrade blood flow (TIMI flow grade 3) were achieved.

The primary endpoint was all-cause mortality. The secondary endpoint was major adverse cardiovascular event (MACE), the composite of all-cause death, non-fatal myocardial infarction, and clinically indicated target vessel revascularization (TVR) including PCI and CABG. Non-fatal myocardial infarction was defined based on electrocardiographic findings (new Q waves in two or more contiguous leads) or laboratory criteria (elevated creatine kinase or creatine kinase-myocardial band to at least three times the upper limit of normal in two plasma samples during hospitalization) [22–24].

Statistical analysis

Continuous variables are given as mean ± standard deviation (SD), or median and interquartile range, and categorical variables presented as frequencies and percentages. Normality of distribution was assessed by the Kolmogorov–Smirnov test. Continuous variables were tested for differences with the unpaired Student's t test or the Mann–Whitney U test, and categorical variables with the Pearson's χ^2 test or the Fisher's exact test, respectively. Logistic regression and Cox proportional hazards models were utilized to assess adjusted risks of the outcome variables (procedural success, the composite MACE, and the individual MACE components). Models were adjusted for selected variables showing significant differences between groups ($p < 0.05$), including age, gender, diabetes, smoking, hypertension, estimated glomerular filtration rate, prior myocardial infarction, prior percutaneous coronary revascularization, prior coronary artery bypass grafting, left ventricular ejection fraction <40%, target vessel, moderate/severe calcification, and procedural success. Cox proportional hazards regression test of interaction (MVD/SVD status by procedural success/failure status) was used to assess whether there was a differential effect of procedural success by MVD/SVD status. Kaplan–Meier survival curves were generated using the log-rank test to assess differences between groups. A two-sided p value of <0.05 was considered statistical significant. All statistical analyses were performed using IBM-SPSS version 24 (IBM Corp.).

Results

Patient characteristics

Median follow-up was 2.6 (1.1–3.1) years. A total of 1634 (81.6%) patients had MVD; two- and three-vessel disease was present in 572 (28.6%) and 1062 (53.0%) patients.

Patients with MVD had a higher baseline risk profile than patients with SVD (Table 1). Patients with MVD were older ($p<0.001$) and more frequently male ($p<0.001$) as compared with patients with SVD. Multi-vessel disease was associated with a higher prevalence of diabetes ($p=0.001$), hypertension ($p<0.001$), prior myocardial infarction ($p<0.001$), chronic kidney disease ($p=0.003$), and left ventricular systolic dysfunction ($p<0.001$). Patients with SVD were more frequently smoking ($p=0.001$) and had a higher rate of prior failed CTO PCI attempts ($p=0.045$).

Angiographic and procedural characteristics

Target vessels for CTO PCI differed significantly between patients with and without MVD ($p<0.001$, Table 2). The left anterior descending coronary artery was more frequently affected in SVD patients ($p<0.001$), and left circumflex coronary artery lesions more often encountered in MVD patients ($p<0.001$). Moderate to heavy calcifications were more frequently observed in the MVD group ($p<0.001$). Procedural complexity as reflected by a higher amount of contrast volume ($p<0.001$), a longer fluoroscopy time ($p<0.002$), and an increased radiation dose ($p<0.003$) was higher in patients with MVD. The retrograde approach was more frequently used in SVD as compared to MVD patients ($p=0.008$).

Table 1 Baseline characteristics

	SVD ($n=368$)	MVD ($n=1634$)	p value
Demographic and clinical characteristics			
Age, years	62 ± 10.9	65.9 ± 10.4	<0.001
Female gender	85 (23.1)	247 (15.1)	<0.001
Body mass index, kg/m^2	27.9 ± 4.2	28.2 ± 4.4	0.228
Diabetes mellitus	83 (22.6)	507 (31.0)	0.001
Current smoking	97 (26.4)	304 (18.6)	0.001
Dyslipidemia	312 (84.8)	1414 (86.5)	0.211
Hypertension	273 (74.2)	1374 (84.1)	<0.001
Family history of coronary artery disease	145 (39.4)	603 (36.9)	0.201
Prior myocardial infarction	58 (15.8)	435 (26.6)	<0.001
Prior CABG	3 (0.8)	289 (17.7)	<0.001
Prior PCI	27 (7.3)	283 (17.3)	<0.001
Previous failed attempt	80 (21.7)	290 (17.7)	0.045
Laboratory and echocardiographic characteristics			
CKD (stage 4), n (%)	54 (14.7)	340 (20.9)	0.003
eGFR (Cockcroft), ml/min	94.2 ± 34.1	87.4 ± 33.9	0.001
Total cholesterol, mmol/l	195.1 ± 47.1	188 ± 47.5	0.01
HDL cholesterol, mmol/l	50.5 ± 15.2	49.1 ± 14.4	0.093
LDL cholesterol, mmol/l	119.1 ± 40.1	116 ± 40.7	0.188
LVEF <40%	41 (11.1)	307 (18.8)	<0.001

Values are given as mean and standard deviation or number and percentage

CABG coronary artery bypass grafting, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LVEF* left ventricular ejection fraction, *MVD* multi-vessel disease, *PCI* percutaneous coronary intervention, *SVD* single-vessel disease

Outcomes

Procedural success was lower in the MVD (81.5%) as compared to the SVD group (89.7%, $p<0.001$). Multi-vessel disease was significantly associated with procedural failure (adjusted OR 1.59, 95% CI 1.09–2.32, $p=0.02$). Rates of in-hospital procedural complications were low, and were observed in 28 (1.7%) and 3 (0.8%) patients in the MVD and the SVD groups. In MVD patients, cardiac tamponade occurred in ten (0.6%), coronary perforation in five (0.3%), aortic dissection in two (0.1%), and cerebrovascular accident in two (0.1%) patients. Vascular access site complications were observed in six (0.4%) and two (0.5%) patients in the MVD and SVD groups, and bleeding requiring transfusion of red packed blood cells in nine (0.6%) and three (0.8%) patients, respectively.

All-cause mortality was significantly higher in MVD as compared to SVD group (13.5 versus 5.7%, $p<0.001$, Table 3; Fig. 1a). This difference in all-cause mortality between groups was mitigated after multivariable adjustment for baseline characteristics (adjusted HR 1.51, 95% CI 0.98–2.33, $p=0.06$). Rates of MACE were higher in the MVD as compared to the SVD group (33.3 versus 19.8%, $p<0.001$, Fig. 1b). A significant difference in MACE rate persisted after adjusting for baseline differences (adjusted HR 1.65, 95% CI 1.28–2.12, $p<0.001$). The composite of all-cause death and myocardial infarction was observed in 16.7% and 7.9% (p=0.02), and target vessel revascularization in 19.7% and 13.0% ($p=0.002$) of patients in the MVD and SVD groups, respectively.

Cumulative event curves for all-cause mortality and MACE are displayed in Fig. 2. In the MVD group, all-cause mortality was significantly reduced in patients with procedural success (11.0 versus 24.5%, adjusted HR 0.60, 95% CI 0.45–0.80, $p<0.001$). A consistent relative risk reduction for all-cause mortality ($P_{\text{interaction}}=0.65$, Fig. 3) was found in the SVD group, albeit without reaching statistical significance (5.2 versus 10.5%, adjusted HR 0.75, 95% CI 0.24–2.26, $p=0.59$). Given the higher baseline risk in the MVD group, the absolute survival benefit was higher in the MVD as compared to the SVD group (14.5 versus 5.3%). Numerically, survival benefit of

Table 2 Angiographic and procedural characteristics

	SVD (n = 368)	MVD (n = 1634)	*p* value
Lesion characteristics			
CTO target vessel			<0.001
LM	0 (0)	15 (0.9)	0.09
LAD	146 (39.7)	410 (25.1)	<0.001
LCX	46 (12.5)	454 (27.8)	<0.001
RCA	176 (47.8)	755 (46.2)	0.60
Lesion length >20 mm	276 (75)	1248 (76.4)	0.309
Moderate or severe calcifications	166 (45.1)	955 (58.4)	<0.001
Procedural characteristics			
Procedural success	330 (89.7)	1332 (81.5)	<0.001
Drug-eluting stent	320 (97.0)	1234 (92.)	0.002
Bare metal stent	9 (2.7)	65 (4.9)	0.055
Drug-eluting balloon	0 (0.0)	7 (0.5)	0.212
Number of stents	1.4 ± 0.8	1.3 ± 1.0	0.047
Total stent length, mm	38.0 ± 24.9	34.1 ± 26.5	0.011
Retrograde approach	106 (28.8)	370 (22.6)	0.008
Contrast volume, ml	268 ± 139	332 ± 158	<0.001
Fluoroscopy time, min	30.9 ± 30.4	37.4 ± 38.1	0.002
Kerma-area-product, cGy cm^2	10,525 ± 14,654	12,845 ± 13,341	0.003

Values are given as mean and standard deviation or number and percentage

CTO chronic total occlusion, *LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery, *LM* left main coronary artery, *MVD* multi-vessel disease, *RCA* right coronary artery, *SVD* single-vessel disease

Table 3 Long-term outcomes of patients with single- versus multi-vessel disease

	SVD (*n* = 368)	MVD (*n* = 1634)	Crude		Adjusted*	
			HR (95% CI)	*p* value	HR (95% CI)	*p* value
All-cause death	21 (5.7%)	220 (13.5%)	2.55 (1.63-4.0)	<0.001	1.51 (0.98–2.33)	0.062
All-cause death and/or myocardial infarction	29 (7.9%)	273 (16.7%)	2.28 (1.56–3.5)	<0.001	1.58 (1.06–2.36)	0.023
Target vessel revascularization	48 (13.0%)	322 (19.7%)	1.69 (1.25–2.29)	<0.001	1.65 (1.20–2.26)	0.002
MACE	73 (19.8%)	544 (33.3%)	1.94 (1.52–2.48)	<0.001	1.65 (1.28–2.12)	< 0.001

*Adjusted for baseline variables showing differences ($p < 0.05$) between SVD and MVD patients, including age, gender, diabetes, smoking, hypertension, estimated glomerular filtration rate, prior myocardial infarction, prior percutaneous coronary revascularization, prior coronary artery bypass grafting, left ventricular ejection fraction <40%, target vessel, moderate/severe calcifications, and procedural success

Values are given as numbers and percentages

CI confidence interval, *HR* hazard ratio, *MACE* major adverse cardiovascular events, *MVD* multi-vessel disease, *SVD* single-vessel disease

successful CTO revascularization was larger in patients with three-vessel disease (11.9 versus 26.5%, adjusted HR 0.57, 95% CI 0.40–0.80, $p = 0.001$) than in those with two-vessel disease (9.2 versus 20.8%, adjusted HR 0.63, 95% CI 0.37–1.07, $p = 0.09$, $P_{\text{interaction}} = 0.54$). Effects of successful CTO PCI on MACE rates were consistent among patients with MVD (30.9 versus 43.7%, adjusted HR 0.70, 95% CI 0.58–0.86, $p = 0.001$) and SVD (19.4 versus 23.7%, adjusted HR 1.12, 95% CI 0.55–2.29, $p = 0.76$, $P_{\text{int}} = 0.23$), albeit without reaching statistical significance in the latter. In MVD patients, benefits of successful CTO revascularization on the incidence of MACE were observed in both the three- (34.8 versus 47.4%, adjusted HR 0.69, 95% CI 0.55–0.88, $p = 0.002$) and the two-vessel disease groups (23.8 versus 36.8%, adjusted HR 0.68, 95% CI 0.47–0.99, $p = 0.048$). There was no differential effect of procedural success on outcomes by MVD/SVD status ($P_{\text{interaction}} \geq 0.1$ for all-cause death, all-cause death/myocardial infarction, TVR, and MACE, Fig. 3).

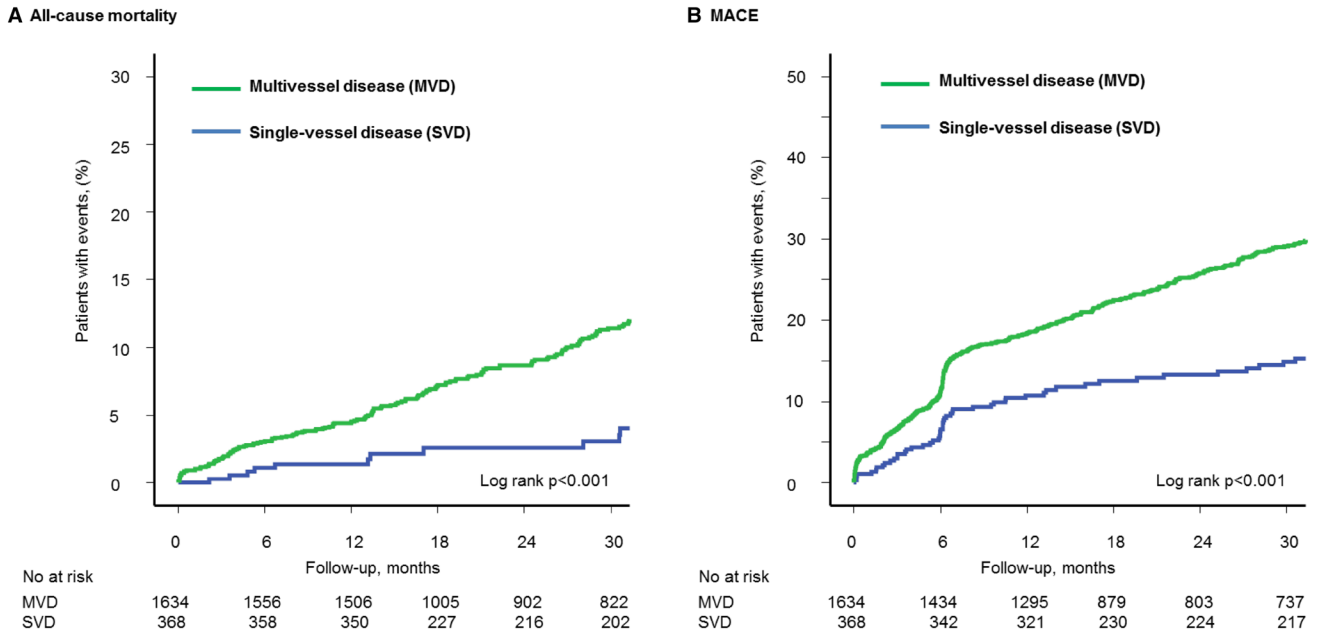

Fig. 1 Kaplan–Meier estimates for all-cause mortality (**a**) and major adverse cardiovascular events (**b**) in patients with single- and multi-vessel disease. *MACE* major adverse events (the composite of all-cause death, non-fatal myocardial infarction, and target vessel revascularization), *MVD* multi-vessel disease, and *SVD* single-vessel disease

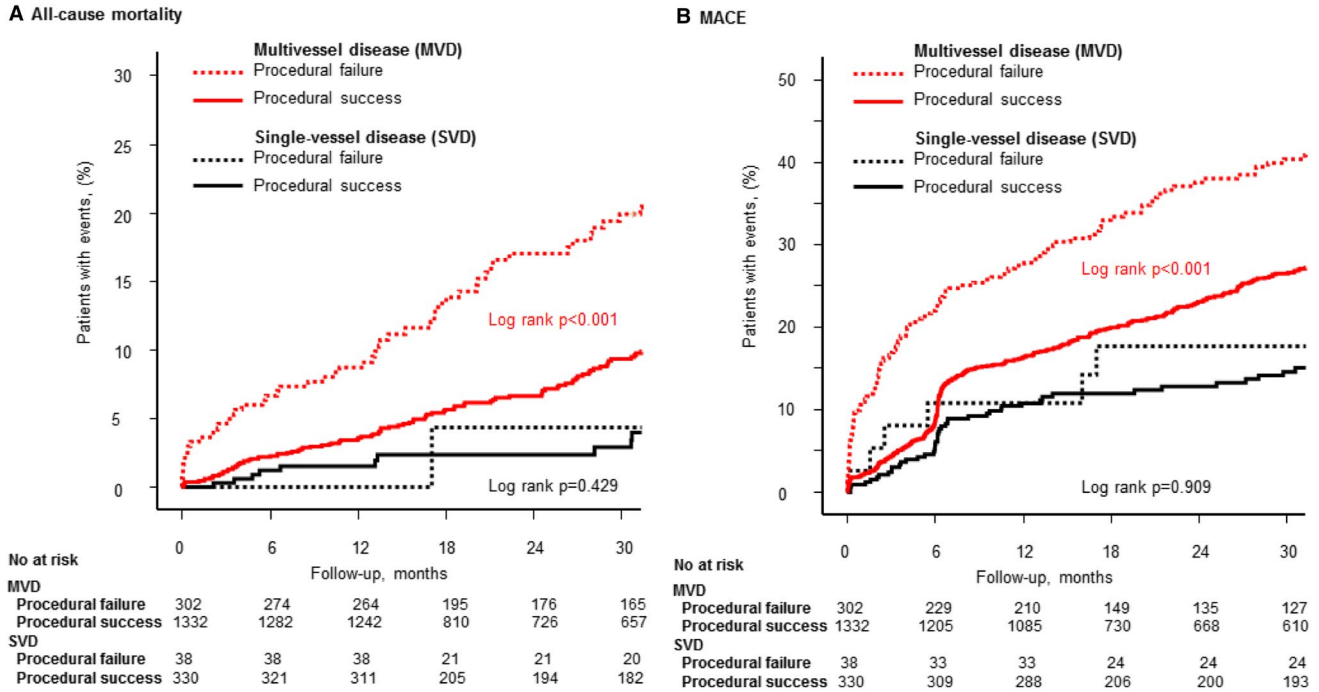

Fig. 2 Kaplan–Meier estimates for all-cause mortality (**a**) and major adverse cardiovascular events (**b**) in patients with single- and multi-vessel disease stratified for procedural success. *MACE* major adverse events (the composite of all-cause death, non-fatal myocardial infarction, and target vessel revascularization), *MVD* multi-vessel disease, *SVD* single-vessel disease

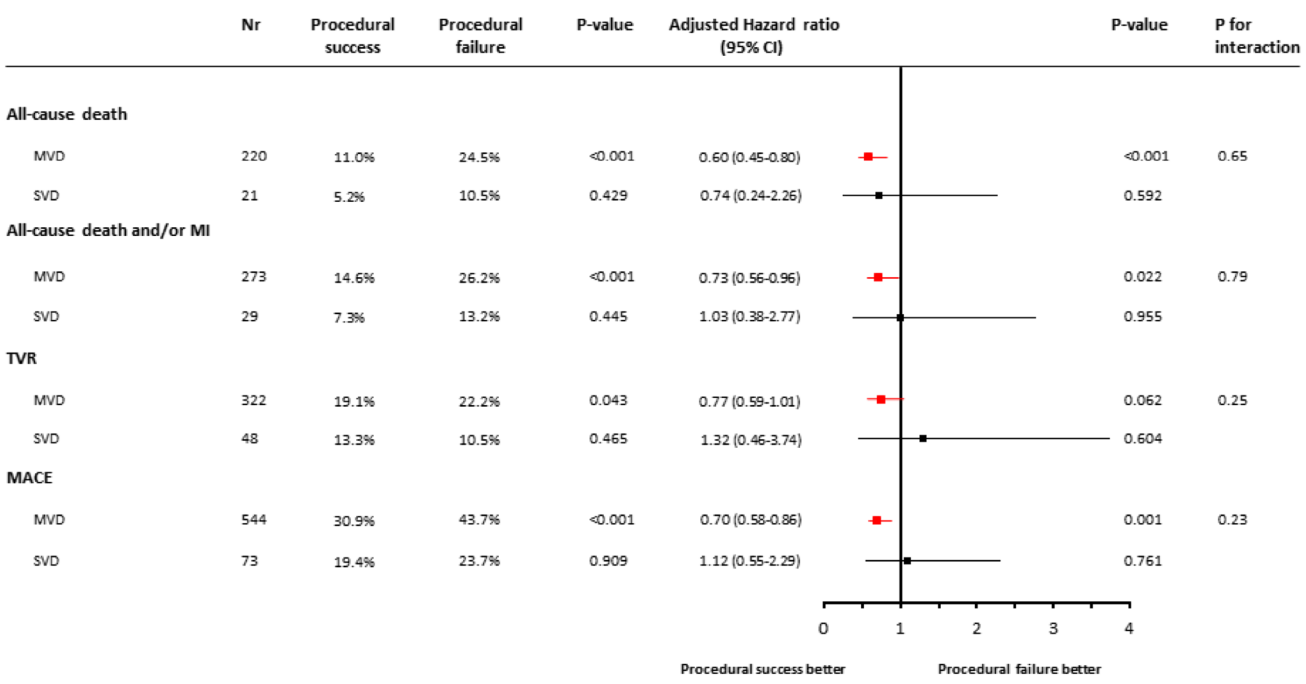

Fig. 3 Hazard ratios for adverse events in patients with single- and multi-vessel disease stratified for procedural success. Forest plot showing associations for different endpoints in patients with single- and multi-vessel disease. *MACE* major adverse events (the composite of all-cause death, non-fatal myocardial infarction, and target vessel revascularization), *MVD* multi-vessel disease, and *SVD* single-vessel disease

Discussion

This analysis demonstrated that the absolute survival benefit of successful CTO PCI increases with the extent of coronary artery disease. The relative risk reductions by successful CTO PCI for mortality and MACE were not significantly different between patients with and without MVD. In addition, due to higher baseline risks, we found substantially higher absolute risk reductions for death and MACE in patients with MVD as compared with SVD.

Procedural outcomes

Patients with MVD disease were at an increased baseline risk as evidenced by an advanced age and a higher prevalence of cardiovascular comorbidities. About 30% of MVD patients had prior myocardial infarction, and 35% previous coronary revascularization by either coronary artery bypass grafting or PCI. Given the higher baseline risk and an increased procedural complexity, procedural success rates were lower in MVD as compared to SVD patients. Consistent with our findings, lower procedural success rates following CTO PCI were observed in patients with complex coronary artery disease as reflected by a high SYNTAX score [16, 17], and MVD has been identified as independent predictor of procedural failure in previous studies [4, 14]. However, high procedural success rates of 89.7% and 81.5% were achieved in both SVD and MVD patients in this cohort, which is consistent with data reported from other experienced centers [25, 26]. The lower rate of retrograde attempts observed in MVD as compared to SVD patients may be due to a less pronounced formation of collateral channels suitable for retrograde wiring in MVD, and may at least in part have contributed to a lower procedural success rate as technical strategies may be limited in these patients.

Long-term clinical outcomes

All-cause mortality following CTO PCI was higher in MVD as compared to SVD patients, but differences mitigated after adjustments for baseline characteristics, indicating that differences in comorbidities between groups largely account for the increased mortality rates in patients with MVD. As adjusted MACE rates, mostly driven by the need for TVR, were higher in MVD patients, it is likely that additional lesion characteristics reflecting a more complex and advanced disease state or factors not taken into account in the multivariate models may explain the increased need for TVR in MVD patients.

In this registry, successful CTO recanalization was associated with higher absolute survival benefits in

patients with MVD as compared with those with SVD, and largest benefits were observed in patients with three-vessel disease. In patients with MVD, a successfully recanalized CTO may afford a particular benefit by mitigating detrimental effects of an acute event in other coronary territories [27]. Such events are more likely to occur in MVD than in SVD patients. These findings underline the need to offer coronary revascularization to these patients despite their increased baseline risk and the observed lower procedural success rates. No significant survival benefit of successful CTO PCI was observed in SVD patients. This lack of survival benefit is in line with recently reported registry data [28]. The limited survival benefit of adding coronary revascularization to optimal medical therapy in patients with SVD and low cardiovascular risk highlights the need for future studies designed to better identify SVD patients who may have a prognostic benefit from CTO recanalization beyond symptomatic improvement [29]. In addition, it may be speculated that differences in survival benefits in SVD patients may exist according to the extent of ischemia or myocardial viability in the territory supplied by the CTO vessel.

Limitations

The single center observational design is a limitation of the retrospective analysis. Nevertheless, comprehensive clinical, angiographic and procedural data of a large patient cohort undergoing CTO PCI was available. Further, we cannot exclude completely that confounding factors not taken into account in the multivariate models may have affected the outcome measures. In addition, comparisons among different treatment strategies including medical management and coronary artery bypass grafting were not possible, as only patients undergoing CTO PCI were included in this database.

Conclusions

A significant prognostic benefit of successful CTO recanalization was observed in patients with MVD, particularly in those with three-vessel disease. Due a lower baseline risk in patients with SVD, survival benefits of successful CTO were smaller and did not reach statistical significance. These findings extend our knowledge about prognostic benefits associated with successful CTO revascularization, and suggest that beneficial effects of CTO PCI depend on the coronary artery disease extent. Thus, MVD justifies more extensive efforts and procedural risk with PCI for CTO than SVD.

References

1. Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH, Kapadia SR (2005) Effect of chronic total coronary occlusion on treatment strategy. Am J Cardiol 95(9):1088–1091
2. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S et al (2012) Current perspectives on coronary chronic total occlusions: the Canadian multicenter chronic total occlusions registry. J Am Coll Cardiol 59(11):991–997
3. Toma A, Gick M, Minners J, Ferenc M, Valina C, Loffelhardt N et al (2016) Survival after percutaneous coronary intervention for chronic total occlusion. Clin Res Cardiol 105(11):921–929
4. Jones DA, Weerackody R, Rathod K, Behar J, Gallagher S, Knight CJ et al (2012) Successful recanalization of chronic total occlusions is associated with improved long-term survival. JACC Cardiovasc Interv 5(4):380–388
5. Mehran R, Claessen BE, Godino C, Dangas GD, Obunai K, Kanwal S et al (2011) Long-term outcome of percutaneous coronary intervention for chronic total occlusions. JACC Cardiovasc Interv 4(9):952–961
6. Valenti R, Migliorini A, Signorini U, Vergara R, Parodi G, Carrabba N et al (2008) Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. Eur Heart J 29(19):2336–2342
7. Joyal D, Afilalo J, Rinfret S (2010) Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. Am Heart J 160(1):179–187
8. George S, Cockburn J, Clayton TC, Ludman P, Cotton J, Spratt J et al (2014) Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central Cardiac Audit Database. J Am Coll Cardiol 64(3):235–243
9. Cassese S, Kufner S, Xhepa E, Byrne RA, Kreutzer J, Ibrahim T et al (2016) Three-year efficacy and safety of new- versus early-generation drug-eluting stents for unprotected left main coronary artery disease insights from the ISAR-LEFT MAIN and ISAR-LEFT MAIN 2 trials. Clin Res Cardiol 105(7):575–584
10. Ong P, Sechtem U (2016) Controversies in the treatment of patients with STEMI and multivessel disease: is it time for PCI of all lesions? Clin Res Cardiol 105(6):467–470
11. Lee SY, Hong MK, Shin DH, Kim JS, Kim BK, Ko YG et al (2016) Clinical outcomes of dual antiplatelet therapy after implantation of drug-eluting stents in patients with different cardiovascular risk factors. Clin Res Cardiol. doi:10.1007/s00392-016-1035-4
12. Kato M, Kimura T, Morimoto T, Nishikawa H, Uchida F, Suzuki H et al (2012) Comparison of five-year outcome of sirolimus-eluting stent implantation for chronic total occlusions versus for non-chronic total occlusion (from the j-Cypher registry). Am J Cardiol 110(9):1282–1289
13. Rathore S, Matsuo H, Terashima M, Kinoshita Y, Kimura M, Tsuchikane E et al (2009) Procedural and in-hospital outcomes after percutaneous coronary intervention for chronic total occlusions of coronary arteries 2002 to 2008: impact of novel guidewire techniques. JACC Cardiovasc interv 2(6):489–497
14. Olivari Z, Rubartelli P, Piscione F, Ettori F, Fontanelli A, Salemme L et al (2003) Immediate results and 1-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOAST-GISE). J Am Coll Cardiol 41(10):1672–1678
15. Sapontis J, Christopoulos G, Grantham JA, Wyman RM, Alaswad K, Karmpaliotis D et al (2015) Procedural failure of

chronic total occlusion percutaneous coronary intervention: Insights from a multicenter US registry. Catheter Cardiovasc Interv 85(7):1115–1122
16. Shiba M, Nagashima Y, Sugi K, Nakamura M (2014) SYNTAX-score based assessment of appropriate candidates for percutaneous coronary intervention among patients with chronic total occlusion. Int J Cardiol 176(3):1270–1272
17. Nagashima Y, Iijima R, Nakamura M, Sugi K (2015) Utility of the SYNTAX score in predicting outcomes after coronary intervention for chronic total occlusion. Herz 40(8):1090–1096
18. Ferenc M, Buettner HJ, Gick M, Comberg T, Rothe J, Khoury F et al (2016) Clinical outcome after percutaneous treatment of de novo coronary bifurcation lesions using first or second generation of drug-eluting stents. Clin Res Cardiol 105(3):230–238
19. Stahli BE, Gebhard C, Gick M, Herman C, Ferenc M, Mashayekhi K et al (2016) Impact of body mass index on long-term mortality in women and men undergoing percutaneous coronary intervention for chronic total occlusion. Int J Cardiol 224:305–309
20. Toma A, Stahli BE, Gick M, Colmsee H, Gebhard C, Mashayekhi K et al (2016) Long-term follow-up of patients with previous coronary artery bypass grafting undergoing percutaneous coronary intervention for chronic total occlusion. Am J Cardiol 118(11):1641–1646
21. Sianos G, Werner GS, Galassi AR, Papafaklis MI, Escaned J, Hildick-Smith D et al (2012) Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. EuroIntervention 8(1):139–145
22. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD et al (2012) Third universal definition of myocardial infarction. J Am Coll Cardiol 60(16):1581–1598
23. Thygesen K, Alpert JS, White HD, Joint ESCAAHAWH-FTFftRoMI (2007) Universal definition of myocardial infarction. J Am Coll Cardiol 50(22):2173–2195
24. Teramoto T, Tsuchikane E, Matsuo H, Suzuki Y, Ito T, Ito T et al (2014) Initial success rate of percutaneous coronary intervention for chronic total occlusion in a native coronary artery is decreased in patients who underwent previous coronary artery bypass graft surgery. JACC Cardiovasc Interv 7(1):39–46
25. Morino Y, Kimura T, Hayashi Y, Muramatsu T, Ochiai M, Noguchi Y et al (2010) In-hospital outcomes of contemporary percutaneous coronary intervention in patients with chronic total occlusion insights from the J-CTO Registry (Multicenter CTO Registry in Japan). JACC Cardiovasc Interv 3(2):143–151
26. Thompson CA, Jayne JE, Robb JF, Friedman BJ, Kaplan AV, Hettleman BD et al (2009) Retrograde techniques and the impact of operator volume on percutaneous intervention for coronary chronic total occlusions an early U.S. experience. JACC Cardiovasc Interv 2(9):834–842
27. Claessen BE, van der Schaaf RJ, Verouden NJ, Stegenga NK, Engstrom AE, Sjauw KD et al (2009) Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. JACC Cardiovasc Interv 2(11):1128–1134
28. Lee PH, Lee SW, Park HS, Kang SH, Bae BJ, Chang M et al (2016) Successful recanalization of native coronary chronic total occlusion is not associated with improved long-term survival. JACC Cardiovasc Interv 9(6):530–538
29. Borgia F, Viceconte N, Ali O, Stuart-Buttle C, Saraswathyamma A, Parisi R et al (2012) Improved cardiac survival, freedom from MACE and angina-related quality of life after successful percutaneous recanalization of coronary artery chronic total occlusions. Int J Cardiol 161(1):31–38