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Coronary dominance and prognosis in patients with chronic total occlusion treated with percutaneous coronary intervention

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Abstract

Aim: The prognostic value of coronary artery dominance pattern in patients with chronic total occlusions (CTO) is unknown. The aim of this study was to assess the influence of coronary vessel dominance on short and long-term outcomes in patients undergoing percutaneous coronary intervention (PCI) for CTO.

Methods and results: Our study population consisted of 2002 consecutive patients (17% females, mean age 65.2 ± 10.7 years) who underwent PCI of at least one coronary CTO lesion at our center between 01/2005 and 12/2013. Based on the origin of the posterior descending coronary artery, coronary circulation was categorised into left, right, and balanced coronary dominance. Right coronary dominance (RD) was present in 88% ($n = 1759$), left coronary dominance (LD) in 7% ($n = 136$), and balanced coronary dominance (BD) in 5% ($n = 107$) of the study population. After a median follow-up duration of 2.6 years [interquartile range 1.1–3.1 years] all-cause mortality was significantly higher in patients with LD as compared with RD and BD (log rank = 0.001). Accordingly, the presence of a LD system was identified as a significant predictor for all-cause mortality (adjusted HR 1.7, 95% CI: 1.2-2.6, $P = .007$) and major adverse cardiac events (MACE) (adjusted HR 1.4, 95% CI: 1.1-1.8, $P = 0.02$).

Conclusion: Our data suggest that LD is an independent predictor of increased all-cause death and MACE in patients with CTO. Therefore, assessment of coronary vessel dominance by angiography may contribute to risk stratification in these patients.

KEYWORDS
angiography, coronary artery chronic total occlusion, coronary dominance, percutaneous coronary intervention

1 | INTRODUCTION

Anatomical coronary dominance is defined by the origin of the posterior descending artery (PDA), which supplies the posterior portion of the interventricular septum. In a right-dominant circulation (RD), the right coronary artery (RCA) gives off the PDA, while in a left-dominant circulation (LD) the left circumflex (LCX) artery supplies this territory. In a codominant circulation, supply of the posterior interventricular septum is shared by the RCA and LCX. RD is the most prevalent pattern of coronary circulation. It is found in 72–90% of individuals, while prevalence of LD and balanced coronary dominance (BD) is reported to be 8–33% and 3–7%, respectively [1]. Studies suggest that the relatively low prevalence of LD and its decreasing prevalence with age may reflect a biologic disadvantage relative to RD [2–5]. Indeed, in patients undergoing cardiac catheterization for an acute coronary syndrome (ACS), LD seems to be independently associated with increased mortality and re-infarction and may predispose individuals to mechanical complications of myocardial infarction (MI) [3–7]. In contrast, there is conflicting data on the association of LD and outcomes in patients with stable coronary artery disease (CAD): while a computed

tomography coronary angiography (CCTA) study found LD to be an independent predictor of non-fatal MI and all-cause mortality in a heterogeneous population of patients with chest pain, other studies did not observe differences in clinical endpoints between dominance groups [8–10].

Despite rapid evolution and technical refinement, percutaneous treatment of coronary chronic total occlusions (CTO) remains one of the major challenges in the field of interventional cardiology. This is mirrored by a small number of attempted CTO revascularizations and their relatively low procedural success rate of 70–86% as compared with subtotal stenoses (98%) [11–17]. Indeed, percutaneous coronary interventions (PCI) of CTOs account for only 10–20% of all PCI activity, although concurrent CTOs are found in 15–30% of all patients referred for coronary angiography and in 12–13% of patients with an ACS [18–24]. Thus, many CTO lesions are left untreated. Uncertainty regarding procedural success and long-term benefit account for this, which is attributable to lack of data on predictors and outcomes of attempted CTO PCI. In fact, patients with CTO lesions have widely varying risks, with some subgroups facing high morbidity and mortality. In addition, not all CTO lesions are created equal and the importance of lesion localization can be different in different types of coronary dominance. Although coronary vessel dominance is easily assessed on coronary angiography, no reports are available on the prevalence and prognostic value of coronary vessel dominance in patients with CTO referred for revascularization. Therefore, the goal of the present study was to assess the influence of coronary vessel dominance on short and long-term outcomes in patients undergoing PCI for CTO.

2 | METHODS

2.1 | Patient population

All patients who underwent PCI for at least one coronary CTO at our institution between January 2005 and December 2013 were included in this study. Patient data were entered into a dedicated clinical database as part of the quality management program at our institution, and followed regularly by outpatient visits or telephone contacts. All patients had symptomatic angina and/or a positive functional ischemia study. The procedures used were in accordance with the recommendations found in the Helsinki declaration. The study was approved by our institution's ethics committee. Clinical data including age, gender, cardiovascular risk factors, medical history, and laboratory analysis were acquired on admission. Left ventricular ejection fraction (LVEF) was obtained by echocardiography before PCI.

2.2 | Image interpretation and procedural techniques

Images of the coronary angiography were obtained using standardized angiographic projections according to the guidelines of the American College of Cardiology/American Heart Association and stored digitally [25]. All images were retrospectively reviewed for coronary dominance by two experienced observers. The coronary artery system was classified as right dominant if the RCA, as left dominant if the LCX, or as balanced if RCA and LCX gave rise to the PDA. The extent of significant CAD was expressed as the presence of one-, two-, or three-vessel disease (stenosis causing $\geq$50% luminal narrowing). The localization of stenoses was attributed to LCX, left main coronary artery (LM), RCA and LAD. Coronary CTOs were defined as angiographic evidence of a total occlusion with Thrombolysis In Myocardial Infarction (TIMI) grade 0 flow and estimated duration of at least 3 months [26]. Patients were considered to have had retrograde CTO PCI if a guidewire was introduced into a collateral channel that supplied the target CTO vessel distal to the lesion. Procedural success was defined as achievement of $<$30% residual diameter stenosis within the treated segment and restoration of TIMI grade 3 antegrade flow. All procedures were performed via the femoral route. Intravenous heparin was given at the start of the procedure to maintain an activated clotting time of 200–300 s. All procedural decisions, including material selection and adjunctive pharmacotherapy, were made at the discretion of the operator.

2.3 | Follow-up and definition of clinical endpoints

Follow-up data were prospectively obtained from hospital readmission, outpatient records and telephone interview with the patient and/or referring physician. The following endpoints were evaluated to compare patients according to their coronary dominance pattern: Primary endpoint: all-cause mortality; secondary endpoint: major adverse cardiac events (MACE). MACE included any of the following adverse events during follow-up: death, non-fatal MI, and clinically indicated target vessel revascularization (TVR). Nonfatal MI was defined as ischemic symptoms associated with cardiac enzyme elevation $\geq$ 3 times the upper limit of the normal value according to the ESC/ACCF/AHA/WHF consensus document on the universal definition of non-fatal MI [27]. TVR was defined as any repeat revascularization to treat a vessel.

2.4 | Statistical analysis

SPSS version 23.0 (SPSS, Chicago, IL) was used for all statistical analyses. Categorical variables are presented as frequencies and continuous variables as mean $\pm$ SD or median and interquartile range (IQR), as appropriate. Variables were compared with chi-square test or Fisher's exact test for categorical variables and one-way analysis of variance for continuous variables. The Kruskal-Wallis test was used to compare non-parametric data. The primary outcome variable was all-cause mortality; secondary outcomes were composites of MACE, non-fatal MI, and TVR. Follow-up was censored at date of last follow-up or at 5 years, whichever came first. Survival curves were constructed for time-to-event variables with Kaplan-Meier methodology and compared by log-rank test. Multivariable analyses were calculated with the multivariate Cox regression models for prediction of the primary and secondary combined end-points. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Known predictive factors such as age, multivessel disease, prior CABG or MI, diabetes, left ventricular dysfunction, kidney failure and procedural success were included in the multivariate model. This selection was made on the basis of the well-described association of these covariates with cardiac mortality. A

TABLE 1 Baseline demographics of the study population by coronary dominance

	Baseline demographic characteristics				
	Left dominant $n = 136$ (6.8%)	Right dominant $n = 1759$ (87.9%)	Balanced $n = 107$ (5.3%)	Total $n = 2002$	*P*-value
Age, mean ± SD	66.5 ± 10.4	65.1 ± 11.0	65.2 ± 11.0	65.2 ± 10.7	0.33
Female sex, *n* (%)	27 (19.9)	287 (16.3)	18 (16.8)	332 (16.6)	0.56
BMI, median [IQR]	27 [27–29]	28 [25–30]	27 [25–30]	28 [25–30]	0.70
Diabetes, *n* (%)	31 (22.8)	524 (29.8)	35 (32.7)	590 (29.5)	0.17
Current smoking, *n* (%)	32 (23.5)	350 (19.9)	19 (17.8%)	401 (20)	0.49
Dyslipidemia, *n* (%)	114 (83.8)	1516 (86.2)	96 (89.7)	1726 (86.2)	0.41
Hypertension, *n* (%)	110 (80.9)	1448 (82.3)	89 (83.2)	1647 (82.3)	0.88
Family History of CAD, *n* (%)	52 (38.2)	659 (37.5)	37 (34.6)	748 (37.4)	0.81
eGFR < 60 ml/min, *n* (%)	30 (22.2)	340 (19.4)	24 (22.6)	394 (19.8)	0.55
Previous MI, *n* (%)	43 (31.6)	425 (24.2)	25 (23.4)	493 (24.6)	0.14
Previous CABG, *n* (%)	26 (19.1)	251 (14.3)	15 (14)	292 (14.6)	0.30
Previous PCI, *n* (%)	27 (19.9)	261 (14.8)	22 (20.6)	310 (15.5)	0.09
LVEF < 40%, *n* (%)	29 (21.3)	303 (17.2)	16 (15)	348 (17.4)	0.37

Abbreviations: BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction. Data are presented as *n* (%), as mean ± SD or median [interquartile range, IQR].

covariate was allowed in the model if it influenced the model with a likelihood ratio significance level of $P < 0.05$ and removed if its significance level exceeded $P < 0.1$. In addition, the prognostic value of CTO location was determined for patients with a right, left, and balanced dominant coronary artery system by using multivariate Cox regression. A two-tailed *P*-value of 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics and angiographic findings

From January 2005 to December 2013, a total of 2002 consecutive patients with at least one occluded coronary artery were referred to our centre for PCI. Patients (16.6% females, mean age 65.2 ± 10.7) were followed for a median of 2.6 years (IQR 1.1–3.1 years). RD was present in 87.9% ($n = 1759$), LD in 6.8% ($n = 136$), and BD in 5.3% ($n = 107$) of the study population (Table 1). 29.5% ($n = 590$) of patients were diabetic, 19.8% ($n = 394$) of patients had chronic kidney disease stage 3 or higher, 17.4% ($n = 348$) of patients had a LVEF <40%, 493 patients (24.6%) had a history of MI, and 292 (14.6%) had undergone surgery for CABG (Table 1). In our study cohort, 1,634 patients (81.6%) were diagnosed with three-vessel disease and 817 patients (40.8%) underwent multivessel PCI (Table 2). Successful PCI of CTO was achieved in 1662 (83%) patients and a retrograde approach was used in 476 (23.6%) patients (Table 2). Overall, baseline and angiographic characteristics were similar between coronary dominance groups, although significant differences were observed for utilization of the retrograde approach (25.2% for RD vs. 11.8% and 15% for LD and BD, respectively, $P < 0.001$, Table 2), CTO localization ($P < 0.001$, Table 2), and postdilatation balloon size ($P < 0.001$, Table 2). Indeed, patients with a LD system tend to have more often significant stenosis in the LAD or LCX ($P < 0.001$ vs. RD and BD), while patients with RD had more often significant disease in the RCA ($P < 0.001$ vs. LD, Table 2). Tables 1 and 2 depict baseline demographic and angiographic characteristics of the patient population, categorized by coronary vessel dominance. When stratified for sex, RD was detected in 88.1% of men and in 86.4% of women, LD was found in 6.5% of men and in 8.1% of women, and BD was found in 5.3% of men and in 5.4% of women. No significant differences were detected between the sexes regarding the type of coronary dominance (P = NS, data not shown).

3.2 | Short-term adverse clinical events

Among patients who died during follow-up, 15 patients (6.2%) died within the first 30 days following CTO PCI. Furthermore, 69 patients (11.1%) experienced a MACE within the first 30 days after CTO PCI. Survival during 30 days of follow-up was similar in all coronary dominance groups (P = NS, Figure 1A), while significantly more patients in the LD group experienced a MACE (7.3% of LD patients vs. 3.2% of RD patients and 1.9% of BD patients, log rank $P = 0.02$, Figure 1B).

3.3 | Adverse clinical events during long-time follow-up

After a median follow-up of 2.6 years [IQR 1.1–3.1 years] a total of 241 (12%) deaths as well as 617 (30.8%) MACE were recorded. When comparing event-free survival during follow up in patients with LD,

TABLE 2 Baseline angiographic and procedural characteristics by coronary dominance

	Baseline angiographic and procedural characteristics				
	Left dominant $n = 136$	**Right dominant** $n = 1759$	**Balanced** $n = 107$	**Total** $n = 2002$	***P* value**
Multivessel disease, *n* (%)	113 (83.1%)	1437 (81.7%)	84 (78.5%)	1634 (81.6%)	0.64
Multivessel PCI, *n* (%)	54 (39.7%)	712 (40.5%)	51 (47.7%)	817 (40.8%)	0.26
CTO vessel					<0.001
LAD, *n* (%)	58 (42.6%)	468 (26.6%)	31 (29%)	557 (27.8%)	
RCX, *n* (%)	70 (51.5%)	400 (22.7%)	30 (28%)	500 (25%)	
RCA, *n* (%)	7 (5.1%)	878 (49.9%)	45 (42.1%)	930 (46.5%)	
LM, *n* (%)	1 (0.7%)	13 (0.7%)	1 (0.9%)	15 (0.7%)	
CTO length > 20 mm, *n* (%)	94 (69.1%)	1348 (76.6%)	82 (76.6%)	1524 (76.1%)	0.13
>Moderate calcification, *n*(%)	73 (53.7%)	992 (56.4%)	56 (52.3%)	1121 (56%)	0.61
Balloon size predilatation (mm, mean ± SD)	2.22 ± 0.40	2.47 ± 2.05	2.21 ± 0.44	1.2.44 ± 1.93	0.24
Inflation pressure pre (atm, mean ± SD)	14.7 ± 4.3	14.7 ± 3.9	14.9 ± 3.5	14.8 ± 3.9	0.90
Balloon size postdilatation (mm, mean ± SD)	2.82 ± 0.38	2.98 ± 0.43	2.87 ± 0.40	2.96 ± 0.43	<0.001
Inflation pressure post (atm, mean ± SD)	14.71 ± 3.26	15.18 ± 2.99	15.37 ± 2.83	15.16 ± 3.00	0.25
Total stent length, mm, median [IQR]	28 [10–42]	33 [18–51]	33 [20–51]	33 [18–51]	0.62
Retrograde approach, *n* (%)	16 (11.8%)	444 (25.2%)	16 (15%)	476 (23.8%)	<0.001
CTO PCI success, *n* (%)	107 (78.7%)	1461 (83.1%)	94 (87.9%)	1662 (83%)	0.16
Contrast volume ml, median [IQR]	305 [210–470]	280 [200–400]	300 [220–410]	280 [200–400]	0.08
Fluoroscopy time, min, median [IQR]	28 [15–44]	33 [18–51]	33 [20–51]	26 [15–46]	0.96
Kerma-area-product, cG*cm^2, median [IQR]	8,427 [4815–16,066]	8,700 [5200–14,731]	9,738 [5726–14,379]	8,703 [5200–14,735]	0.72

Abbreviations: CTO, chronic total occlusion; LAD, left anterior descending artery; RCX, Left circumflex artery; RCA, right coronary artery; LM, left main coronary artery; PCI, percutaneous coronary intervention. Data are presented as n (%), as mean ± SD or median [interquartile range, IQR].

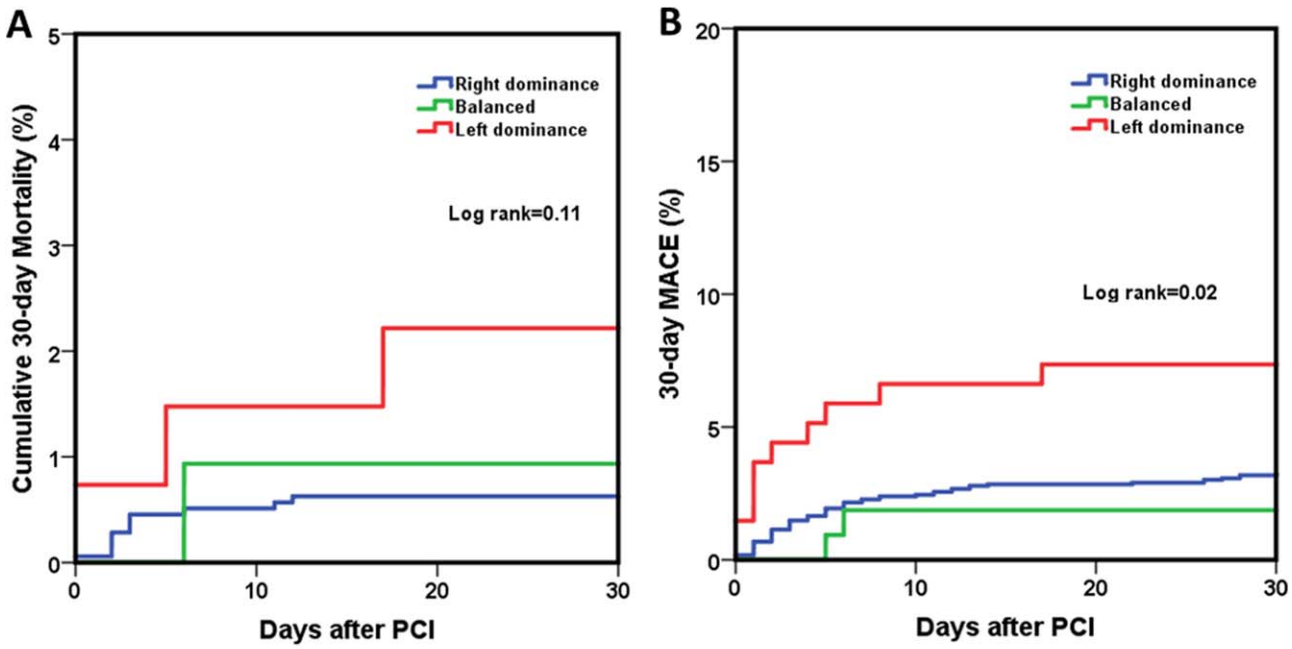
BD, and RD, the incidence of all-cause mortality was significantly increased in patients with a LD system as opposed to BD and RD system (log rank = 0.001, Figure 2A). Similarly, the MACE (log rank $P = 0.048$, Figure 2B) as well as the combined incidence of all-cause mortality and non-fatal MI (log rank $P = 0.013$, data not shown) were increased in the LD group as compared with BD and RD. These results remained the same when a subgroup analysis was conducted in patients who were diagnosed with multivessel disease ($n = 1634$, log rank $P = 0.001$ for all-cause mortality and log rank $P = 0.017$ for MACE, Figure 3). When stratified for sex, event-free survival did not differ between males and females with a LD system (log rank $P = 0.9$, data not shown).

3.4 | Prognostic value of coronary dominance

Multivariate Cox regression analysis adjusting for comorbidities, extent of CAD, LVEF, and procedural success, confirmed that coronary vessel dominance was an independent predictor of both the primary and secondary endpoints during a median follow-up of 2.6 years (Table 3). In detail, a LD system was associated with a adjusted HR of 1.8 (95% CI 1.2–2.7, $P = 0.003$) for all-cause mortality and a HR of 1.4 (95% CI 1.1–1.8, $P = 0.02$) for MACE. Of note, amongst all covariates, success of CTO recanalization was the only significant and negative predictor of adverse outcomes remaining in the model [adjusted HR of 0.63 (95% CI 0.48–0.83, $P < 0.001$) for all-cause mortality, and adjusted HR of 0.72 [95% CI 0.59–0.87, $P < 0.001$)] (Table 3). However, this effect was not modified by coronary vessel dominance pattern ($P_{interaction} > 0.1$). Risk estimates of a LD system were even more pronounced when only patients with multivessel disease ($n = 1,634$) were included in the analysis: In this subset of patients, a LD system was associated with a HR of 1.9 (95% CI 1.3–2.9, $P = 0.002$) for all-cause mortality and a HR of 1.5 (95% CI 1.1–2.0, $P = 0.01$) for MACE (data not shown).

3.5 | Prognostic value of CTO localization according to coronary dominance

Target lesions were more frequently located in dominant arteries. A CTO lesion in the left coronary system (LM, LAD, and LCX) was observed in 129 (95%) patients with LD and in 881 (50.1%) patients with RD (Table 1) while a CTO in the RCA was seen in 7 (5.1%) patients with LD and in 878 (49.9%) patients with RD ($P < 0.001$, Table 2).



Patients at risk	0 days	10 days	20 days	30 days
Right dominance	1759	1747	1745	1744
Balanced	107	106	105	105
Left dominance	136	133	132	131

Patients at risk	0 days	10 days	20 days	30 days
Right dominance	1759	1716	1709	1701
Balanced	107	105	105	105
Left dominance	136	127	126	126

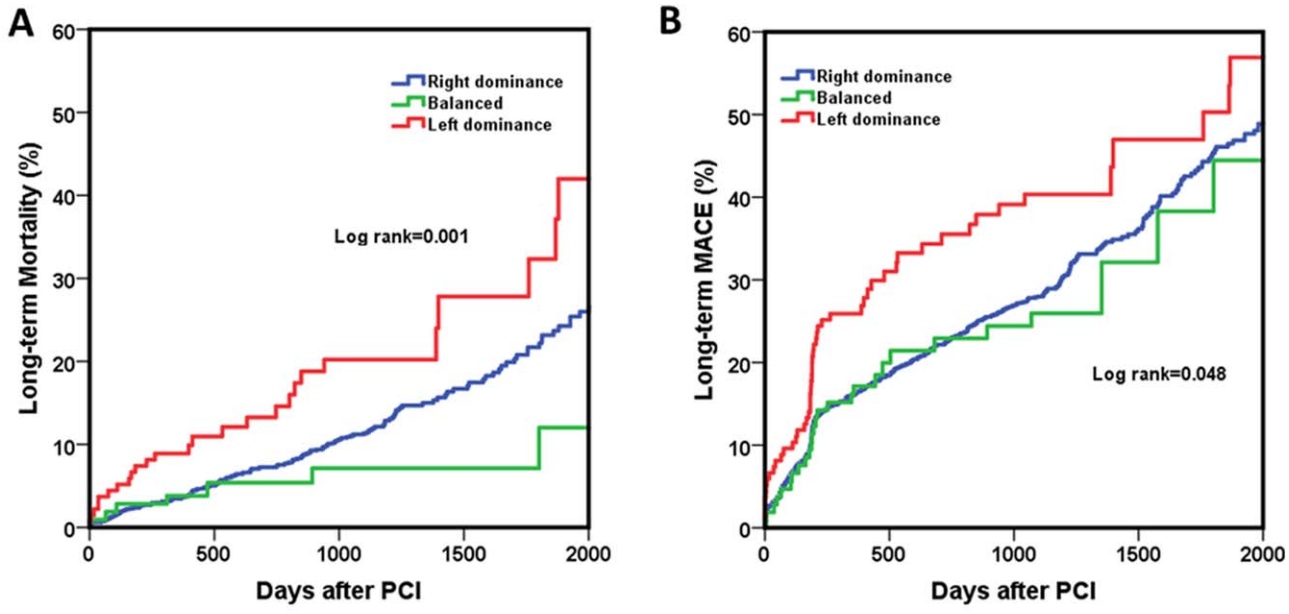
FIGURE 1 **A,** Event free survival (Kaplan Meier curve) from all-cause mortality during 30 days follow-up after PCI for chronic total coronary occlusion in patients with right, left and balanced coronary dominance. **B,** Event free survival from MACE during 30 days follow-up after PCI for chronic total coronary occlusion in patients with right, left and balanced coronary dominance. PCI, percutaneous coronary intervention [Color figure can be viewed at wileyonlinelibrary.com]

After stratification according to CTO location, cumulative event rates for patients with LD and a coronary occlusion of the LAD were 19% for all-cause mortality and 29.7% for MACE, while in patients with RD and coronary occlusion of the RCA event rates were 11.5% for all-cause mortality and 30.8% for MACE. A significantly increased risk of all-cause mortality was seen in patients with a LD system and coronary occlusion of the LCX (adjusted HR 3.6 (95% CI: 1.9–0.6, $P < 0.001$ vs. RD, Table 4) while this was not the case for a coronary occlusion of the LAD (adjusted HR 1.4, 95% CI: 0.7–2.8, $P =$ NS vs. RD, Table 4) or the RCA (adjusted HR 0.4, 95% CI: 0.1–3.1, $P =$ NS vs. RD, Table 4). There was no statistical evidence for effect modification by culprit lesion vessel in patients with a BD system ($P =$ NS, Table 4).

4 | DISCUSSION

In this single centre study, we evaluated the prognostic value of coronary dominance in 2002 patients undergoing PCI for at least one coronary CTO. When comparing event-free survival according to coronary vessel dominance, survival rates for all-cause mortality, MACE and the composite of all-cause mortality and non-fatal MI were significantly reduced in patients with LD as compared to RD and BD. Accordingly, in our study cohort, LD was a significant and independent predictor of increased mortality and MACE following PCI for CTO even after adjustment for important demographic, clinical and angiographic variables.

Our findings confirm previous studies in patients undergoing PCI demonstrating that LD was associated with increased odds of death or re-infarction during long-term follow-up [3,7,9]. However, in contrast to several recent studies in patients with ACS, we did not observe an association between LD and 30-days mortality following PCI [4–6,9,28]. In addition, our data contrast with a previous observation in 6,382 patients referred for CCTA showing no risk modification by coronary dominance during a 5-year follow-up period [10]. Of note, these previous studies enrolled patients with varying risks, including high risk ACS patients or healthy individuals, which may have accounted for the observed discrepancies. Data describing the effects of coronary dominance in stable CAD patients undergoing elective PCI are scarce and a significant association between LD and worse long-term outcomes in patients with stable CAD was observed in only one recent study [9]. Analogous to our study, this previous investigation enrolled a high number (>50%) of patients presenting with complex coronary lesions



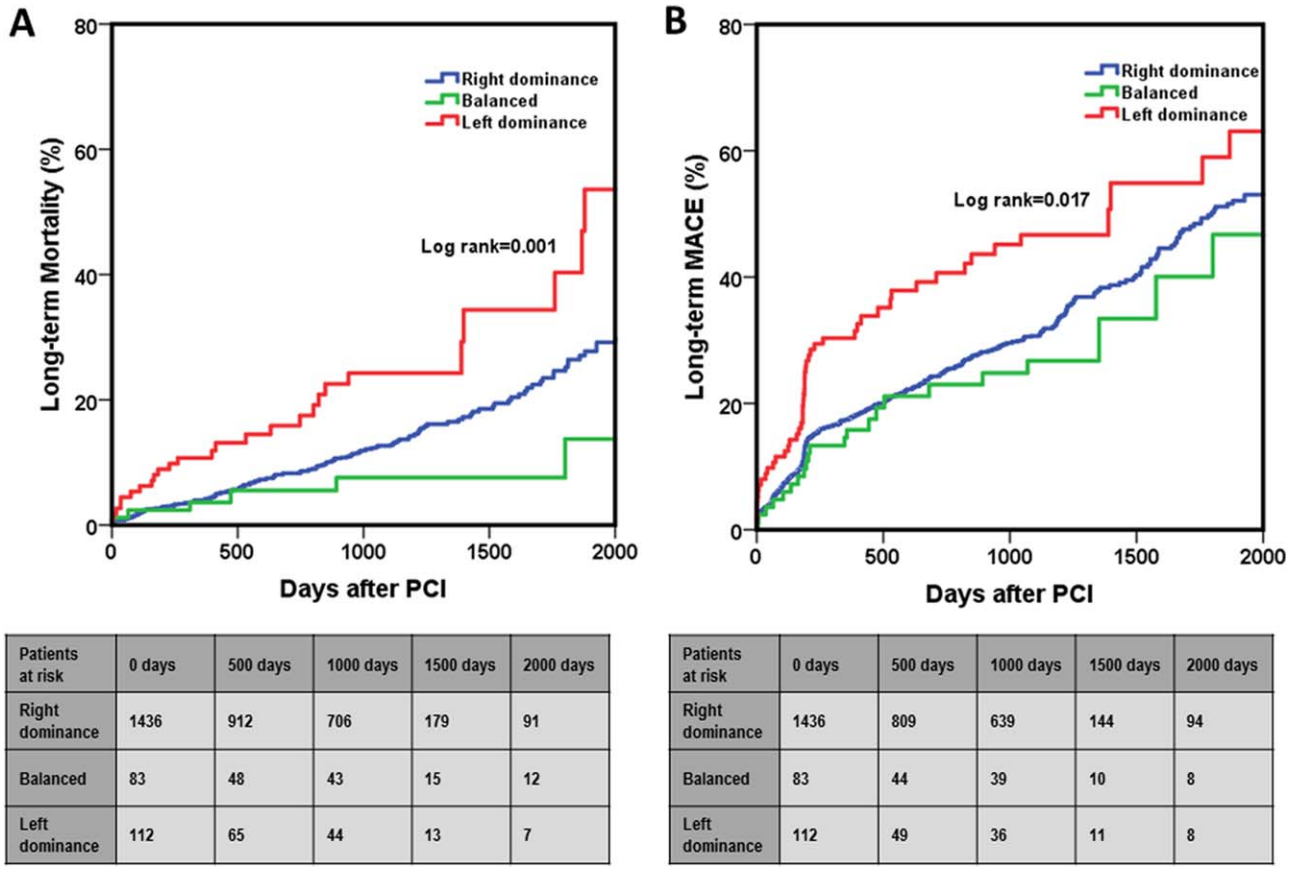
Patients at risk	0 days	500 days	1000 days	1500 days	2000 days
Right dominance	1758	1117	883	221	118
Balanced	106	58	51	19	14
Left dominance	135	79	56	19	11

Patients at risk	0 days	500 days	1000 days	1500 days	2000 days
Right dominance	1758	1018	829	196	123
Balanced	106	54	49	11	9
Left dominance	135	63	50	16	11

FIGURE 2 **Event-free survival stratified by coronary dominance. A,** Event free survival (Kaplan Meier curve) from all-cause mortality during a median follow-up of 2.6 years after PCI for chronic total coronary occlusion in patients with right, left and balanced coronary dominance. **B,** Event free survival (Kaplan Meier curve) from MACE during a median follow-up of 2.6 years after PCI for chronic total coronary occlusion in patients with right, left and balanced coronary dominance. PCI, percutaneous coronary intervention [Color figure can be viewed at wileyonlinelibrary.com]

or multivessel disease. Similarly, a recent CCTA study identified LD as an independent predictor of non-fatal MI and all-cause mortality. This observation was mainly driven by a strong negative prognostic value of LD in a subset of patients with severe obstructive CAD [8]. Thus, it is conceivable that the association between coronary dominance and mortality differs across the spectrum of CAD patients. In fact, the anatomical disadvantages of a LD system, such as the absence of a double supply to the myocardium and the technical challenges of a dominant LCX intervention, may be particularly important in patients with severe, obstructive CAD or in patients with ACS. This hypothesis is supported by the fact that significant and positive associations between severity of CAD and LD have been reported [10,29,30]. Therefore, intensive treatment such as PCI or CTO procedures may have a particularly large impact on outcomes in these patients.

A number of mechanisms may account for the specific association between LD and increased mortality following PCI. The potential to form collaterals might be impaired in patients with a LD system since the small RCA is usually not sufficient to perfuse the myocardium in case of LCA obstruction [31–33]. Indeed, the better prognosis in patients with a RD system was recently attributed to more collateral development [34]. Of note, however, this observation was made in patients presenting with STEMI, while no difference in coronary collateral formation was detected in other subgroups [34]. In our dataset, significantly more RD patients than LD patients were treated by using a retrograde approach via septal and epicardial collaterals, which may point towards a better collateral development in the RD group. Nevertheless, a causal relationship between coronary vessel dominance, coronary collateral circulation, and prognosis has yet to be established, and to date no study has taken into account whether the collaterals found are functional or not. Thus, further studies using functional tests are needed to assess the effect modification by coronary collateral formation in patients with LD. Further, coronary artery variations and myocardial bridging appear to be more common in patients with LD, which may have prognostic implications [10,29,30,35]. However, potential clinical implications of myocardial bridging, in which a segment of an epicardial artery is covered by myocardium, are controversially discussed and vary from protection against atherosclerosis to systolic vessel compression and subsequent exercise-induced myocardial ischemia [2]. Therefore, the combined role of myocardial bridging and coronary dominance in risk prediction is difficult to elucidate. Finally, the higher in-hospital mortality in LD patients with ACS led to the hypothesis that a LD system may represent a less well-balanced



Patients at risk	0 days	500 days	1000 days	1500 days	2000 days
Right dominance	1436	912	706	179	91
Balanced	83	48	43	15	12
Left dominance	112	65	44	13	7

Patients at risk	0 days	500 days	1000 days	1500 days	2000 days
Right dominance	1436	809	639	144	94
Balanced	83	44	39	10	8
Left dominance	112	49	36	11	8

FIGURE 3 **Event-free survival stratified by coronary dominance in patients with multivessel-disease ($n = 1,634$). A,** Event free survival (Kaplan Meier curve) from all-cause mortality during a median follow-up of 2.6 years in patients with multivessel disease stratified by coronary dominance. **B,** Event free survival (Kaplan Meier curve) from MACE during a median follow-up of 2.6 years. PCI, percutaneous coronary intervention [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Cox regression analysis to assess independent correlates of adverse events following PCI for CTO during long-term follow-up

	Primary endpoint (All-cause mortality)			Secondary endpoint (MACE)		
	Multivariate Cox regression					
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.04	1.03–1.06	<0.001	1.00	1.00–1.02	NS
Male gender	1.11	0.8–1.5	NS	1.05	0.85–1.30	NS
Diabetes	1.48	1.13–1.94	0.004	1.31	1.10–1.55	0.002
Multivessel disease	1.78	1.12–2.83	0.015	1.72	1.33–2.21	<0.001
eGFR	0.99	0.98–0.99	<0.001	1.00	1.00–1.00	NS
Prior MI	0.83	0.61–1.14	NS	1.00	0.83–1.22	NS
Prior CABG	1.11	0.78–1.56	NS	1.07	0.86–1.33	NS
Success CTO PCI	0.63	0.48–0.83	0.001	0.72	0.59–0.87	0.001
LVEF < 40%	3.85	2.92–5.08	<0.001	1.69	1.40–2.05	<0.001
Right dominance	Reference (1.0)			Reference (1.0)		
Left dominance	**1.82**	**1.22–2.73**	**0.003**	**1.39**	**1.05–1.84**	**0.020**
Balanced dominance	**0.67**	**0.33–1.37**	**NS**	**0.89**	**0.61–1.31**	**NS**

Multivariate analysis was adjusted for comorbidities, LVEF, and procedural success.
Abbreviations: HR, hazard ratio, CI, confidence interval; MACE, major adverse cardiac events; TVR, target vessel revascularisation; MI, myocardial infarction. PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction.

TABLE 4 Univariate and multivariate Cox regression analysis for the primary endpoint of all-cause mortality stratified by CTO localization

	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
CTO LCX						
Right dominance ($n = 400$)	Reference (1.0)			Reference (1.0)		
Balanced ($n = 30$)	0.96	0.35–2.68	NS	1.22	0.42–3.51	NS
Left dominance ($n = 70$)	2.48	1.40–4.38	0.002	3.57	1.94–6.55	<0.001
CTO LAD						
Right dominance ($n = 468$)	Reference (1.0)			Reference (1.0)		
Balanced ($n = 31$)	No events			No events		
Left dominance ($n = 58$)	1.30	0.67–2.53	NS	1.36	0.67–2.76	NS
CTO RCA						
Right dominance ($n = 878$)	Reference (1.0)			Reference (1.0)		
Balanced ($n = 45$)	0.84	0.30–2.11	NS	0.80	0.29–2.18	NS
Left dominance ($n = 7$)	0.81	0.11–6.00	NS	0.40	0.05–3.06	NS

Multivariate analysis was adjusted for comorbidities, LVEF, and procedural success.
Abbreviations: HR, hazard ratio, CI, confidence interval; LAD, left anterior descending artery; LCX, left circumflex coronary artery, RCA, right coronary artery.

circulation with more myocardium at risk in the event of an ACS. In particular in cases of acute occlusion of the LCX, RD may confer a protective effect due to back-up supply, thereby reducing infarct size [36]. Indeed, previous studies have demonstrated that acute occlusion of a proximal dominant LCX resulted in a higher proportion of patients presenting with cardiogenic shock as opposed to patients with a proximal LAD occlusion [34]. In addition, the technical challenges of LCX interventions have been shown to result in a higher rate of unsuccessful PCIs in LD patients with LCX occlusion, thereby further enhancing risk in these patients [37]. In support of this notion, we observed a significantly increased risk for all-cause mortality in LD patients with complete occlusion of the LCX in our study, while this association was not seen in patients with LAD and RCA occlusions.

The anatomic importance of stenosis localization in patients with LD might indeed be different from that in patients with RD or BD. Thus, it seems reasonable that a proximal stenosis in the LCA may result in more extensive ischemia in a LD system as compared to a RD system. In a LD system, the LAD is usually long and wraps around the apex in 87% of LD cases, while the RCA is frequently small, does not reach the acute margin of the heart and may therefore not be sufficient to perfuse the myocardium in the event of a proximal LAD occlusion [33,38]. At present, however, little is known about the prognostic value of stenosis location in relation to coronary vessel dominance. While it has been shown that a LM coronary artery stenosis was associated with an increased risk of adverse events in patients with LD but not in RD [4,10], two previous studies have failed to demonstrate a significant difference in risk estimates between LD and RD when a stenosis in the left coronary system (LCX or LAD) was present [8,10]. In the present report, we did not observe any effect modification by CTO lesions located in the LM or LAD, while only LCX lesions were associated with an increased risk in patients with a LD system as compared to RD. Thus, taken together, it is likely that both, technical and procedural challenges of a dominant LCX intervention and the absence of a double supply to the myocardium in a LD system might have accounted for the worse outcomes observed in patients with LCX CTO and LD system. Of note, only 0.7% of our study population presented with a proximal occlusion of the left coronary system. Yet, our study was likely statistically underpowered to detect effect modification between LD and RD in this subgroup of patients.

As with any study, certain design limitations are inherent. First, our single centre, retrospective analysis was based on an existing database and, accordingly, data were not independently adjudicated. Thus, despite the use of multivariate analysis, it remains unknown if residual confounders may have affected the outcome in the present analyses. Second, given that multiple groups and endpoints were assessed, the potential effects of multiplicity need to be taken into account when interpreting our data. Third, consistent with the low prevalence of left and co-dominant coronary circulation in the general population is low, the number of patients in the LD and BD groups in our study were small. Thus, a potential selection due to small populations cannot be ruled out completely and our findings should therefore be confirmed through larger and sufficiently powered, randomized studies with long-term follow-up. Finally, as we report all-cause mortality rather than cardiac death, it is possible that noncardiac disease processes could have affected the outcome.

5 | CONCLUSIONS

Taken together, our findings suggest that LD confers a higher risk of death and MACE than RD and BD in patients undergoing PCI for CTO. This increase in risk estimates was particularly pronounced in patients

with a CTO lesion located in the LCX. Since successful CTO recanalization was a strong and negative predictor of adverse events in our study, our data emphasize the need to minimize procedural risk in these patients. Given the low prevalence of LD in the general population, further investigation from larger cohorts is needed to confirm our findings.

CONFLICT OF INTEREST

There is no conflict of interest.

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