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The Impact of Right Coronary Artery Chronic Total Occlusion on Clinical Outcome of Patients Undergoing Percutaneous Coronary Intervention for Unprotected Left Main Disease

Angela Migliorini, MD, Renato Valenti, MD, Guido Parodi, MD, Piergiovanni Buonamici, MD, Giampaolo Cerisano, MD, Nazario Carrabba, MD, Ruben Vergara, MD, David Antoniucci, MD

Florence, Italy

Objectives The aim of the present study was to investigate whether right coronary artery chronic total occlusion (CTO) carries prognostic implications in patients undergoing drug-eluting stent–supported percutaneous coronary intervention (PCI) for unprotected left main disease (ULMD).

Background No data exist on the prognostic implication of CTO in patients undergoing PCI for ULMD.

Methods Prospective registry of consecutive patients undergoing PCI for ULMD. Patients with ST-segment elevation myocardial infarction were excluded. Primary endpoints were 6-month and long-term cardiac mortality.

Results From January 2004 to December 2009, 330 patients underwent PCI for ULMD. Of the 330 patients, 78 (24%) had CTO of the right coronary artery, 22 (7%) had CTO of the left anterior descending artery, and 16 (5%) had CTO of the left circumflex artery. Patients with right coronary artery CTO had a higher risk profile compared with patients without right coronary artery CTO. The 6-month mortality rate was 12.8% in patients with right coronary artery CTO, and 3.6% in patients without right coronary artery CTO ($p < 0.002$), and the 3-year cardiac survival rate was 76.4 ± 6.8% and 89.7 ± 2.7% ($p < 0.003$), respectively. By multivariable analysis, the only 2 independent predictors of 3-year cardiac mortality were right coronary artery CTO (hazard ratio: 2.15, 95% confidence interval: 1.02 to 4.50; $p = 0.043$) and EuroSCORE (hazard ratio: 1.03, 95% confidence interval: 1.02 to 1.05; $p < 0.001$).

Conclusions Right coronary artery CTO occurs frequently and is a significant predictor of mortality in patients with ULMD undergoing PCI. (J Am Coll Cardiol 2011;58:125–30) © 2011 by the American College of Cardiology Foundation

Data from registries and randomized trials show an increasing use of percutaneous coronary intervention (PCI) for unprotected left main disease (ULMD), and a study comparing PCI with coronary surgery, the SYNTAX (SYNergy between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery) trial, showed in patients with ULMD that the 2 revascularization strategies are equivalent in terms of mortality (1–8). However, the SYNTAX trial has shown that in the subset of patients with ULMD, a high coronary anatomy complexity, as defined by a SYNTAX score of ≥33, is associated with a significant increase in the rate of major adverse cardiovascular events and death (7,8).

High coronary anatomy complexity may result in an incomplete revascularization PCI, and a large survey study in the drug-eluting stent (DES) era showed that incomplete revascularization associated with coronary chronic total occlusion (CTO) carries a worse outcome and a higher risk of death compared with complete revascularization (9).

There are no data on the impact of right coronary artery CTO on the outcome of patients undergoing DES-supported PCI for ULMD.

The aim of the present study was to investigate whether right coronary artery CTO carries prognostic implications in patients undergoing DES-supported PCI for ULMD.

Methods

All consecutive patients who underwent PCI for ULMD from January 2004 to December 2009 were enrolled in a prospective registry. Patients with stable coronary artery disease as well as acute coronary syndromes and acute

From the Division of Cardiology, Careggi Hospital, Florence, Italy. The authors have reported that they have no relationships to disclose.

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Abbreviations and Acronyms

CK-MB = creatine kinase-myocardial band

CTO = chronic total occlusion

DES = drug-eluting stent(s)

PCI = percutaneous coronary intervention

ULMD = unprotected left main disease

non–ST-segment elevation myocardial infarction were included irrespective of the coronary anatomy. Patients underwent PCI instead of coronary surgery either because of patient preference or the high risk associated with surgery. High surgical risk was defined as a logistic EuroSCORE of ≥6 (10).

The study exclusion criteria were: 1) acute ST-segment elevation myocardial infarction; and 2) anticipated noncompliance with dual antiplatelet treatment for at least 12 months. Multivessel disease was defined as stenosis >70% of 1, 2, or 3 major coronary arteries on visual assessment at baseline angiography in addition to the left main coronary artery lesion. Disease of the left anterior descending artery and the circumflex artery included lesions beyond 10 mm from the ostia. CTO was defined as complete occlusion (Thrombolysis In Myocardial Infarction flow grade 0) lasting >3 months. Right coronary artery CTO included only dominant right coronary arteries. Patients were treated with the intention to achieve complete revascularization. Completeness of revascularization was defined as the successful revascularization of all vessels with a diameter stenosis >70% and a diameter >2 mm on visual assessment achieved either during the index hospitalization or at any time within 30 days after a first PCI.

PCI was performed using standard techniques. For distal left main disease, a single-stent technique was preferred in patients with a normal or diminutive-appearing side branch, whereas a double-stent technique was considered in patients with disease of both the ostia and proximal segments of the left anterior descending artery and circumflex artery. Whichever stenting technique was used, routine final kissing balloon post-dilation with noncompliant balloons had to be performed in all cases. Procedural adjunctive antithrombotic therapy included unfractionated heparin (an initial bolus of 70 U/kg and additional boluses during the procedure to achieve an activated clotting time of 200 to 250 s), whereas the use of glycoprotein IIb/IIIa inhibitors was at discretion of the operator. Chronic antithrombotic treatment included aspirin (300 mg/day indefinitely) and clopidogrel (75 to 150 mg/day for at least 1 year).

The primary endpoints of the study were 6-month and long-term cardiac mortality. All deaths were considered cardiac related unless an unequivocal noncardiac cause could be documented. Secondary endpoints were: 1) myocardial infarction; and 2) repeat percutaneous or surgical coronary revascularization. The diagnosis of non–Q-wave myocardial infarction was based on an increase in creatine kinase-myocardial band (CK-MB) isoenzyme or troponin I >3 times the upper limit of normal or, for patients with elevated values on admission, a re-elevation of CK-MB or troponin I values. Q-wave myocardial infarction was defined as the development of new Q waves in ≥2 electrocardiographic leads in addition to CK-MB or troponin I elevation. CK-MB fraction and troponin I were routinely assessed 12 h after PCI in all patients and at least 3 times every 6 h in patients with recurrent chest pain. Stroke was defined as an acute neurological defect lasting longer than 24 h.

All patients were scheduled for clinical follow-up at 1, 6, and 12 months and yearly thereafter. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries were entered into the prospective database. The treatment protocol included routine 6- to 9-month angiographic follow-up. Unscheduled angiography was allowed on the basis of clinical indication.

The study was approved by the institutional review committee, and all patients gave informed written consent to undergo intervention and participate in the study.

Statistical analysis. Discrete data are summarized as frequencies, whereas continuous data are mean ± SD or median (interquartile range), as appropriate. The chi-square test was used for comparison of categorical variables, and the unpaired 2-tailed Student *t* test or Mann-Whitney rank-sum test was used to test differences among continuous variables. Survival curves were generated using the Kaplan-Meier method, and the difference between groups was assessed by a log-rank test. The multivariable analysis to evaluate the independent contribution of clinical, angiographic, and procedure variables to the primary endpoints was performed by a forward stepwise Cox proportional hazards model. The variables entered into the model were age (years), male sex, diabetes mellitus, serum creatinine level >150 μmol/l, history of myocardial infarction, acute coronary syndrome on admission, left ventricular ejection fraction <40%, left main plus 3-vessel coronary disease, right coronary artery CTO, left anterior descending artery CTO, left circumflex artery CTO, EuroSCORE >6, left main bifurcation lesion, left main stenting of both branches, left main stent length >24 mm, abciximab use, intra-aortic balloon counterpulsation, and Thrombolysis In Myocardial Infarction major bleeding (11). A Cox proportional hazards model was used to test interaction among covariates. A propensity score analysis was performed using a logistic regression model from which the probability for a patent right coronary artery was calculated for each patient. Model discrimination was assessed with the c-statistic and goodness-of-fit with Hosmer and Lemeshow test. Thereafter, a Cox multivariate analysis was performed to adjust right coronary CTO for a propensity score. A p value <0.05 was considered significant. Analyses were performed using the software package SPSS version 11.5 (SPSS Inc., Chicago, Illinois).

Results

From January 2004 to December 2009, 374 patients underwent PCI for ULMD. Of these, 44 had acute ST-segment elevation myocardial infarction and were excluded from the

analysis. Table 1 shows the baseline characteristics of the 330 patients eligible for the study.

Of the 330 patients, 78 (24%) had a right coronary artery CTO. CTO of the left anterior descending artery or left circumflex artery was revealed in 21 patients (6%) and 19 patients (6%), respectively.

The majority of patients were high surgical risk patients (182 patients had a EuroSCORE of >6). Patients with right coronary artery CTO had a higher risk profile compared with patients without right coronary artery CTO with a higher EuroSCORE (median score 9.6 and 6.1, respectively; $p = 0.002$) and a lower left ventricular ejection fraction (39 ± 14% and 47 ± 12%, respectively; $p < 0.001$). Moreover, more patients in the right coronary artery CTO group had severe disease of both the left anterior descending artery and circumflex artery (49% and 33%, respectively; $p < 0.001$), and 8 patients had a double CTO.

Table 2 shows the procedure characteristics. Placement of a single stent in the left main and left anterior descending arteries was accomplished more frequently in the right coronary CTO group, whereas there were no differences between groups with regard to the other procedure characteristics (stenting technique, use of rotational atherectomy, total stent length, type of DES, use of abciximab, use of intra-aortic balloon counterpulsation). Right coronary artery CTO PCI attempt was performed in 39 patients (50%). Reasons to not attempt the CTO PCI were: 1) no evidence of a significant area of viable myocardium in the territory supplied by the right coronary artery (n = 20); 2) renal insufficiency contraindicating the use of a large amount of dye (n = 7); and 3) a low likelihood of PCI success as evaluated by the operator (n = 12). Of the 39 right coronary artery CTO PCIs attempted, 21 (54%) were performed in the same left main procedure, whereas 18 were staged. In all cases, the left coronary artery procedure was performed first, and the decision to stage or not to stage the right coronary artery CTO PCI was made according to the procedure time, fluoroscopy time, and amount of contrast used for the left coronary artery procedure. Right coronary artery CTO PCI was successful in 35 patients (90%). Most of the occlusions were treated with long stents and multiple stents (median stent length, 43 mm; interquartile range, 35 to 56 mm). PCI was attempted in 19 of 21 patients with left anterior descending artery CTO and was successful in 18 patients, whereas PCI was attempted in 13 of 19 patients with left circumflex artery CTO and was successful in 11.

Overall, complete revascularization was achieved in 77% of patients. Complete revascularization was achieved in 44% of patients with right coronary artery CTO and 88% of patients without right coronary artery CTO ($p < 0.001$). As a consequence, the majority of patients without complete revascularization (59%) had CTO of the right coronary artery.

Table 3 and Figure 1 summarize the clinical outcome. The median length of follow-up was 16.1 months (interquartile range: 6.4 to 37.8 months), and the follow-up rate was 100%. At 6 months, the cardiac mortality rate was 12.8% in patients

Table 1 Baseline Characteristics

	All Patients (n = 330)	Patients Without RCA CTO (n = 252)	Patients With RCA CTO (n = 78)	p Value
Age, yrs	72 ± 10	72 ± 10	71 ± 11	0.728
Male	259 (78)	192 (76)	67 (86)	0.782
Current smokers	62 (19)	47 (19)	15 (19)	0.909
Arterial hypertension	256 (77)	196 (78)	60 (77)	0.874
Diabetes mellitus	98 (30)	71 (28)	27 (35)	0.277
Hypercholesterolemia	215 (65)	165 (65)	50 (64)	0.824
Peripheral vascular disease	105 (32)	77 (31)	28 (36)	0.376
Previous myocardial infarction	83 (25)	59 (23)	24 (31)	0.191
Previous PCI	114 (35)	92 (36)	22 (28)	0.178
NSTEMI	58 (18)	40 (16)	18 (23)	0.144
Unstable angina	177 (54)	135 (54)	42 (54)	0.917
Creatinine >150 μmol/l	59 (18)	41 (16)	18 (23)	0.170
LVEF, %	45 ± 13	47 ± 12	39 ± 14	<0.001
LVEF ≤40%	177 (54)	135 (54)	42 (54)	0.966
EuroSCORE	6.8 (3.4–18.6)	6.1 (3.2–14.5)	9.6 (4.5–28)	0.002
EuroSCORE ≥6	182 (55)	129 (51)	53 (68)	0.009
LM plus 2-vessel disease	142 (43)	105 (42)	37 (47)	0.368
LM plus 3-vessel disease	96 (28)	58 (33)	38 (49)	<0.001
CTO lesion	118	33	85	
Left anterior descending artery	21 (6)	19 (7.5)	2 (2.6)	0.116
Circumflex artery	19 (6)	14 (5.6)	5 (6.4)	0.777
Distal LM location	283 (86)	218 (85)	65 (88)	0.429

Value are mean ± SD, n (%), median (interquartile range), or n.

CTO = chronic total occlusion; LM = left main; LVEF = left ventricular ejection fraction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

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with right coronary artery CTO and 3.6% in patients without right coronary artery CTO (p = 0.002). The 6-month cardiac mortality rate was 8.6% in patients with successfully treated right coronary artery CTO and 16.3% in patients with untreated coronary artery CTO or failed right coronary artery CTO PCI (p = 0.311). The 6-month mortality rate was 4.8% and 0% in patients with CTO of the left anterior descending artery and left circumflex artery, respectively. The 3-year cardiac survival rates was 76.4 ± 6.8% in patients with right coronary artery CTO and 89.7 ± 2.7% in patients without right coronary artery CTO (p = 0.003).

Most of cardiac deaths (83%) occurred in patients with a EuroSCORE of ≥6.

No significant interactions were found between right coronary artery CTO and other covariates.

By multivariable analysis, the only 2 independent predictors of 3-year cardiac mortality were right coronary artery CTO (hazard ratio: 2.15, 95% confidence interval: 1.02 to 4.50; p = 0.043) and EuroSCORE (hazard ratio: 1.03, 95% CI: 1.02 to 1.05; p < 0.001). Multivariable analysis was also performed using the propensity score and right coronary artery CTO as covariates. The c-statistic of the regression model of the propensity score was 0.83 (Hosmer and Lemeshow goodness-of-fit test, p = 0.323). After adjusting for the propensity score, right coronary artery CTO remained significantly related to the risk of cardiac death (hazard ratio: 2.37, 95% confidence interval: 1.09 to 5.15; p = 0.029).

Table 2 Procedure Characteristics of LM Intervention in Patients With and Without RCA CTO

	Patients Without RCA CTO (n = 252)	Patients With RCA CTO (n = 78)	p Value
LM stenting alone	49 (19)	7 (9)	0.092
Single LM-LAD stenting	100 (40)	42 (54)	0.027
Single LM-LCx stenting	17 (7)	5 (6)	0.508
LM stenting of both branches	86 (34)	24 (31)	0.582
T-stenting	55	19	
Crush stenting	24	5	
V-stenting/culotte stenting	7	0	
Rotablator	19 (8)	6 (8)	0.731
Total LM stent length, mm	22 ± 11	21 ± 13	0.692
IVUS guidance	82 (32)	23 (29)	0.613
Abciximab	138 (55)	37 (47)	0.257
IABP	17 (7)	10 (13)	0.087
Stent type			0.909
Sirolimus-eluting	30 (12)	11 (14)	
Paclitaxel-eluting	169 (67)	52 (67)	
Everolimus-eluting	53 (21)	15 (19)	
Maximum pressure inflation, atm	20 ± 3	20 ± 3	0.939
RVD pre-PCI, mm	3.64 ± 0.39	3.67 ± 0.39	0.553
MLD post-PCI, mm	3.71 ± 0.34	3.73 ± 0.33	0.648
CTO PCI attempted	26/33 (79)	43/85 (51)	0.005
CTO PCI success	23/26 (88)	40/43 (93)	0.515

Values are n (%), n, or mean ± SD.

IABP = intra-aortic balloon pump; IVUS = coronary intravascular ultrasound; LAD = left anterior descending artery; LCx = left circumflex artery; MLD = minimum lumen diameter; RVD = reference vessel diameter; other abbreviations as in Table 1.

Table 3 Clinical Outcome

	Patients Without RCA CTO (n = 252)	Patients With RCA CTO (n = 78)	p Value
6-month outcome			
Overall mortality	13 (5.2)	11 (14)	0.008
Cardiac mortality,	9 (3.6)	10 (12.8)	0.002
RCA CTO PCI success, %		8.6*	
RCA CTO none or failed, %		16.3*	
MI	2 (0.8)	1 (1.3)	0.691
Left main rePCI	30 (11.9)	6 (7.7)	0.297
Any revascularization, %	51 (20)	16 (20)	0.958
PCI	51	16	
CABG	0	0	
Stroke	0	1 (1.3)	0.072
Long-term outcome†			
Cardiac mortality			0.003
1-yr, % (n = 210)	4.7 ± 1.4	12.9 ± 3.8	
2-yr, % (n = 138)	6.1 ± 1.7	19.2 ± 5.6	
3-yr, % (n = 95)	10.3 ± 2.6	23.6 ± 6.8	
3-yr MI, %	6.3 ± 4.3	13.1 ± 7.3	0.065
Any 3-yr revascularization, %	43.5 ± 4.7	45.7 ± 8.7	0.155

Values are n (%), n, or mean ± SD. *p = 0.311. †Kaplan-Meier estimate.

CABG = coronary artery bypass grafting; CTO = chronic total occlusion; MI = myocardial infarction; other abbreviations as in Table 1.

The angiographic follow-up rate was 88% (n = 290). The left main angiographic restenosis rate was 12%.

Discussion

The main findings of the present study are the following: 1) more than one-third of patients undergoing PCI for

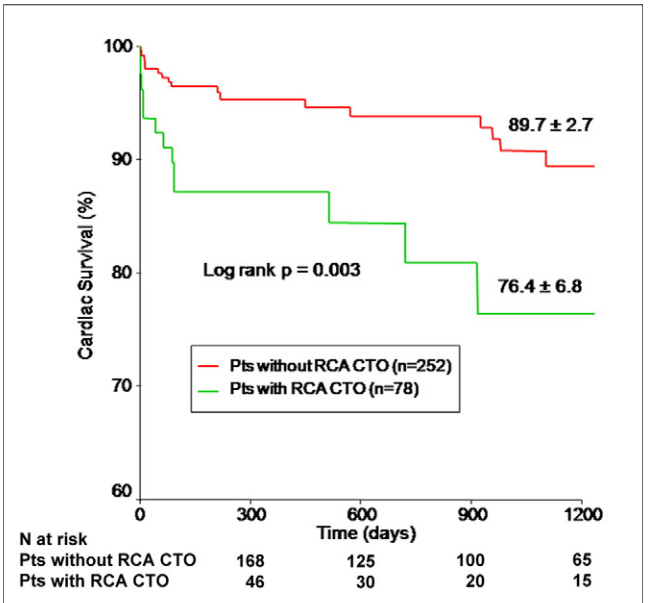

Figure 1 Long-Term Survival

Kaplan-Meier analysis of cardiac survival for patients with and without right coronary artery chronic total occlusion (RCA CTO).

ULMD have at least 1 CTO, and right coronary artery CTO was revealed in nearly one-fourth of patients; 2) right coronary artery CTO is a predictor of mortality; 3) right coronary artery CTO PCI is attempted less frequently than left anterior descending artery or circumflex artery CTO PCI; 4) the completeness of revascularization in patients with disease of vessels other than the left main coronary artery is frequently dependent on successful revascularization of right coronary artery CTO; 5) other angiographic features such as distal left main disease or 3-vessel disease have no significant impact on survival; and 6) the EuroSCORE is a valid score for the definition of the risk of patients undergoing PCI for ULMD.

Coronary CTO occurs frequently, and registry studies report an incidence of 30% to 50% in patients with significant coronary artery disease undergoing coronary angiography (12–15). CTO is the most frequent reasons for referral of patients who need revascularization for coronary artery bypass graft surgery (12–15), and this fact may explain the relatively low incidence of right coronary artery CTO in previous studies on ULMD PCI, including the randomized SYNTAX trial (7). In the SYNTAX trial, only 10% of patients randomized to PCI had right coronary artery CTO, whereas the incidence of CTO was 56.4% in patients excluded from randomization and enrolled in the coronary bypass graft registry (7).

In this study, right coronary artery CTO was revealed in nearly one-fourth of patients who underwent ULMD PCI. This finding may be explained by the fact that, in 2004, with the unrestricted availability of DES, specific institutional programs for routine percutaneous treatment of CTO and ULMD started (16,17).

Right coronary artery CTO is independently related to the risk of cardiac death. It has been shown that in patients with multivessel disease undergoing PCI, incomplete revascularization due to untreated CTO carries a higher risk of mortality compared with patients with complete revascularization (9,18). Patients with successful PCI of right coronary artery CTO had a lower mortality rat compared with patients with no or a failed PCI; however, this difference did not reach significance. Moreover, in this cohort of patients, one-half of patients with right coronary artery CTO had no indication for PCI because of the lack of viable myocardium or renal insufficiency that may be associated with an increased risk of death. Thus, right coronary artery CTO might be linked to mortality also through associated comorbidities known to have a significant impact on mortality. Conversely, CTO of the left anterior descending artery or circumflex artery PCI was attempted in the majority of patients, indicating the presence of viable myocardium and the lack of renal insufficiency contraindicating the use of large amount of dye or a relatively less severe atherosclerotic burden making a PCI attempt likely successful.

In this study, coronary anatomy features other than right coronary artery CTO such as 3-vessel disease and a distal location of left main disease and CTO of the left anterior descending artery or left circumflex artery had no impact on survival. Again, this finding may be related to more frequently achieving complete revascularization in these subsets of patients or to a better risk profile allowing PCI to be attempted more frequently and with a high likelihood of success. This finding is not consistent with the results of the SYNTAX trial. In the 357 patients randomized to PCI of the ULMD-SYNTAX substudy, the mortality rate increased with the increase in the diffusion and angiographic complexity of coronary artery disease. The 1-year mortality rate in patients with more complex coronary disease as defined by a SYNTAX score of $\geq$33 was 9.7% compared with the 0.9% and 1% of patients with low (SYNTAX score of $\leq$22) or intermediate morphological complexity (SYNTAX score of 23 to 32), respectively (8). The major differences between the 2 patient populations may help to explain these discrepancies: the randomized SYNTAX population had a lower EuroSCORE (3.9 $\pm$ 2.8) and a lower incidence of right coronary artery CTO (10.1%) and of complete revascularization (complete revascularization was achieved in 64.5% of patients randomized to PCI) compared with this patient cohort (8).

In this study, the EuroSCORE was a good predictor of mortality, and this finding is consistent with most of the previous studies on ULMD PCI showing that this scoring system based on clinical variables is a valid predictor of patient outcome (4,6,8,19).

Study limitations. One limitation of the study involves the lack of a surgical group. This would have allowed the assessment of the value of revascularization of occluded vessels for which a PCI attempt was deemed not indicated. However, this comparison was beyond the aim of this study. Another limitation is the relatively small number of patients and events that make possible type II errors in which differences in baseline or procedure characteristics are not found to be predictors of long-term outcome, but that in a larger study could be statistically significant. The high number of predictors screened by stepwise analysis may result in an overfitting. However, to resolve this problem and to yield consistent results, we performed a propensity score–adjusted analysis. It must be acknowledged that this study does not show a cause-and-effect relationship between the presence of right coronary artery CTO and mortality but only an association. Therefore, the results of the study are only hypothesis generating.

Conclusions

The results of this study show that right coronary artery CTO occurs frequently and is a significant predictor of mortality in patients with ULMD undergoing PCI.

Reprint request and correspondence: Dr. David Antoniucci, Division of Cardiology, Careggi Hospital, Viale Morgagni, I-50139 Florence, Italy. E-mail: david.antoniucci@virgilio.it.

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Key Words: chronic total occlusion ■ left main disease ■ percutaneous coronary intervention.