Impact of Elective, Uncomplicated Target Lesion Revascularization on Cardiac Mortality After Elective Percutaneous Coronary Intervention of Unprotected Left Main Coronary Artery Disease

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This study sought to investigate the impact of elective, uncomplicated target lesion revascularization (TLR) on long-term cardiac mortality after percutaneous coronary intervention (PCI) of unprotected left main coronary artery (ULMCA) disease. Consecutive patients undergoing PCI for ULMCA disease between January 2003 and December 2015 in 1 interventional center in Northern Italy were included. Patients presenting with cardiogenic shock, ST-segment elevation myocardial infarction (MI), as well as those undergoing urgent or complicated TLR were excluded. The primary endpoint of the study was cardiac mortality. Among the 418 patients fulfilling the study criteria, 79 (18.46%) underwent elective, uncomplicated TLR. After a median follow-up of 5.5 years, there were 23 cardiac deaths among patients undergoing elective, uncomplicated TLR versus 50 in patients not undergoing TLR. After adjusting for possible confounders, TLR was an independent predictor of cardiac mortality (Hazard ratio [HZ] = 1.92, 95% confidence interval [CI]: 1.05 to 3.49; p = 0.03). Patients undergoing TLR had also significantly higher rates of the composite of cardiac death, MI and stroke compared with the no TLR group (adjusted HR = 1.76, 95% CI 1.14 to 2.72). In conclusion, elective, uncomplicated TLR after PCI of ULMCA disease is associated with increased risk of long-term cardiac mortality. Reducing the risk of TLR after PCI of ULMCA disease may potentially improve the survival of these patients. **(Am J Cardiol 2020;128:94−100)**

Percutaneous coronary intervention (PCI) appears a reasonable alternative to coronary artery bypass graft (CABG) in selected groups of patients with unprotected left main coronary artery (ULMCA) disease.[1−5] Despite technological progression, improved operator skills and introduction of drug-eluting stents (DES), in-stent restenosis (IRS) still remains a major limitation after PCI of ULMCA disease.[6−9] In nonleft main intervention, ISR is generally considered a benign event, although severe restenosis may present as acute myocardial infarction (MI).[10] Recent data have challenged this notion reporting significantly higher rates of mortality in patients with elective, uncomplicated target lesion revascularization (TLR) compared with patients with no TLR.[11] However, in that study patients undergoing PCI of ULMCA stenosis were not included, and therefore the prognostic implication of TLR after PCI for ULMCA disease have remained uncertain. For these reasons, we investigated the association between elective, uncomplicated TLR and cardiac mortality after PCI of ULMCA disease.

Methods

The Bologna Registry is an observational, single-center, retrospective study including consecutive patients undergoing PCI of ULMCA stenosis.[12] The objective of this study was to investigate the association between cardiac mortality and elective, uncomplicated TLR in patients undergoing elective PCI of ULMCA stenosis. Thus, patients presenting at the index procedure with cardiogenic shock or ST-segment elevation MI, those dying in-hospital, as well as those dying the same day as or the day after the TLR procedure or with an MI the day before, the same day as or the day after TLR were excluded from the analyses. The primary endpoint of the study was cardiac mortality, defined as death due to MI, congestive heart failure, arrhythmia, or sudden death. The secondary endpoints of the study were all-cause death, MI, stroke as individual endpoints, or the composite of cardiac death, MI or stroke defined as major adverse cardiac events (MACE). For the purpose of the study, patients with TLR were compared with patients with no TLR, including those with no-TLR TVR, no TVR and no repeat revascularization. TLR was defined as any repeat revascularization (with either PCI or coronary artery bypass graft) of ULMCA, performed for restenosis of the prior stent, including 5 mm proximal or distal to the stent. No-TLR TVR was defined as any revascularization of either left anterior descending artery, circumflex artery, the ramus,

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See page 100 for disclosure information.

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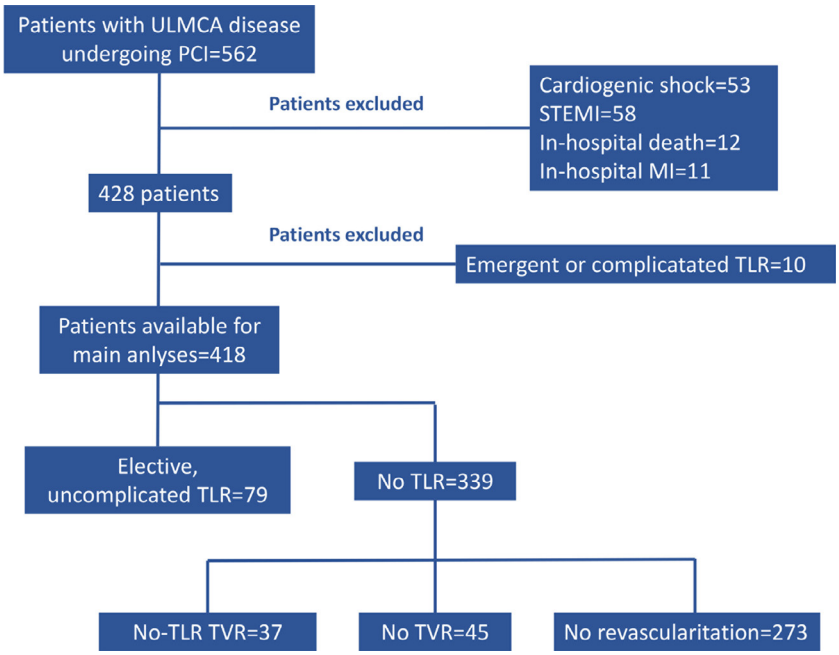

Figure 1. Study flowchart. Among 562 patients undergoing percutaneous coronary intervention (PCI) of unprotected left main coronary artery (ULMCA), 428 patients fulfilled the inclusion criteria of the study and were included in the analyses. MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TLR= target lesion revascularization; TVR = target vessel revascularization. No TLR includes: no-TLR TVR, no TVR, and no revascularization.

or their respective branches of bifurcation. Non-TVR was defined as any revascularization of the right coronary artery. Continuous variables are presented as means ± standard deviations (SD) and were compared with the Student *t* test. Categorical variables are presented as frequencies and percentages and were compared with the Chi-square statistic or the Fisher's exact test, as appropriate. To take into account the time-dependent nature of survival analyses, computations were performed using the Simon-Makuch method.[13] In contrast to the Kaplan-Meier method, which is typically used for fixed covariates, in the Simon-Makuch analysis the number of subjects at risk is not fixed at time 0. The method can therefore include subjects who may begin follow-up at one level of some exposure and subsequently change to another level of exposure. Accordingly, the number at risk for each group reported at the time point on the x-axis of the survival analysis curves identifies "risk episodes" rather than "subjects at risk," as in the Kaplan-Meier curves. Cardiac death was also studied by fitting competing risk regression based on Fine and Gray approach with death-for-non-cardiac cause as competing event.

Independent predictors of long-term cardiac mortality and of MACE were analyzed using Cox proportional hazard regression models applying the Breslow method for ties. The variables included in the models are specified in the relative Tables, with TLR and MI during follow-up included as time-dependent covariates. All reported p values are 2-sided. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using STATA version 14.2 College Station, Texas.

Results

Between January 2003 and December 2015, 562 patients underwent PCI of ULMCA stenosis. The study flow is reported in Figure 1. Of 418 patients finally included in the study, 79 underwent elective, uncomplicated TLR and 339 had no TLR. Demographic, clinical, angiographic, and procedural characteristics of patients stratified by TLR occurrence are shown in Table 1. Compared with patients with no TLR, those undergoing elective, uncomplicated TLR had more often bifurcation lesions, greater number of stents implanted in the LM, smaller stent diameter, greater total stent length, and were treated more often with bare-metal stents (BMS) than DES. The incidence of elective, uncomplicated TLR was 4.07 per 100 patient-years, and the majority (70.9%) of TLR occurred within the first year of the index procedure.

After a median follow-up of 5.5 years, there were 23 cardiac deaths and 35 MACE in the TLR group versus 50 cardiac deaths and 82 MACE in the no TLR group. As shown in Table 2 and in Figure 2, patients with TLR had significantly higher rates of cardiac mortality (3.83% vs 2.81%, respectively; $p = 0.02$) compared with patients with no TLR. There were 13 sudden deaths in the TLR group versus 30 in the no TLR group (incidence rate = 2.17% vs 1.69%, respectively; adjusted HR = 1.61, 95% CI: 0.81 to 3.21; $p = 0.18$); 6 deaths due to acute MI in the TLR group versus 7 in the no TLR group (incidence rate = 1.00% vs 0.39 %, respectively), and 4 deaths due to congestive heart failure in the TLR group versus 13 in the no TLR group (incidence rate = 0.67% vs 0.73 %, respectively). In the competitive risk analysis, the subhazard of cardiac mortality of TLR compared with no TLR was 2.25 (95% CI 1.39 to 3.63). After adjusting for potential confounders, elective uncomplicated TLR was an independent predictor of cardiac mortality (HR = 1.92, 95% CI: 1.05 to 3.49; $p = 0.03$). Other variables significantly associated with cardiac mortality are shown in Table 3.

As shown in Table 2 and in Figure 3, patients with TLR had also significantly higher rates of MACE compared with

Table 1
Baseline demographic, clinical, angiographic and procedural characteristics of patients enrolled in the registry stratified by the occurrence of target lesion revascularization

VARIABLE	TLR (n = 79)	No TLR (n = 339)	p value
Age (years)	71.5 ± 11.1	73.5 ± 11.5	0.16
Men	54 (68%)	241 (71%)	0.68
Hypertension	61 (77%)	247 (73%)	0.48
Diabetes mellitus	24 (30%)	91 (27%)	0.58
Hypercholesterolemia°	53 (67%)	224 (66%)	0.90
Current or former smoking habits	38 (48%)	166 (49%)	0.90
Previous myocardial infarction	27 (34%)	126 (37%)	0.70
Previous percutaneous coronary intervention	30 (38%)	94 (28%)	0.08
Previous stroke	2 (3%)	27 (8%)	0.14
Clinical presentation			0.08
Stable angina pectoris	24 (30%)	61 (19%)	
Unstable angina pectoris	20 (25%)	89 (26%)	
NSTEMI	27 (34%)	137 (40%)	
Silent myocardial ischemia	8 (11%)	52 (15%)	
Chronic obstructive pulmonary disease	11 (14%)	58 (17%)	0.61
Chronic renal failure*	5 (6%)	29 (9%)	0.65
Peripheral arterial disease	14 (18%)	91 (27%)	0.11
Neoplasm	7 (9%)	26 (8%)	0.65
Left Ventricular Ejection Fraction	55.7 ± 17.4	52.2 ± 13.9	0.06
Multivessel coronary artery disease	62 (79%)	230 (69%)	0.08
Number of narrowed coronary artery, per patient†	2.2 ± 0.8	2.0 ± 0.9	0.07
Total number of stents per patient	2.8 ± 1.3	2.6 ± 1.5	0.28
Left main disease			
Ostial disease only	7 (9%)	63 (19%)	0.04
All Bifurcations	70 (89%)	247 (73%)	<0.01
Bifurcation only	59 (84%)‡	222 (90%)‡	0.19
Ostial and LM and bifurcation	9 (13%)‡	20 (8%)‡	<0.01
Isolated ostial left anterior descending artery disease	2 (3%)‡	5 (2%)‡	0.66
True bifurcation§	28 (40%)‡	90 (36%)‡	0.59
Trifurcation	5 (6%)	13 (4%)	0.34
Left main procedure			
Total number of stents per patient	1.3 ± 0.7	1.0 ± 0.7	<0.01
Total stent length per patient, mm	21.4 ± 9.5	17.6 ± 8.9	<0.01
Minimum stent diameter per patient, mm	3.2 ± 0.5	3.4 ± 0.6	<0.01
Bare metal stent	28 (35%)	73 (22%)	0.01
First generation drug-eluting stent	58 (74%)	180 (53%)	<0.01
Second generation drug-eluting stent	26 (33%)	151 (45%)	0.08
Left main revascularization technique¶			
Single stent	35 (60%)	149 (66%)	0.40
Double stent	23 (40%)	76 (33%)	0.21
Crush	7 (12%)	14 (6%)	
T stenting	16 (28%)	62 (28%)	

Values are reported as mean ± SD or n (%).

LM = left-main; NSTEMI = non-ST-segment elevation myocardial infarction; TLR = target lesion revascularization. °Defined as the presence of plasma cholesterol levels> 200 mg/dl or as current statin therapy.

* Defined as creatinine levels > 2mg/dl;

† Referred to left anterior descending artery, circumflex artery or right coronary artery;

‡ The percentage refers to all bifurcations;

§ Defined as bifurcation type 1,1,1 according to Medina classification;

¶ This data were available for 58/70 TLR patients and 225/247 no TLR patients, respectively.

patients with no TLR (5.17% vs 4.61%, respectively; p = 0.03). After adjusting for potential confounders, elective uncomplicated TLR was an independent predictor of MACE (Table 4). The incidence of other clinical outcomes is reported in Table 2 and in Figure 4. As reported in Figure 5, patients with TLR had higher rates of cardiac mortality compared also with patients not undergoing any repeat revascularization during follow up (incidence rate = 3.83% vs 2.93%, respectively; p = 0.02). As shown in Supplemental Figure 1, among patients with TLR, those with MI occurring after TLR had a trend towards higher rates of cardiac mortality compared with those without MI after TLR (HR 2.73, 95% CI: 0.93 to 8.02; p = 0.07).

Similar results were obtained in a sensitivity analysis in which we removed patients treated with BMS (Supplemental Figure 2). However, in the multivariable analysis the

Table 2
Rates of cardiac death and major adverse cardiovascular events

Variable	TLR	No TLR
All-cause deaths	40	153
Incidence rate of all-cause death	6.67%	8.60%
Number of cardiac deaths	23	50
Incidence rate of cardiac deaths	3.83%	2.81%
Number of sudden cardiac deaths	13	30
Incidence rate of sudden cardiac deaths	2.17%	1.69%
Number of MI	13	30
Incidence rate of MI	2.17%	1.69%
Number of stroke	4	14
Incidence rate of stroke	0.67%	0.79%
Number of MACE	35	82
Incidence rate of MACE	5.17%	4.61%

MACE = major adverse cardiac events including the composite of cardiac death, myocardial infarction, or stroke; MI = myocardial Infarction; TLR = target lesion revascularization; incidence rates are reported per 100 patient-years.

Table 3
Multivariable predictors of long-term cardiac mortality

VARIABLE	HR (95% CI)	p value
Target lesion revascularization*	1.92 (1.05−3.49)	0.03
Age	1.04 (1.02−1.07)	<0.01
Men	2.10 (1.13−3.90)	0.02
Diabetes mellitus	1.90 (1.17−3.07)	0.01
Chronic renal failure†	2.43 (1.16−5.11)	0.02
Chronic obstructive pulmonary disease	0.80 (0.40−1.51)	0.44
Neoplasm	1.80 (0.78−4.18)	0.17
Initial presentation with NSTEMI	1.70 (1.02−2.82)	0.04
Number of narrowed coronary artery‡	1.03 (0.80−1.37)	0.83
reMI*	1.06 (0.70−1.60)	0.80

CI = confidence interval; HR = Hazard ratio; MI = myocardial infarction; NSTEMI= non-ST-segment elevation myocardial infarction.
* Included as a time-dependent covariate;
† Defined as creatinine levels >2 mg/dl;
‡ Referred to left anterior descending artery, circumflex artery or right coronary artery.

precision of the point estimate of the risk of cardiac mortality or MACE was reduced, likely due to the reduced statistical power (adjusted HR for cardiac mortality = 1.82 [95% CI 0.86 to 3.86], adjusted HR for MACE = 1.54 [95% CI 0.96 to 2.48]).

Discussion

This is the first study to investigate the association between elective, uncomplicated TLR and cardiac mortality after elective PCI of ULMCA disease. The major finding of this study is that patients undergoing TLR have an increased risk of cardiac mortality compared with patients with no TLR, and after adjusting for potential confounders, TLR was an independent predictor of cardiac mortality. In addition, the composite of cardiac death, MI and stroke was also higher in patients with TLR compared with patients with no TLR, and again TLR was an independent predictor of this composite endpoint.

Although the clinical outcomes of patients undergoing PCI has progressively improved over time due to iteration of devices and improvements in adjunct pharmacotherapy, imaging, and technique, restenosis continues to limit its utility, especially in patients with complex multivessel coronary artery disease.[6] Restenosis and TLR are in general perceived as benign entities. However, some studies have reported that patients with restenosis may present with an acute coronary syndrome, and a recent patient level pooled analysis of more than 32,000 patients undergoing PCI reported higher rates of mortality in patients with TLR versus no TLR.[11] These findings may be of particular concern in patients with ULMCA disease treated with PCI because

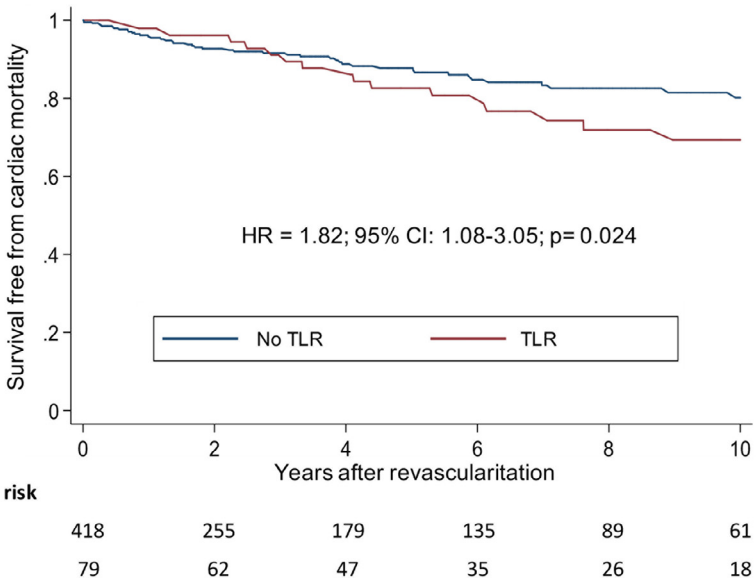

Figure 2. Simon-Makuch survival analysis on cardiac mortality. Patients with elective, uncomplicated TLR had significantly higher rates of cardiac mortality compared with patients with no TLR.

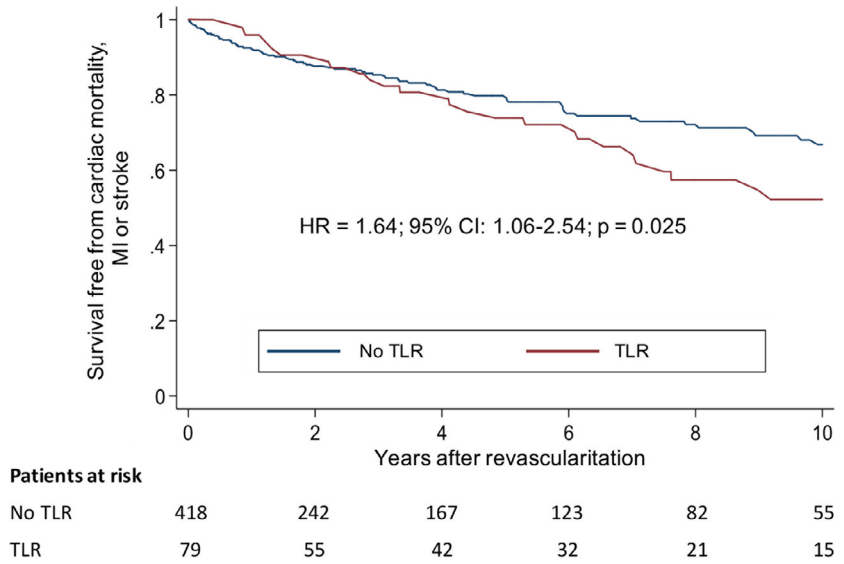

Figure 3. Simon-Makuch survival analysis on the composite of cardiac death, MI or stroke. Patients undergoing elective and uncomplicated TLR had significantly higher rates of cardiac death, myocardial infarction or stroke compared with those with no TLR.

of the large amount of myocardium at risk. However, no study has ever investigated the prognostic implications of TLR in this high-risk setting of patients.

On this background, we performed a retrospective observational study investigating the prognostic implications of TLR among 562 consecutive patients treated with PCI of ULMCA disease treated at our center from January 2003 to December 2015. We included patients treated with BMS, first generation and second generation DES, but excluded patients presenting with STEMI and cardiogenic shock at the index procedure, as well as those dying in-hospital after the procedure. In addition, to evaluate the prognostic implications of elective, uncomplicated TLR, we excluded patients presenting with restenosis and MI, as well as those dying or presenting with an MI the same day as or the day after the TLR. Consistent with prior findings, our study confirm the significant and independent association between TLR and cardiac mortality.

Table 4
Independent predictors of major adverse cardiac events

VARIABLE	HR (95% CI)	p value
Target lesion revascularization*	1.76 (1.14−2.72)	0.01
Age	1.02 (1.00−1.04)	0.03
Men	1.62 (1.02−2.58)	0.04
Diabetes mellitus	1.57 (1.06−2.31)	0.03
Chronic renal failure†	2.83 (1.59−5.03)	<0.01
Chronic obstructive pulmonary disease	1.01 (0.60−1.72)	0.95
Peripheral artery disease	1.05 (0.67−1.62)	0.85
Initial presentation with NSTEMI	1.98 (1.33−2.93)	<0.01
Number of narrowed coronary artery‡	1.15 (0.28−1.21)	0.15

CI = confidence interval; HR = hazard ratio; NSTEMI = non-ST-segment elevation myocardial infarction.

* Included as time-dependent covariates;

† Defined as creatinine levels >2 mg/dl;

‡ Referred to left anterior descending artery, circumflex artery or right coronary artery.

The mechanistic underpinnings of this association remain speculative. Multiple layers of stents implanted to treat restenosis may be associated with an increased risk of stent thrombosis, recurrent restenosis, and MI.[14−16] In addition, patients undergoing repeated procedures have to undergo prolonged dual antiplatelet therapy, which is associated with an increased risk of bleeding and bleeding-related mortality.[17−19] In our study, patients with MI after TLR had greater rates of mortality compared with patients with TLR and no MI, suggesting a possible association between TLR, MI and subsequent mortality. The increased rate of MI in patients with TLR continued to accrue during follow-up with no evidence of plateau, in agreement with previous studies.[11]

This study has several limitations. First, our work is an observational, retrospective study and therefore it is affected by all limitations inherent to retrospective studies. Second, some important procedural variables, as lesion length and overlapping of stents, were not systematically collected. Third, routine angiographic follow-up was not performed in all the patients. For this reason, we were not able to determine the real incidence of left main restenosis. Fourth, the study encompassed a relatively long period of time in which stents, techniques, and therapy have significantly improved, possibly impacting the results of the study. In particular, we included also patients treated with BMS, which are not used any more for the treatment of this complex disease. Finally, most patients enrolled in the study underwent angio-guided PCI, and not IVUS-guided PCI which is the standard of care for patients undergoing this kind of procedure. Despite these limitations, the strength of this study is the focus on the prognostic impact of elective, uncomplicated TLR analyzed as a time-dependent variable across a long span of time (10 years).

In conclusion, elective, uncomplicated TLR after PCI of ULMCA disease is associated with an increased risk of cardiac mortality, suggesting that new therapies that limit restenosis may improve survival in patients with coronary artery disease undergoing PCI of ULMCA disease.

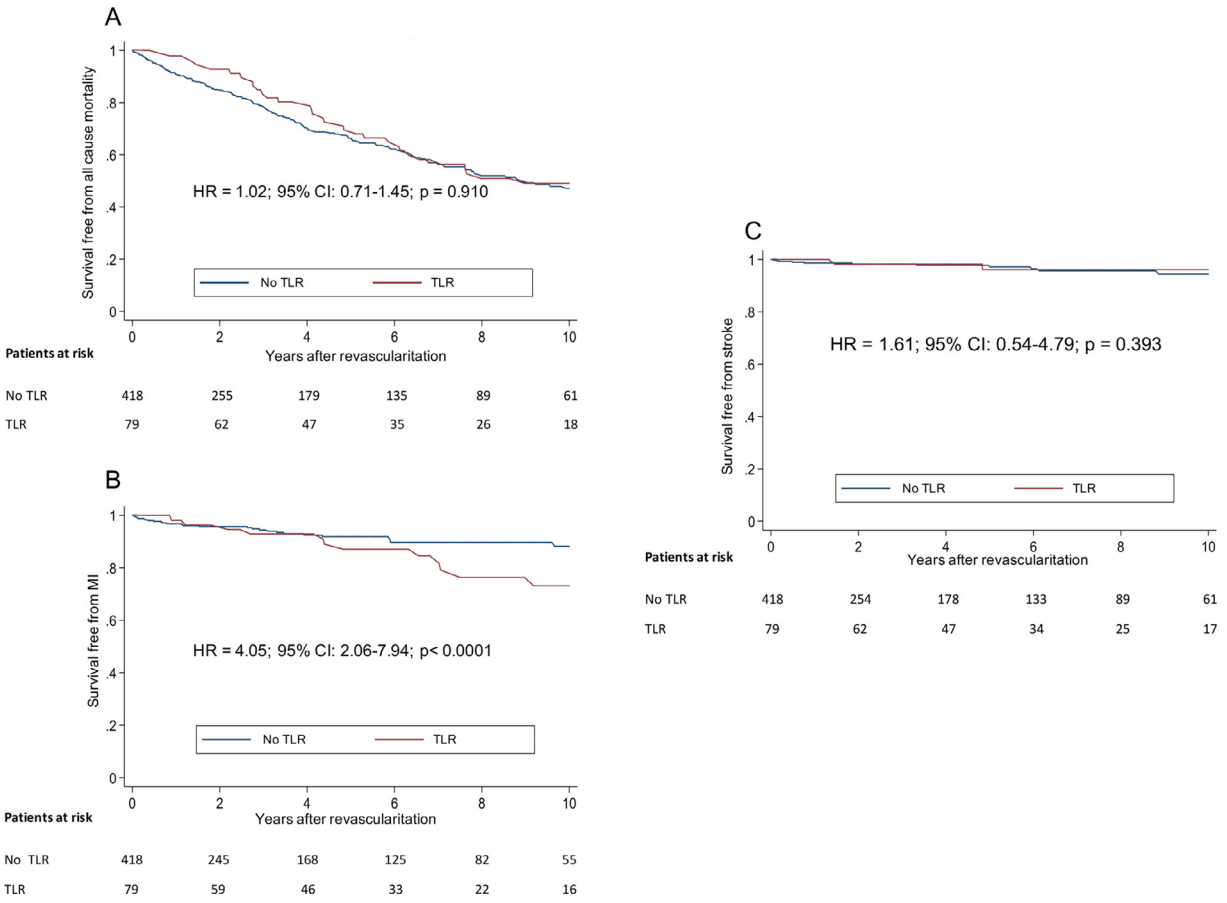

Figure 4. Simon-Makuch survival analysis on all-cause mortality, myocardial infarction, and stroke. Patients undergoing elective and uncomplicated TLR had A) similar rates of all-cause death; B) higher rates of MI; and C) and similar rates of stroke compared to patients with no TLR.

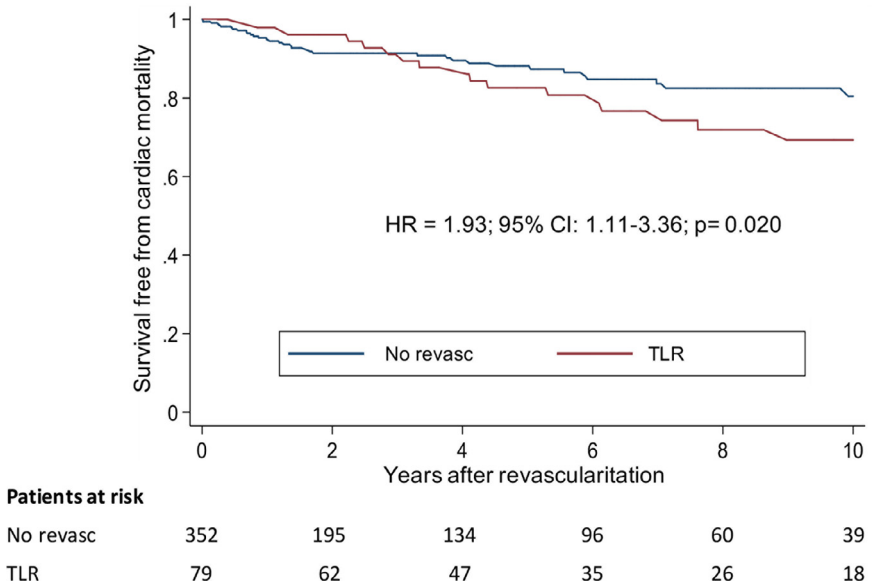

Figure 5. Simon-Makuch survival analysis on cardiac mortality in patients with TLR versus those with no revascularization. Patients with elective, uncomplicated TLR had significantly higher rates of cardiac mortality compared with patients who did not undergo any revascularization procedure (no revasc).

Authors' contribution

Miriam Compagnone: Writing - Original Draft, Investigation. Nevio Taglieri: Validation, Methodology. Mihail Celeski: Data Curation, Investigation. Gabriele Ghetti Resources. Cinzia Marrozzini: Project administration. Maria-Letizia Bacchi Reggiani and Elena Nardi: Formal analysis and Software. Mateusz Orzalkiewicz and Antonio

G. Bruno Resources. Nazzareno Galiè: Supervision. Francesco Saia: Visualization. Tullio Palmerini: Conceptualization, Writing - Review & Editing.

Finally all authors have read and approved the manuscript.

Disclosures

Dr. Palmerini has received lecture fee from Abbott; Dr. Saia reports receiving consulting fees from Edwards, Medtronic, Abbott Vascular, Eli Lilly, Astra Zeneca, St.Jude Medical, and speaker's fees from Abbott Vascular, Eli Lilly, Astra Zeneca, St. Jude Medical, Terumo, Biosensors, Edwards, Boston Scientific. All other authors have nothing to disclose.

Supplementary materials

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