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# Mortality Following Nonemergent, Uncomplicated Target Lesion Revascularization After Percutaneous Coronary Intervention

## An Individual Patient Data Pooled Analysis of 21 Randomized Trials and 32,524 Patients

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**CME/MOC Objective for This Article:** At the end of the activity the reader should be able to: 1) recognize that restenosis and target lesion revascularization (TLR) are not benign entities, as they may be associated per se with increased rates of mortality independent from clinical presentation and procedural complications; 2) appraise that the magnitude of the association between repeat revascularization and mortality varies according to the type of repeat revascularization being greater for TLR compared with non-TLR, target vessel revascularization, and non-target vessel revascularization; and 3) identify that severe restenosis may present as acute coronary syndrome or acute myocardial infarction.

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## ABSTRACT

**OBJECTIVES** This study sought to investigate the impact of nonemergent, uncomplicated target lesion revascularization (TLR) on the risk of long-term mortality after percutaneous coronary intervention (PCI).

**BACKGROUND** Restenosis requiring TLR after PCI is generally considered a benign event.

**METHODS** The study pooled patient-level data from 21 randomized trials. Subjects dying the same day as or the day after the TLR procedure as well as those with myocardial infarction (MI) the day before, the same day as or the day after TLR were excluded. The primary endpoint of the study was all-cause mortality.

**RESULTS** The dataset included 32,524 patients who were stratified according to whether repeat TLR was performed during follow-up. During a median follow-up of 37 months, 2,330 (7.2%) patients underwent a nonemergent, uncomplicated TLR procedure. After adjusting for potential confounders, TLR was an independent predictor of mortality (hazard ratio: 1.23, 95% confidence interval: 1.04 to 1.45; $p = 0.02$). Patients undergoing nonemergent, uncomplicated TLR had significantly higher rates of non–procedure-related MI compared with those without TVR. Among patients undergoing elective TLR, MI occurring after TLR was an independent predictor of mortality (hazard ratio: 3.82; 95% confidence interval: 2.44 to 5.99; $p < 0.0001$).

**CONCLUSIONS** Nonemergent, uncomplicated TLR after PCI is an independent predictor of long-term mortality, an association in part explained by higher rates of MI occurring after TLR. Efforts aimed at reducing TLR risk may translate into prognostic benefits including reduced rates of MI and survival. (J Am Coll Cardiol Intv 2018;11:892–902)


Although percutaneous coronary intervention (PCI) has significantly improved the prognosis for patients with coronary artery disease, restenosis remains a limitation of this procedure. With technological progress from balloon angioplasty to bare-metal stents (BMS) and then to first- and second-generation drug-eluting stents (DES), restenosis rates have progressively declined from 30 to 50% to 5% to 15%, depending on patient and lesion characteristics (1). Ischemia-driven or clinically-driven target lesion revascularization (TLR) is a common measure of device efficacy (2,3), reflecting angiographic restenosis. Restenosis requiring TLR is generally considered a benign event in most patients, although severe restenosis may present as acute myocardial infarction (MI) (4). Late revascularization after PCI may also be required due to progressive disease in the target vessel outside the prior treatment zone (target vessel revascularization [TVR] not related to TLR) or in a non-target vessel. All repeat revascularization procedures (whether PCI or coronary artery bypass grafting

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**ABBREVIATIONS AND ACRONYMS**

**BMS** = bare-metal stent(s)

**CABG** = coronary artery bypass grafting

**CI** = confidence interval

**DES** = drug-eluting stent(s)

**HR** = hazard ratio

**IQR** = interquartile range

**MACE** = major adverse cardiovascular event(s)

**MI** = myocardial infarction

**PCI** = percutaneous coronary intervention

**TLR** = target lesion revascularization

**TVR** = target vessel revascularization

[CABG]) carry the risk of potential periprocedural and late complications. Repeat PCI, in particular, may require additional stents, which increases the risk of stent thrombosis, MI, and recurrent restenosis, and necessitates prolonging dual antiplatelet therapy, the bleeding complications from which have been associated with subsequent mortality (5–7). Thus, the clinical impact of TLR is not fully understood and has not been examined in large-scale studies. In this regard, whether TLR per se is associated with an increased risk of mortality, independent from clinical presentation and procedural complications is unknown. We therefore investigated the association between nonemergent, uncomplicated TLR and mortality in a large cohort of patients included in randomized stent trials.

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## METHODS

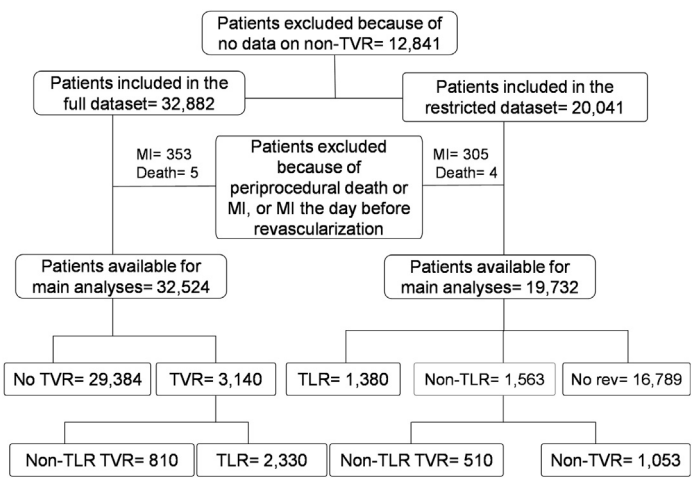
**STUDY DESIGN, OBJECTIVES, AND ENDPOINTS.** As part of an ongoing academic project, the data from 21 randomized stent trials (BMS vs. DES and DES vs. DES) were pooled in a common database at the Cardiovascular Research Foundation (New York, New York) for individual patient data analysis. Selected demographic, angiographic, and outcomes data that were common to most of the trials were analyzed.

The primary endpoint of the present study was all-cause mortality. Our primary objective was to examine the relationship between nonemergent, uncomplicated TLR procedures and subsequent all-cause mortality at the longest follow-up time available. The secondary objective was to examine the relationship between nonemergent, uncomplicated non-TLR procedures and subsequent all-cause mortality. We also sought to determine whether any identified risk of repeat revascularization was due to an association between the revascularization event and either subsequent MI or stent thrombosis. We defined a repeat revascularization procedure as emergent or complicated if an MI occurred the day before, the same day as, or the day after the procedure. Thus, we excluded patients undergoing revascularization in response to an MI (e.g., emergent primary PCI for ST-segment elevation MI or urgent revascularization for non-ST-segment elevation acute coronary syndromes), as well as those in whom a periprocedural MI complicated the follow-up revascularization procedure (occurring on the day of or the day after the procedure). Similarly, we excluded patients who died the same day as or the day after the revascularization procedure.

TLR was defined in all trials as revascularization of the target vessel with either PCI or CABG due to restenosis of the prior stent, including a 5-mm proximal or distal margin. TVR was defined as any repeat revascularization in the epicardial vessel of the prior stent (main branch or side branches). Non-TLR was defined as any revascularization performed either in the epicardial coronary artery of the prior stent, excluding the region of the stent and its 5-mm proximal and distal margins (non-TLR TVR), or in a non-stent-related epicardial coronary artery (non-TVR). All endpoints as defined and adjudicated in each individual trial were utilized.

**STATISTICAL ANALYSIS.** For continuous variables, univariate comparisons were made across the 3 groups using 1-way analysis of variance with post hoc pairwise comparisons using Scheffé's test. Binary variables were compared using a generalized linear mixed model employing a binary distribution and logit link function with Scheffé's adjustment for post hoc comparisons. Both types of models included a random effect for study. Unadjusted incidence densities were generated for elective revascularization procedures as well as for MI and all-cause death. To take into account the time-dependent nature of survival analyses, the survival computations were

**FIGURE 1 Study Flow Chart**




After excluding patients with periprocedural death or myocardial infarction (MI), 32,524 patients remained in the main analysis dataset reporting target vessel revascularization (TVR), and 19,732 patients remained in the restricted analysis dataset reporting all repeat revascularizations. TLR = target lesion revascularization.

**TABLE 1 Baseline Characteristics**

| | TLR (n = 2,330) | Non-TLR TVR (n = 810) | No TVR (n = 29,384) | p Value |
|---|---|---|---|---|
| Age, yrs | 62.2 ± 10.7*† | 62.0 ± 10.5 | 62.8 ± 11.1 | 0.004 |
| Male | 69.3 (1,615/2,330)*† | 74.4 (603/810) | 72.3 (21,237/29,379) | 0.003 |
| Hypertension | 69.2 (1,609/2,324)*† | 69.3 (560/808) | 64.0 (18,748/29,313) | 0.001 |
| Diabetes mellitus | 30.6 (712/2,326)*† | 32.4 (262/810)*† | 23.8 (6,988/29,322) | <0.0001 |
| Hyperlipidemia | 69.1 (1,597/2,311)*† | 70.8 (566/799) | 61.9 (17,988/29,075) | 0.0001 |
| Smoking | 24.8 (574/2,312)*† | 27.6 (220/797) | 28.3 (8,255/29,133) | 0.018 |
| Prior myocardial infarction | 25.0 (575/2,300) | 27.2 (215/792) | 24.5 (7,113/28,999) | 0.18 |
| Prior percutaneous coronary intervention | 28.8 (665/2,313)*† | 31.2 (250/801)*† | 23.3 (6,785/29,186) | <0.0001 |
| Prior coronary artery bypass graft surgery | 13.1 (305/2,326)*† | 11.2 (90/806)*† | 9.0 (2,640/29,305) | <0.0001 |
| Clinical presentation | | | | |
| Stable coronary artery disease | 43.5 (940/2,163) | 51.1 (380/743) | 35.2 (9,733/27,650) | |
| Acute coronary syndromes | 56.5 (1,223/2,163)*† | 48.9 (363/743)*† | 64.8 (17,917/27,650) | <0.0001 |
| Stented coronary artery | | | | |
| Left main | 1.7 (40/2,328)† | 0.3 (2/807)*† | 1.6 (479/29,316) | 0.008 |
| Left anterior descending | 53.7 (1,250/2,328)*† | 42.6 (344/807)*† | 50.3 (14,746/29,316) | <0.0001 |
| Left circumflex | 29.4 (685/2,328) | 27.9 (225/807) | 33.2 (9,743/29,316) | 0.48 |
| Right | 38.5 (897/2,328)† | 44.0 (355/807)*† | 41.7 (12,221/29,316) | 0.004 |
| Stents per patient | 1.62 ± 0.99*† | 1.39 ± 0.70*† | 1.48 ± 0.90 | <0.0001 |
| Total stent length per patient, mm | 24.0 (18.0–36.0)† | 20.0 (16.6–32.0)*† | 24.0 (18.0–36.0) | <0.0001 |
| Type of stent | | | | |
| Bare metal | 36.9 (859/2,330)*† | 21.2 (172/810) | 19.1 (5,605/29,384) | <0.0001 |
| Paclitaxel eluting | 25.7 (598/2,330)*† | 29.5 (239/810) | 29.1 (8,558/29,384) | 0.002 |
| Sirolimus eluting | 5.2 (120/2,330)*† | 7.8% (63/810) | 8.4 (2,472/29,384) | <0.0001 |
| Cobalt-chromium everolimus eluting | 14.9 (347/2,330) | 22.5 (182/810) | 18.0 (5,278/29,384) | 0.11 |
| Zotarolimus eluting | 8.9 (208/2,330)† | 7.4 (60/810) | 10.1 (3,000/29,384) | 0.006 |
| Platinum-chromium everolimus eluting | 4.5 (104/2,330) | 8.3% (67/810) | 7.7 (2,249/29,384) | 0.68 |
| Biolimus eluting | 3.2 (75/2,330)*† | 3.0 (24/810)*† | 5.7 (1,675/29,384) | <0.0001 |
| No stent | 0.8 (19/2,330)*† | 0.4 (3/810)*† | 1.9 (547/29,384) | <0.0001 |

Values are mean ± SD, % (n/N), or median (interquartile range). All revascularization procedures were nonemergent and uncomplicated. *p < 0.05 compared with the no target vessel revascularization (TVR) group. †p < 0.05 compared with the non-target lesion revascularization (TLR) TVR group.

made using the methodology proposed by Simon and Makuch (8) rather than the Kaplan-Meier method typically employed for fixed covariates. The 2 methods differ in that the number of subjects at risk within each of the covariate levels is fixed at time 0 in the Kaplan-Meier method but not in the Simon-Makuch method. As such, the Simon-Makuch method creates product-limit estimates of survival functions that correspond to episodes of risk defined by certain covariate levels, rather than for static groups of individual subjects. The method can therefore accommodate subjects who may begin follow-up at level A of some exposure and subsequently change to level B. 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. Between group comparisons were analyzed by the Mantel-Byar test, which is a score test for a proportional hazards model with time-dependent covariates. The proportional hazards assumption was assessed graphically by comparing the hazard functions across each level of the predictor variables. In cases in which these plots indicated disordinal interactions (i.e., crossing of the hazard functions), plots of the hazard functions were shown without estimation of hazard ratios (HRs).

The multivariable relationship of repeat revascularization procedures and time to death were estimated using Cox proportional hazards regression models. Variables included in the models were: age, sex, diabetes, previous MI, previous PCI, previous CABG, presentation with MI before the index procedure, post-procedure MI, stent thrombosis, and repeat revascularization (the latter 3 event variables as time-dependent covariates). Models were also adjusted for study by including it as a random effect. The following revascularization procedures were evaluated in separate models: TLR, non-TLR TVR, and all TVR. For the 12 trials in which all cases of repeat revascularization were also reported, additional models were generated for non-TLR (i.e., the composite of non-TLR TVR and non-TVR). For patients with multiple types of revascularization

**TABLE 2 Mortality Rates According to Follow-Up Revascularization**

| | 21 Trials (N = 32,524) Reporting TVR | | | | 12 Trials (N = 19,732) Reporting TVR and Non-TVR | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Incidence Rate of Revascularization* | Number of Deaths | Incidence Rate of Death* | n | Incidence Rate of Revascularization* | Number of Deaths | Incidence Rate of Death* |
| No revascularization† | 29,384 | – | 1,739 | 1.87 | 16,789 | – | 1,097 | 1.78 |
| TLR | 2,330 | 2.40 | 144 | 2.45 | 1,380 | 2.07 | 90 | 2.44 |
| TVR | 3,140 | 3.23 | 193 | 2.50 | 1,890 | 2.84 | 124 | 2.56 |
| Non-TLR TVR | 810 | 0.83 | 49 | 2.67 | 510 | 0.77 | 34 | 2.96 |
| Non-TVR | – | – | – | – | 1,053 | 1.58 | 50 | 1.85 |
| Non-TLR‡ | – | – | – | – | 1,563 | 2.35 | 84 | 2.18 |
| Any revascularization | – | – | – | – | 2,943 | 4.42 | 174 | 2.31 |

*Per 100 patient-years. †No revascularization in the target vessel for the 21-trial cohort and no revascularization in any vessel for the 12-trial cohort. ‡Non-TLR TVR or non-TVR. All revascularization procedures were nonemergent and uncomplicated.

Abbreviations as in Table 1.

procedures on different days, the first occurrence was considered primary. Two-sided p values <0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

## RESULTS

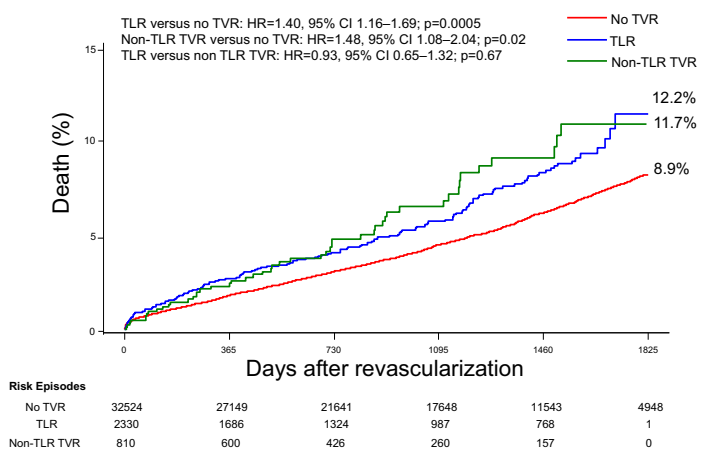
The pooled dataset consisted of individual patient data from 21 randomized trials that enrolled 32,882 patients. The study flow is reported in Figure 1. After excluding 5 patients who died the same day as or the day after the TVR procedure and 353 (1.1%) patients who had an MI the day before, the same day as, or the day after TVR, 32,524 patients remained for analysis in whom either a nonemergent, uncomplicated repeat TVR or no repeat TVR was required during follow-up. The main characteristics of the included trials and their relative reference appear in Online Table 1. The major inclusion and exclusion criteria, and internal validity assessment for each trial are reported in Online Table 2. The definitions of the clinical endpoints in each trial are reported in Online Table 3.

**INCIDENCE AND PREDICTORS OF TLR.** During a median follow-up of 1,095 days (interquartile range [IQR]: 395 to 1,807 days), 2,330 (7.2%) patients underwent a nonemergent, uncomplicated TLR procedure (incidence rate 2.40 per 100 patient-years) at median time after PCI of 271 days (IQR: 174 to 522 days), and 810 (2.5%) patients underwent a nonemergent, uncomplicated non-TLR TVR procedure (incidence rate 0.83 per 100 patient-years) at median time of 537 days (IQR: 247 to 1,015 days). In total, 3,140 (9.7%) TVR procedures (incidence rate 3.23 per 100 patient-years) were performed at a median time of 288 days (IQR: 184 to 712 days).

Clinical, angiographic, and procedural characteristics of patients stratified by the occurrence of nonemergent, uncomplicated TLR are reported in Table 1. Patients undergoing nonemergent, uncomplicated TLR during follow-up were younger, more often women, and more frequently had diabetes and other comorbidities compared with patients without TVR. Most TLR procedures were elective; only 93 of the 2,330 (4.0%) TLR procedures were performed after an MI occurring between 1 and 30 days earlier.

**MORTALITY AFTER TLR.** As shown in Table 2, there were 1,932 deaths during follow-up; 1,739 occurred in patients without TVR (incidence rate 1.87 per 100 patient-years), 144 occurred in patients with nonemergent, uncomplicated TLR (incidence rate 2.45 per 100 patient-years), and 49 occurred in patients with non-TLR TVR (incidence rate 2.67 per 100

**FIGURE 2 Simon-Makuch Analysis Showing Mortality Rates in Patients With Nonemergent, Uncomplicated TLR, Non-TLR TVR, and No TVR**




Patients with nonemergent, uncomplicated target lesion revascularization (TLR) and non-TLR TVR had significantly higher rates of mortality compared with patients with no target vessel revascularization (TVR). The number at risk reported for each group identifies risk episodes. CI = confidence interval; HR = hazard ratio.

patient-years). Thus, 193 deaths occurred in patients with any TVR (incidence rate 2.50 per 100 patient-years). The median durations from the performance of the TLR and non-TLR TVR procedures to the end of follow-up were 884 days (IQR: 299 to 1,554 days) and 797 days (IQR: 339 to 1,280 days), respectively. As shown in Figure 2, patients with nonemergent, uncomplicated TLR had significantly higher rates of mortality than patients not undergoing TVR. After adjusting for potential confounders, nonemergent, uncomplicated TLR was an independent predictor of mortality (HR: 1.23; 95% confidence interval [CI]: 1.04 to 1.45; p = 0.02), whereas non-TLR TVR was not significantly associated with mortality (Table 3). Other variables significantly associated with mortality were post-PCI MI or stent thrombosis, age, diabetes, male sex, clinical presentation with MI before the index procedure, previous CABG, and previous MI. Nonemergent, uncomplicated TLR remained an independent predictor of mortality in sensitivity analyses in which the 130 patients presenting with an MI between 1 day and 1 month earlier were excluded (HR: 1.27; 95% CI: 1.07 to 1.50; p = 0.006), in which patients with periprocedural MI occurring the day after the TLR were included (HR: 1.22; 95% CI: 1.03 to 1.45; p = 0.02), and in which the 273 patients in whom TLR was performed in a vein graft were excluded (HR: 1.20; 95% CI: 1.02 to 1.41; p = 0.03).

**RISK OF MI AFTER TLR.** As shown in Figure 3, 1,080 MIs occurred during follow-up, including 89 MIs that occurred at a median time of 364 days (IQR: 135 to 708 days) after nonemergent, uncomplicated TLR (incidence rate 1.59 per 100 patient-years) and 973 MIs that occurred in patients without TVR (incidence rate 1.08 per 100 patient-years). In addition, 18 MIs occurred at a median time of 446 days (IQR: 109 to 768 days) after non-TLR TVR (incidence rate 1.02 per 100 patient-years) (HR compared with no TVR not determined because of violation of the proportional hazards assumption). Thus, 107 MIs at a median time of 367 days (IQR: 123 to 753 days) occurred after TVR (incidence rate 1.45 per 100 patient-years). Among patients with TLR, non-TLR TVR, and any TVR, MI before the revascularization procedure occurred in 166 (7.1%), 62 (7.6%), and 228 (7.3%) patients, respectively.

As shown in Figure 4, among patients with TLR, those with MI occurring after TLR had significantly higher rates of mortality compared with those without MI after TLR (incidence rate 9.42 per 100 patient-years vs. 1.44 per 100 patient-years, respectively). Among patients with TLR, MI occurring during follow-up after TLR was an independent predictor of mortality (HR: 3.82; 95% CI: 2.44 to 5.99; p < 0.0001) after adjusting for measured confounders. Finally, when all patients who developed an MI during follow-up (including those due to stent thrombosis) were eliminated, by multivariable analysis the association between TLR and subsequent mortality remained significant (HR: 1.25; 95% CI: 1.04 to 1.50; p = 0.02).

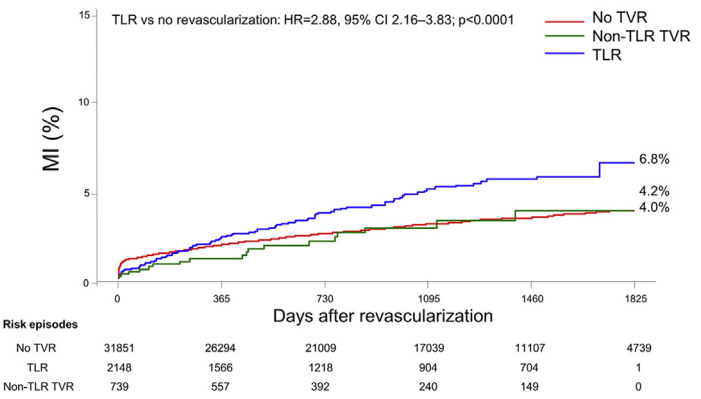
**TABLE 3 Multivariable Predictors of Long-Term Mortality in 21 Trials in Which TVR Rates Were Reported**

| | All Patients | | Excluding Patients Presenting With MI Within 1 Month of the TVR | |
|---|---|---|---|---|
| | HR (95% CI) | p Value | HR (95% CI) | p Value |
| TVR* | 1.23 (1.04–1.45) | 0.02 | 1.27 (1.07–1.50) | 0.006 |
| Non-TLR TVR | 1.23 (0.83–1.82) | 0.31 | 1.33 (0.91–1.95) | 0.15 |
| MI or stent thrombosis during follow-up*† | 4.26 (3.16–5.74) | <0.0001 | 4.38 (3.25–5.90) | <0.0001 |
| Age (per 1 yr) | 1.07 (1.07–1.08) | <0.0001 | 1.07 (1.07–1.08) | <0.0001 |
| Diabetes | 1.60 (1.46–1.76) | <0.0001 | 1.61 (1.47–1.77) | <0.0001 |
| Male | 1.16 (1.08–1.25) | <0.0001 | 1.17 (1.09–1.26) | <0.0001 |
| Previous coronary artery bypass grafting | 1.35 (1.21–1.52) | <0.0001 | 1.34 (1.19–1.51) | <0.0001 |
| Previous MI | 1.32 (1.23–1.40) | <0.0001 | 1.32 (1.24–1.41) | <0.0001 |
| Previous percutaneous coronary intervention | 0.97 (0.87–1.07) | 0.39 | 0.96 (0.86–1.07) | 0.42 |
| Presentation with MI‡ | 1.47 (1.23–1.75) | <0.0001 | 1.47 (1.22–1.77) | <0.0001 |

*Included as a time-dependent covariate. †Myocardial infarction (MI) or stent thrombosis occurring after the index procedure. ‡Refers to the index procedure.

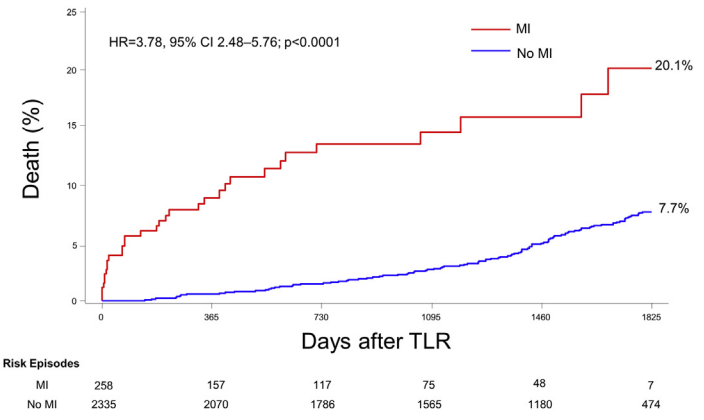
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

**FIGURE 3 Simon-Makuch Analysis Showing MI Rates in Patients With Nonemergent, Uncomplicated TLR, Non-TLR TVR, and No TVR**




Patients undergoing nonemergent, uncomplicated TLR during follow-up had significantly higher rates of MI compared with patients not undergoing TVR. As the proportional hazards assumption was not met for the comparison between non-TLR TVR and non-TVR, corresponding HRs are not reported. The number at risk reported for each group identifies risk episodes. Abbreviations as in Figures 1 and 2.

**FIGURE 4 Simon-Makuch Analysis Showing Mortality Rates Stratified by the Occurrence of MI Occurring After Nonemergent, Uncomplicated TLR**




Among patients with TLR, those with an MI after revascularization had significantly higher rates of mortality compared with those without an MI. The number at risk reported for each group identifies risk episodes. Abbreviations as in Figures 1 and 2.

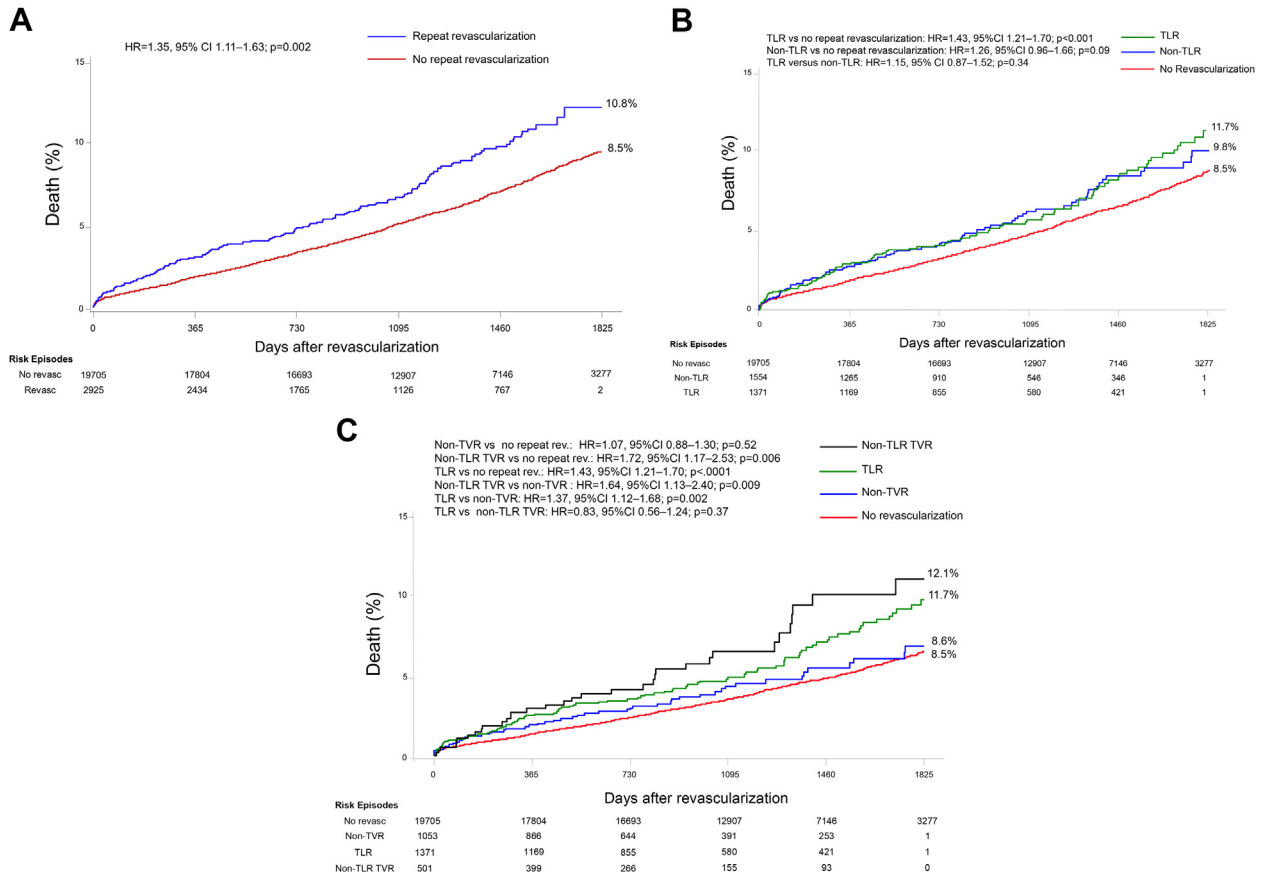
**MORTALITY AFTER ANY REPEAT REVASCULARIZATION.** Twelve trials that enrolled 20,041 patients reported all cases of repeat revascularization, including non-TVR. After excluding 4 patients who died the same day as or the day after any repeat revascularization and 305 (1.5%) patients with an MI the day before, the same day as, or the day after any repeat revascularization procedure, 19,732 patients remained available for the analysis. During a median follow-up of 1,122 days (IQR: 1,095 to 1,811 days), 2,943 (14.7%) patients underwent any repeat revascularization, including 1,380 TLR procedures and 1,563 non-TLR procedures, the latter consisting of 510 non-TLR TVR procedures and 1,053 non-TVR procedures. The incidence rates of repeat revascularization and their respective mortality rates are reported in Table 2. As shown in Figure 5A, patients undergoing any nonemergent, uncomplicated repeat revascularization procedure had significantly higher rates of mortality compared with those not undergoing repeat revascularization. Patients with TLR had higher rates of mortality compared with patients not undergoing any repeat revascularization, whereas mortality was not significantly increased in patients undergoing non-TLR procedures versus those not undergoing repeat revascularization (Figure 5B). Finally, patients undergoing TLR or non-TLR TVR had increased rates of mortality compared with patients not undergoing any repeat revascularization, whereas mortality was not significantly increased in patients undergoing non-TVR procedures versus those not undergoing repeat revascularization (Figure 5C). As shown in Online Table 4, after adjusting for potential confounders, the performance of a nonemergent, uncomplicated repeat revascularization procedure was an independent predictor of mortality (HR: 1.26; 95% CI: 1.02 to 1.56; p = 0.04). When any revascularization was replaced in the model by TLR and non-TLR, TLR was a significant independent predictor of mortality (HR: 1.33; 95% CI: 1.08 to 1.64; p = 0.006), whereas non-TLR was not (HR: 1.18; 95% CI: 0.90 to 1.55; p = 0.22) (Table 4). Finally, when non-TLR was replaced in the model by non-TLR TVR and non-TVR, TLR remained an independent predictor of mortality (HR: 1.33; 95% CI: 1.06 to 1.67; p = 0.01), non-TLR TVR was of borderline statistical significance (HR: 1.46; 95% CI: 1.00 to 2.12; p = 0.048), and non-TVR (HR: 1.08; 95% CI: 0.88 to 1.33; p = 0.44) was not significantly associated with mortality.

## DISCUSSION

The present study, based on an analysis of 32,524 patients enrolled in 21 randomized stent trials, is the largest report to date examining the relationship between repeat revascularization procedures and mortality. The major findings are: 1) During a median follow-up of 2.5 years after PCI, patients undergoing nonemergent, uncomplicated TLR had increased rates of mortality compared with patients not undergoing revascularization of the target vessel, after adjusting for measured confounders; 2) rates of MI following TLR after a median time of 364 days were significantly higher than in patients not undergoing revascularization of the target vessel, and among patients with TLR, MI was an independent predictor of mortality; 3) nonetheless, TLR remained an independent predictor of mortality even after excluding all patients who developed an MI during follow-up, suggesting that other mechanisms in addition to MI underlie the association between TLR and mortality; and 4) in a restricted dataset of 19,732 patients reporting any type of repeat revascularization, TLR and non-TLR TVR were independent predictors of mortality, whereas non-TVR was not significantly associated with mortality.

The clinical outcomes of patients undergoing PCI has progressively improved over time due to advances in devices, adjunct pharmacotherapy, imaging, and technique (9,10). Nonetheless, restenosis and progressive coronary atherosclerosis reduce event-free survival after PCI, and limit its utility in patients with complex multivessel coronary artery

**FIGURE 5** Simon-Makuch Analysis Showing Mortality Rates Stratified by the Type of Repeat Revascularization




Simon-Makuch analysis in 19,736 patients from 12 randomized trials showing survival curves with **(A)** nonemergent, uncomplicated repeat revascularization versus no repeat revascularization; **(B)** nonemergent, uncomplicated TLR versus non-TLR versus no repeat revascularization; and **(C)** nonemergent, uncomplicated TLR versus non-TLR TVR versus non-TVR versus no repeat revascularization. Patients with TLR or non-TLR TVR had significantly higher rates of mortality compared with patients without repeat revascularization, whereas nonsignificantly different rates of mortality were observed in patients with non-TVR and no repeat revascularization. The number at risk reported for each group identifies risk episodes. Abbreviations as in Figures 1 and 2.

**TABLE 4** Multivariable Predictors of Long-Term Mortality in 12 Trials in Which All Revascularization Events Were Reported

| | HR (95% CI) | p Value |
|---|---|---|
| TLR* | 1.33 (1.08–1.64) | 0.006 |
| Non-TLR* | 1.18 (0.90–1.55) | 0.18 |
| MI or stent thrombosis*† | 3.26 (2.27–4.68) | <0.0001 |
| Age (per 1 yr) | 1.08 (1.07–1.08) | <0.0001 |
| Diabetes | 1.50 (1.39–1.61) | <0.0001 |
| Male | 1.20 (1.12–1.29) | <0.0001 |
| Previous coronary artery bypass grafting | 1.36 (1.19–1.56) | <0.0001 |
| Previous MI | 1.33 (1.23–1.44) | <0.0001 |
| Previous percutaneous coronary intervention | 0.91 (0.79–1.06) | 0.24 |
| Initial presentation with MI | 1.40 (1.12–1.75) | 0.003 |

All revascularization procedures were nonemergent and uncomplicated. *During follow-up; included as time-dependent covariates. †Occurring after the index procedure.
Abbreviations as in Tables 1 and 3.

disease, for whom CABG remains the standard of care (11,12).

Although there is a general perception that restenosis requiring TLR is benign, observational studies have noted that restenosis may present with an acute coronary syndrome in up to 40% of cases (4) and may be associated with increased long-term mortality (13). In the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial, patients who underwent repeat revascularization had significantly higher rates of major adverse cardiovascular events (MACE) (death, MI, or stroke) compared with those not undergoing repeat revascularization (14). After adjustment for possible confounders, repeat revascularization remained an independent predictor of MACE after both initial PCI and initial CABG.

Unique aspects of our study are the large sample size (drawn from 21 randomized controlled trials with careful adjudication of events); the focus on mortality as the principal endpoint; the appraisal of repeat revascularization as a time-dependent variable; and analysis stratified by the type of repeat revascularization including TLR, non-TLR TVR, non-TVR, and non-TLR. Moreover, we excluded patients with MI immediately before or after the procedure, thus investigating the implications of nonemergent, uncomplicated revascularization. With more than 32,500 patients included, we observed a significant association between nonemergent, uncomplicated TLR and mortality. The relationship between TLR and death held even after excluding patients presenting with MI within 1 month before TVR, after excluding patients in whom TLR was performed in a vein graft, and after adjusting for multiple potential confounders including follow-up MI and stent thrombosis.

Our findings are consistent with previous studies reporting high rates of recurrent ischemic events in patients undergoing TLR (15). Specifically, 1-year mortality, MI, and MACE rates after TLR have been as high as 7%, 4%, and 20%, respectively, depending on the study and the device used to treat restenosis (1). Even with second-generation DES, ischemic event rates after TLR are substantial. Specifically, in a pooled analysis from the RIBS (Restenosis Intrastent: Balloon Angioplasty Versus Elective Stenting) IV and V randomized trials, the 1-year rates of mortality, MI, and MACE in 249 patients with in-stent restenosis treated with everolimus-eluting stents were 2.6%, 1.0%, and 10.0%, respectively (16). In the RIBS V trial, in which 189 patients were randomized to either drug-coated balloons or everolimus-eluting stents after BMS restenosis, overall 3-year rates of mortality, MI, and MACE were 4.5%, 4.5%, and 11.1%, respectively (17).

Multiple stents, especially when layered to treat in-stent restenosis, carry an increased risk of stent thrombosis, recurrent restenosis, and MI (18), and necessitate prolonged dual antiplatelet therapy, which has been associated with bleeding and late mortality (5,6). In our study, the increased risk of mortality in patients who underwent nonemergent, uncomplicated TLR compared with those not undergoing TVR was in part related to greater subsequent rates of nonperiprocedural MI after TLR. The increased rate of MI in patients with TLR accrued over time with no evidence of plateau, in agreement with previous studies (19). As the database only enabled analysis of the first occurrence of TLR, late MIs may have arisen from recurrent restenosis at the TLR site. It is also possible that TLR is a marker of progressive atherosclerosis in non-stent-treated coronary segments; however, the relationship between TLR and mortality remained significant even after excluding all patients with MI from the multivariable analysis, suggesting that other mechanisms may be responsible for this association.

Of note, in the principal analysis dataset ($n = 32,524$), the adjusted HR of non-TLR TVR for subsequent mortality was similar to that of TLR (both 1.23), although its wider confidence interval precluded reaching statistical significance. In the restricted dataset in which non-TVR could also be assessed ($n = 20,041$), the adjusted HR relating non-TLR TVR to subsequent mortality was somewhat greater (1.46), and the association reached borderline statistical significance ($p = 0.048$). Thus, both TLR and non-TLR TVR procedures (i.e., TVR) may be associated with subsequent mortality. In contrast, non-TVR procedures were not associated with subsequent death, although the upper bound of the 95% CI of the point estimate of 1.33 precludes ruling out the possibility of a modest relationship here as well.

Thus, the major implication of our study is that new therapies that limit restenosis as well as progressive atherosclerosis may reduce MI and improve survival in patients with coronary artery disease undergoing PCI.

**STUDY LIMITATIONS.** Several imbalances in baseline clinical characteristics were apparent between patients undergoing TLR versus control patients. Moreover, several angiographic and procedural variables such as small vessels, long lesions, and overlapping stents were not systematically collected in the 21 randomized trials, and therefore multivariable analysis could not account for these potential unmeasured confounders. Similarly, data on access site, staged procedures. left ventricular function, and medication adherence were not available. As such our analysis can only note associations and not prove causality. Large-scale randomized trials are required to confirm this hypothesis.

Other limitations should be acknowledged. Most of the included studies did not mandate routine angiographic follow-up; therefore, we could not determine the impact of restenosis itself on the risk of mortality, nor we could determine whether there was a correlation between the severity of restenosis and mortality. Definitions of MI were slightly different across trials, potentially introducing imprecision. Whether the late MIs occurred in the target vessel or a

non-target vessel is unknown. Data on bleeding and kidney function were not available, and therefore we could not determine whether bleeding or renal complications may underlie the relationship between TLR and mortality (5). Procedural details of TLR were not collected, and therefore it remains undetermined whether clinical outcomes may vary depending on the device used to treat restenosis. Detailed angiographic follow-up data were also not available (e.g., to determine the extent of progressive atherosclerosis and plaque ruptures). Finally, the case narratives from all studies were not available, and thus determining the relative event timing when MI and TLR occurred on the same day was not possible. The relationship between TLR and subsequent mortality may have been even stronger had we included same-day periprocedural MIs occurring as a consequence of repeat revascularization procedures.

## CONCLUSIONS

In the present analysis of 21 randomized trials and 32,524 patients, nonemergent, uncomplicated TLR was associated with increased mortality during median follow-up of 1,095 days compared with patients not requiring repeat revascularization. Further studies are required to determine the mechanisms underlying this observation, and whether new therapies to prevent restenosis (in addition to limiting atherosclerosis progression) may improve the prognosis of patients with coronary artery disease undergoing PCI.

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## PERSPECTIVES

**WHAT IS KNOWN?** The clinical impact of TLR on mortality alone is not fully understood, and has not been examined in large-scale studies.

**WHAT IS NEW?** The present study is the first to demonstrate that nonemergent uncomplicated TLR per se is an independent predictor of all-cause mortality. The association between TLR and mortality was in part related to the higher risk of late MI after TLR, and may also be related to other factors such as the cumulative effects of contrast, bleeding, or other procedural risks.

**WHAT IS NEXT?** These findings suggest that TLR is not a benign event, and that efforts aimed at reducing restenosis and TLR after PCI may translate into reduced rates of MI and improved patient survival.

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**KEY WORDS** mortality, restenosis, target lesion revascularization

**APPENDIX** For an expanded References section and supplemental tables, please see the online version of this paper.


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