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EDITORIAL COMMENT

A Not Entirely Benign Procedure*

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In the beginning, stent restenosis was simple: homogeneous smooth muscle cell proliferation led to low-risk lesions in selected patients, and this event occurred in the first 9 months after coronary intervention (1). The motivation to decrease stent restenosis was not driven by the high risk for target lesion revascularization (TLR) itself but the frequency of symptomatic stent restenosis. In contrast, stent thrombosis was a rare early phenomenon characterized by platelet activation, thrombus formation, and emergent high-risk TLR (2). This simple beginning has disappeared: pathology and intracoronary imaging demonstrate that drug-eluting stent (DES) restenosis is a far less benign target for repeat intervention (3). Multiple features of high risk-plaque morphology have been identified, including neoatherosclerosis, thrombus, and thin-cap fibroatheroma; thus, the boundary between stent thrombosis and stent restenosis in both timing and presentation is now much less clear.

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In this issue of *JACC: Cardiovascular Interventions*, Palmerini et al. (4) present a pooled analysis of 21 randomized trials including 32,524 patients supporting the argument that restenosis is not an entirely benign event (4). Nonemergent TLR is independently associated with a 20% increased risk for long-term mortality, suggesting that TLR or the restenotic event itself confers inherent risk. This analysis argues that an innocuous nonemergent TLR due to stent restenosis has a mortality risk previously attributed only to acute stent thrombosis. Thus, one can ask how many lives could be saved if we developed a better stent technology that could dramatically reduce the requirement for nonemergent TLR.

TLR AND THE PATHOPHYSIOLOGY OF STENT RESTENOSIS

The underlying premise of this pooled analysis is that TLR is not a nuisance but a real risk for increased mortality. The evolution of our understanding of the complexity of stent restenosis involves clinical, pathological, and imaging insights accumulated over the past decade. Registry studies of patients undergoing revascularization for stent restenosis confirmed that the presenting syndrome was often unstable, with nearly 10% of patients presenting with acute myocardial infarction (MI) (5). Thus, stent restenosis might have similar high-risk features seen in de novo coronary intervention, including platelet activation, thrombus, and plaque rupture. A pathology study involving 299 specimens identified neoatherosclerosis (recognized as clusters of lipid-laden foamy macrophages within the neointima with or without necrotic core formation) and thin-cap fibroatheroma in patients with restenotic lesions consistent with an enhanced risk for TLR (6). Similarly, the advent of optical coherence tomography has allowed the detection of unstable plaques and high-risk pathology in patients presenting with both bare-metal stent and DES restenosis (7).

Thus, it is plausible that TLR is not an entirely benign procedure. Risks associated with platelet activation, thrombus generation, and inflammation are well described after de novo coronary intervention and likely apply to stent restenosis therapies as well. These findings are consistent with the 5-year follow-up of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial, in which repeat revascularization procedures were associated with increased rates of death, MI, and stroke (8). But the mechanism by

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TABLE 1 Potential Predictors of Death After Coronary Intervention

Pre-Procedural	Procedural	Post-Procedural
Clinical presentation	Very visible complications	Clinical events
Cardiogenic shock	Abrupt closure	Stroke
Cardiac arrest	High grade dissection	Major bleeding
Acute myocardial infarction	Coronary perforation	Stent thrombosis
Chronic pulmonary disease	Major side branch loss	Target lesion revascularization
Older age		Nonfatal myocardial infarction
Peripheral vascular disease		
Comorbidities	Less visible complications	Defined laboratory events
Chronic kidney disease	Slow flow: TIMI frame counts	CK-MB elevation
Diabetes mellitus	Poor myocardial perfusion grade	Acute kidney injury
Left ventricular dysfunction	Intraprocedural stent thrombosis	Thrombocytopenia
Laboratory	Procedural adequacy	Less well-defined events
Anemia	Incomplete revascularization	Rise of various biomarkers
Elevated white blood count	Residual SYNTAX score	MRI-defined infarction
Increased C-reactive protein	Statin use at discharge	
Many elevated biomarkers		

CK = creatine kinase; MRI = magnetic resonance imaging; TIMI = Thrombolysis In Myocardial Infarction.

which TLR confers this risk is not clear in either the SYNTAX trial or the present pooled analysis. For example, a plausible mechanism might be enhanced rates of acute stent thrombosis following nonemergent TLR. But the pooled analysis specifically excludes patients who had periprocedural MIs as well as those who died within 24 h of the TLR event. Although this was done to remove confounding by patients who are not truly stable at presentation (i.e., evolving MIs), it leaves us guessing at the pathophysiologic basis of TLR associated mortality.

SHOULD TLR BE A TARGET FOR QUALITY IMPROVEMENT?

There is abundant published research to guide interventional cardiologists on the risk for coronary intervention: pre-procedural, procedural, and post-procedural factors have all been associated with subsequent mortality risk (**Table 1**). In the present analysis of 32,524 patients and 21 randomized trials, TLR is added to the lengthy list of post-procedural complications that confer a death risk. TLR is an especially attractive target for quality improvement, as it is a modifiable event with a technological solution. The potential for development of better DES with decreased late loss, better acute gain, and lesser TLR is exemplified by the benefits seen between first- and second-generation DES technology (9–11). In fact, the development of second-generation DES may have already achieved the goal suggested by this analysis: in the multivariate analysis of predictors of mortality in the 21 pooled trials, use of a cobalt chromium everolimus-eluting stent confers a 24% reduction in death ($p = 0.01$), making it a slightly more powerful predictor than TLR (18% increased risk for death, $p = 0.04$).

Before we put further efforts into reduction of TLR with newer stent technology, we should ask whether TLR in the era of second-generation DES is now more like post-procedural stroke—a low-incidence, clinically significant event that will be difficult to study in clinical trials (12). The incidence of TLR in this pooled analysis was 7.2%, suggesting an event of significant frequency. But these trials span decades of technology: nearly 20% of the patients included in this analysis received bare-metal stents, and the majority of the patients in these trials received non-second-generation DES. If one were to repeat this analysis and confine it to the era of second-generation DES, TLR would be less frequent: in the COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) trial comparing paclitaxel versus everolimus-eluting stents, target vessel revascularization was 61% less likely using a second-generation DES (9). Thus, the pursuit of any superior stent product with respect to TLR (whether metallic or bioresorbable) will require creative study designs or enriched patient groups with enhanced TLR rates to avoid the ambiguity of noninferiority trials and magical endpoints (13).

COMPETING AND CONFOUNDING RISKS

The investigators have shown multiple predictors of death at 3-year follow-up in the current pooled analysis, and TLR is not close to being the most powerful one. MI or stent thrombosis (not associated with TLR) confers a >400% risk for death during follow-up, far greater than the 20% increased risk associated with TLR. Progression of nonculprit disease, subsequent MI, and stent thrombosis are likely the main determinants of longer term death. In the 5-year follow-up of the SYNTAX trial, one-third of deaths were related to MI, and coronary bypass grafting was significantly better than multivessel percutaneous coronary intervention (PCI) in preventing MI-related deaths during follow-up. Furthermore, statin use at discharge independently reduced death risk by 67% in the PCI group ($p = 0.001$) (8,14). Thus, if one wishes to decrease long-term mortality rates after stenting, nonemergent TLR needs to compete with both progression of disease at non-target sites and the ongoing risk for stent thrombosis; systemic lipid-lowering and antiplatelet therapies may ultimately have more impact on death rates over the long term.

Finally, patients undergoing TLR have other risk factors for death. Although the investigators have attempted to control for these confounding variables, there are multiple factors not accounted for in the analysis that raise caution. For example, what if TLR is a marker of patients with small diffusely calcified lesions in the setting of diabetes and a high SYNTAX score? Then, we can agree that patients with TLR will die more than patients without TLR, just as PCI patients with anemia die more than those without anemia (15). But fixing TLR with better DES may not decrease mortality any more than transfusing anemic patients will reduce their risk: the problem for high-risk PCI subgroups is often a combination of anatomic complexity, clinical comorbidities, and competing adverse outcomes (i.e., major bleeding) (16) that confer the underlying mortality risk.

This pooled trial analysis is large, and the event rate is high, thus confirming the importance of developing effective DES that provide the lowest possible risk for death following TLR (9–11). Furthermore, the association of death with TLR supports the complexity that characterizes our current understanding of restenosis pathophysiology (3). So, we can conclude that treatment of stent restenosis with a TLR procedure is not entirely benign. But this important analysis also highlights competing outcomes (stent thrombosis, MI) and confounding variables (diabetes mellitus) that may focus our research and development efforts in other areas in which technology and pharmacology may ultimately have a larger impact.

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