The association between in-stent neoatherosclerosis and native coronary artery disease progression: a long-term angiographic and optical coherence tomography cohort study

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Received 19 December 2014; revised 4 May 2015; accepted 11 May 2015; online publish-ahead-of-print 3 June 2015

See page 2136 for the editorial comment on this article (doi:10.1093/eurheartj/ehv223)

Aims
The purpose of the present study was to investigate the relationship between in-stent neoatherosclerosis (NA) and native atherosclerosis progression of untreated coronary segments.

Methods and results
In-stent NA was assessed by optical coherence tomography (OCT) among patients included in the SIRTAX-LATE OCT study 5 years after drug-eluting stent (DES) (sirolimus-eluting and paclitaxel-eluting stents) implantation. Neoatherosclerosis was defined as the presence of fibroatheroma or fibrocalcific plaque within the neointima of stented segments with a longitudinal extension > 1.0 mm. Atherosclerosis progression in untreated native coronary segments was evaluated by serial quantitative coronary angiography (QCA). The change in minimal lumen diameter (MLD) was serially assessed within matched segments at baseline and 5-year angiographic follow-up. The key clinical endpoint was non-target lesion (non-TL) revascularization throughout 5 years. A total of 88 patients with 88 lesions were available for OCT analysis 5 years after DES implantation. In-stent NA was observed in 16% of lesions with the majority of plaques being fibroatheromas (11.4%) followed by fibrocalcific plaques (5.7%). A total of 704 non-TL segments were serially evaluated by QCA. Between baseline and 5-year follow-up, the reduction in MLD was significantly more pronounced in patients with NA (−0.25 mm, 95% CI −0.36 to −0.17 mm) when compared with patients without NA (−0.13 mm, 95% CI −0.17 to −0.10 mm, P = 0.002). Similarly, non-TL revascularization was more frequent in patients with NA (78.6%) when compared with patients without NA (44.6%, P = 0.028) throughout 5 years.

Conclusions
In-stent NA is more common among patients with angiographic and clinical evidence of native atherosclerosis progression suggesting similar pathophysiological mechanisms. SIRTAX trial is registered at http://www.clinicaltrials.gov/ct2/show/NCT00617084.

Keywords
Drug-eluting stent • Sirolimus-eluting stent • Paclitaxel-eluting stent • Neoatherosclerosis • Target lesion revascularization • Long-term outcomes

Clinical perspective
The significant association between in-stent neoatherosclerosis (NA) and progression of native coronary atherosclerosis suggests similar pathophysiological mechanisms. Therapeutic strategies known to attenuate atherosclerosis progression—such as high-dose statin therapy—may be also effective to suppress the development or progression of NA. In addition, the impact of NA on cardiovascular events has not been sufficiently investigated and requires confirmation in adequately powered observational intra-coronary imaging studies.

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Introduction

Drug-eluting stents (DES) reduce the risk of repeat revascularization compared with bare metal stents, but late stent failure may still occur due to restenosis or stent thrombosis. In-stent neoatherosclerosis (NA)—a novel disease entity—is characterized by the development of atherosclerotic changes in the nascent neointimal tissue within previously implanted stents. Although there is no large-scale prospective study assessing the impact of NA on late stent failure and associated clinical outcomes, NA has been identified as the culprit for delayed in-stent-restenosis or stent thrombosis in intra-coronary imaging studies and case reports.1–3 Accordingly, NA may represent an accelerated and possibly more unstable manifestation of atherosclerosis.1,4 While histological analyses were performed for the documentation of NA in human ex vivo pathology studies, optical coherence tomography (OCT) is able to accurately characterize the in vivo vascular response after stent implantation including the development of in-stent NA.1,3

Despite the potential clinical impact of NA during the long-term course following DES implantation, little is known about the pathophysiological mechanisms underlying the development of NA. Based on histological similarities between NA and native atherosclerosis, we hypothesized that patients with progression of atherosclerosis in native coronary segments would be at increased risk for the development of NA within stented segments.4 We therefore investigated the type and frequency of in-stent NA as assessed by OCT and native atherosclerosis progression in the entire untreated coronary artery tree assessed by quantitative coronary angiography (QCA) among patients included in the SIRTAX-LATE OCT cohort study 5 years after DES implantation.5

Methods

Patient population

The design and results of the SIRTAX and SIRTAX-LATE study (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularisation) have been previously reported.6,7 For the purpose of the present study, we analysed all patients included in the SIRTAX-LATE OCT study. Among 145 patients who underwent angiographic follow-up 5 years after DES implantation between December 2008 and July 2009, 88 patients with 88 lesions were included in the OCT study. A detailed patient flow is shown in Figure 1. The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at Bern University Hospital, Switzerland. All patients provided written informed consent.

Optical coherence tomography imaging and analysis

Optical coherence tomography was performed with a time domain M2 system (Lightlab Imaging, Westford, MA, USA) using a pullback speed of 2 mm/s and the non-occlusive flushing technique. After the diagnostic angiography and administration of 5000 IU unfractionated heparin, the ImageWire (Lightlab Imaging) was carefully advanced distal to the study lesion. Following administration of 200 μg of intra-coronary nitroglycerin, the target vessel was flushed via the guiding catheter with nonionic, isomolar contrast liquid using a power injector with flush rates between 3 and 5 mL/s. Optical coherence tomography pullbacks were assessed offline using a proprietary software (Lightlab Imaging). Stented segments were analysed for strut coverage, apposition, and protrusion at frames with 1-mm interval by two independent analysts blinded (L.R. and S.B.) for stent type. For in-stent NA assessment, frames were analysed at 0.125 mm intervals by two independent investigators (L.R. and M.T.). Frames were considered not analysable when more than one-quarter of the circumference was not visible due to insufficient flush or out of zoom. Definitions used for stent strut analyses were previously reported.5

Neointima was defined as the tissue between the luminal border and the endoluminal border of the struts. Neoatherosclerosis lesion was defined as the presence of a fibroatheroma or fibrocalcific plaques within the neointima of a stented segment with a longitudinal extension of ≥1 mm. A gap of at least 0.5 mm was used to define the boundary between two NA lesions.

Fibroatheroma (FA) were characterized as a signal-poor region displaying a high attenuation (to differentiate from layered neointima) with diffuse borders and a lateral extension of at least one quadrant.8 Thin-cap fibroatheroma (TCFA) were defined as FA with a fibrous cap ≤65 μm and thick-cap fibroatheroma (ThCFA) with a fibrous cap >65 μm. Fibrocalcific plaques were defined as signal-poor region with low attenuation and clear borderlines extending over one quadrant. Whenever the calcific pool was located both inside and behind the stent, we disregarded the presence of NA. Signal rich bands, suggestive of macrophage accumulations, were defined as lines or dots with strong signal attenuation producing a shadow with a sharply delineated lateral border.

Additional characteristics which potentially reflect neoatherosclerotic changes were investigated and their definition are provided in Supplementary material online. Data. To determine the intra- and interobserver reproducibility of NA assessment, 20 OCT pullbacks were randomly chosen and analysed by two assessors at two time points (2 months apart) and then Cohen’s Kappa was calculated.

Quantitative coronary angiography analysis

After administration of intra-coronary nitroglycerin, standard biplane angiographic images were obtained so that each coronary segment was recorded in at least two orthogonal views. All angiographies were analysed by the angiographic core laboratory at Bern University Hospital. Assessors were blinded to the OCT analysis and clinical outcomes. Methods for the serial assessment of the target lesions (TLs) were previously reported.9 All three major untreated epicardial vessels including all side branches with a reference vessel diameter (RVD) of >1.5 mm in diameter were assessed by QCA at baseline and at follow-up using similar projections whenever possible. For this purpose, segments were divided in subsegments according to the modified American Heart Association/American College of Cardiology (AHA/ACC) classification using the QCA—CMS software version 7.3 (Medis Medical Imaging Systems, Leiden, the Netherlands) (Figure 2).9,10 Minimal lumen diameter (MLD), RVD, segment length, and diameter stenosis ([1 – MLD/RVD] × 100) were assessed. In case a segment was revascularized prior to the 5-year follow-up examination, the latest available angiography prior to revascularization was used for analysis. The change of all variables was derived for each segment as outcome (follow-up) – outcome (baseline). The angiographic endpoint was mean change in MLD.

Clinical follow-up

An independent clinical events committee adjudicated all data on case report forms. All adverse events were assessed in hospital, at 1, 6, and 9 months, and on an annual basis up to 5 years. The clinical endpoint of this study was the occurrence of any non-TL revascularization within the 5-year angiographic follow-up window. Non-TL revascularization was defined as any revascularization except for TLR. Definitions of secondary clinical endpoints are provided in the Supplementary material.
online, Data. To further investigate the clinical impact of NA findings, we extended the clinical follow-up to 9 years from index procedure (until July 2013).

**Statistical analysis**

Comparison of baseline characteristics, medication, lipid profiles, and stents were performed with Wilcoxon rank-sum or Fisher’s exact tests.

Stratification: Patients were stratified in two groups according to the presence of at least one NA plaque detected by OCT at 5-year follow-up in the TL (based on criterion that an NA plaque is \( \geq 1.0 \) mm).

Optical coherence tomography: Frame-level OCT outcomes were analysed with linear mixed models with patient as random intercept and lesion-level OCT outcomes with linear models.

Quantitative coronary angiography: Quantitative coronary angiography outcomes were recorded for several segments per patient at baseline and at angiographic follow-up. The absolute change from baseline to follow-up was computed for each segment. Patient-level outcomes and their changes were then derived by taking the arithmetic mean over several segments. To compare the strata, medians taken over the patients are reported with 95% CIs from non-parametric bootstrap with \( P \)-values from Wilcoxon rank-sum tests.

Clinical events: The occurrence of revascularization events up to and including the 5-year angiographic follow-up was compared between the strata. Analyses were based on the first event per patient. Crude percentages are reported, odds ratios and \( P \)-values are from logistic regression models. Statistical analyses were done with the computing environment R (The R Foundation for Statistical Computing) and with Stata (StataCorp, College Station, TX, USA).

## Results

**Frequency, type, and distribution of neoatherosclerosis**

A total of 97% (11 772/12 124 frames) of all OCT frames were suitable for analysis. Neoatherosclerosis formation was observed in 14 (15.9%) of 88 lesions with the majority of plaques fulfilling the diagnostic criteria of fibroatheromas (\( N = 9, 10.2\% \)) and less frequently fibrocalcific plaques (\( N = 4, 4.5\% \)) and both plaque types in one case (\( N = 1, 1.2\% \)) (Table 1, Figure 3). Multiple NA lesions in the same stent were observed in four lesions (4.5%). The intra- and inter-observer reproducibility (Cohen’s Kappa) were 0.886 and 0.857, respectively. The most frequently observed findings potentially related to NA were signal rich bands, which were observed in 31.8% of stents. Other findings potentially related to NA were infrequent (microvessels: 2.3%, surface erosion: 3.4%).

Neoatherosclerosis was more common among lesions treated with PES (25.5%) compared with sirolimus-eluting stent (SES; 4.9%; \( P = 0.009 \)) and differences between stent types applied to both the frequency of fibrocalcific plaques (SES 0 vs. PES 10.6%, \( P = 0.058 \)) as well as fibroatheromas (SES 4.9 vs. PES 17.0%, \( P = 0.10 \)). Similarly, signal rich bands were more frequent among lesions treated with PES than SES (46.8 vs. 14.6%, \( P = 0.001 \)).

**Baseline characteristics of patients with and without neoatherosclerosis**

Baseline clinical, angiographic, and procedural characteristics of patients with and without NA are summarized in Table 2. No significant differences were recorded with the exception of type of implanted stent as mentioned above. We assessed the adherence to cardiovascular medications including acetylsalicylic acid, \( \beta \)-blocker, angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor (AR) blocker, statin, or their combination throughout 5 years. There was no difference in the intake of any of these medications (or combinations of 1, 2, or 3 medications) between patients with compared with those without NA throughout 5 years (Supplementary material online, Table S1). In addition, no difference in lipid levels at baseline or at 5 years was noted and no difference in the reduction of low-density lipoprotein-cholesterol
(LDL-C) over 5 years (NA: 25.9 vs. no-NA: 9.1 mg/dL, $P = 0.62$) or change in high-density lipoprotein-cholesterol (HDL-C) over 5 years (NA: 1.4 vs. no-NA: 2.6 mg/dL, $P = 0.85$) was observed.

**Optical coherence tomography analysis**

Optical coherence tomography findings at 5 years in lesions with and without NA are summarized in Supplementary material online, Table S2. Lesions with NA showed a thicker neointima (0.15 vs. 0.11 mm, $P = 0.001$), neointimal area (1.27 vs. 0.96 mm$^2$, $P = 0.003$), and percent volume obstruction (19.6 vs. 13.0%, $P = 0.001$). Less protruding stent struts were found in lesions with (0.06%) vs. without NA (0.40%, $P = 0.023$).

**Quantitative coronary angiography analysis**

A total of 704 untreated, native coronary artery segments at baseline were matched with the corresponding segments at 5 years follow-up, allowing the assessment of longitudinal changes over time (Table 3). A reduction in MLD was observed in both groups (with and without NA). The reduction in MLD of untreated, native coronary artery segments between baseline and 5-year follow-up was more pronounced in lesions of patients with NA ($-0.25$ mm, 95% CI $-0.36$ to $-0.17$) compared with lesions of patients without NA ($-0.13$ mm, 95% CI $-0.17$ to $-0.10$, $P = 0.002$) (Figure 4). Similarly, the change of % diameter stenosis was higher in lesions of patients with NA (6.0%, 95% CI 5.3–11.1) compared with those without NA (4.3%, 95% CI 2.5–6.2, $P = 0.048$). Two representative examples of patients with NA lesion formation and native atherosclerosis progression are provided in Figure 5. We performed four sensitivity analyses: In the first, we applied a more strict definition of NA lesions requiring a longitudinal extension of 1.5 mm. With this criteria, the difference in mean change in MLD remained unchanged ($-0.32$ vs. $-0.13$ mm, $P = 0.0005$) (Supplementary material online, Table S3). In the second sensitivity analysis, we only included patients treated with PES and found similar MLD changes ($-0.27$ vs. $-0.11$ mm, $P = 0.004$) (Supplementary material online, Table S3).
Third, we applied sensitivity analysis assessing the change in MLD in non-target vessels vs. non-stented target vessels and found consistent results (non-target vessels $-0.26$ vs. $-0.13$ mm, $P = 0.003$), non-stented segments in target vessel ($-0.30$ vs. $-0.09$ mm, $P = 0.02$) (Supplementary material online, Table S5).

Fourth, we compared the change in MLD between ACS and...
stable patients, again with similar results \([\text{ACS} (-0.27 \text{ vs.} -0.11 \text{ mm}, \ P = 0.021), \ 	ext{stable CAD} (-0.25 \text{ vs.} -0.14, \ P = 0.044))]\) (Supplementary material online, Table S6).

No significant difference in terms of the angiographic SYNTAX score at index procedure was observed (NA: 13.3 vs. no-NA: 11.0, \(P = 0.78\)).
Clinical events

Clinical events throughout 5 years are summarized in Table 4. Non-TL revascularizations occurred more frequently in patients with NA (78.6%) when compared with patients without NA (44.6%, odds ratio = 4.56 (95% CI 1.17–17.69), P = 0.028). Similarly, non-TVR (71.4 vs. 43.2%, OR = 3.28 (0.94–11.42), P = 0.06) was more frequently observed in the NA lesion group. We further assessed clinical events over additional 4 years after OCT and did not record any differences between patients with vs. without NA (Supplementary material online, Table S7).

Discussion

This cohort study of patients with coronary artery disease previously treated with DES allowed to correlate the process of in-stent NA with native atherosclerosis progression, due to its design including serial angiographic surveillance, annual clinical follow-up, and intra-coronary imaging using OCT at 5 years.

Association between neoatherosclerosis and native coronary atherosclerosis progression

The principal finding of this cohort study is a significant association between in-stent NA and the progression of native coronary atherosclerosis. The more pronounced reduction in MLD of NA compared with non-NA patients was of similar extent in the target and non-target vessel and in ACS vs. stable CAD patients, attesting to the robustness of the results. The P-value of 0.002 obtained from a robust rank-based method for the comparison of MLD change between patients with and without NA indicates strong evidence against the null hypothesis of no difference, even when considering stringent criteria. In the presence of an initially conservative treatment approach in non-target segments, the ability of MLDs to
plaque phenotypes show a more aggressive NA formation and ease severity. It could be assumed that patients with unfavourable atherosclerosis progression is independent from the initial disease extent. Of note, coronary artery disease complications including statins, but did not observe any differences between groups. Similarly, the reduction in LDL-C and the increase in HDL-C, both known to be associated with atherosclerosis progression, were not different between patients with compared with those without NA lesions. Based on the relatively small sample size and of this cohort, we consider these observations the latter results as indefinite.

**Frequency of neoatherosclerosis**

The reported frequency of in-stent NA substantially differs from previous studies. This is explained at least in part by the variety of NA definitions applied and the substantial differences in patient selection. In a human pathology study, Nakazawa and colleagues reported a frequency of 31% in 209 DES lesions at a mean of 1.2 years after stent implantation by defining NA as the presence of either peri-strut fatty macrophage clusters, fibroatheromas, thin-cap fibroatheromas, or plaque ruptures with thrombosis. More recently, the same group of investigators observed a similar frequency of NA among patients treated with everolimus-eluting stents (29%), SES (35%), and PES (19%) 30 days to 3 years after stent implantation. The overall frequency of any NA-related findings in our OCT investigation (40.9%) was comparable with these two pathology studies with the exception that NA was more frequently observed after PES implantation—which could be explained by a substantially different patient selection and a longer follow-up time. In vivo studies using OCT to describe the frequency of in-stent NA are scarce. Yonetsu and colleagues defined NA as the presence of lipid-laden neointima and reported a frequency of 75% at 4 years of follow-up. We found a lower frequency, even when considering a wider definition including the inclusion of any potential in-stent NA-related findings. A possible explanation for this discrepancy is the higher proportion of symptomatic patients in the study by Yonetsu and colleagues. Another explanation is the risk of overestimation of NA using OCT, as suggested by Nakano and colleagues. In this study, a conservative definition of NA was applied requiring a longitudinal extension of at least 1.0 mm in length under the exclusion of potential macrophage accumulation and fibrin deposition by identifying signal rich bands and peri-strut low-signal intensity areas.

**Predictors of neoatherosclerosis lesion formation**

With the exception of device type, we have not observed any differences in baseline clinical, procedural, or angiographic variables between patients with NA when compared with those without NA at 5 years. In a histology study, younger age, longer implant duration, and SES and PES usage were identified as independent predictors.
Figure 5 (5A) Association between neoatherosclerosis lesion formation and atherosclerosis progression in untreated coronary artery segments. This figure shows a representative example of a patient with a TCFA within the neointima (F and G) displaying a strong attenuation, which prevents the visualization of the stent struts behind the lipid pool/necrotic core. Arrowheads indicate the localization of the minimal cap thickness. In the distal part of the right coronary artery (RCA), a non-significant stenosis at baseline (C) progressed over 5 years to a significant stenosis (D). The longitudinal view is presented in (E). (5B) Association between neoatherosclerosis lesion formation (fibrocalcific plaque) and atherosclerosis progression in untreated coronary artery segments. This figure shows a representative example of a patient with a fibrocalcific plaque within the neointima (F and G) displaying a signal-poor region with low attenuation and sharp borders (asterisk). In the distal LAD and proximal RCA, a non-significant stenosis at baseline (A and C) progressed over 5 years to a significant stenosis (B and D). The longitudinal view is presented in (E).
of NA formation. Moreover, in an in vivo OCT study Yonetsu and colleagues identified time from stent implantation, active smoking, chronic kidney disease, and use of ACE-AR-II as independent predictors of NA. Our study results may assist in understanding why active smoking and chronic kidney disease emerged as predictors for NA formation, both established risk factors for native atherosclerosis.

Clinical impact of neoatherosclerosis

The impact of NA on clinical outcomes has not been prospectively investigated at this point in time. Observational studies and case reports, however, suggest an association between NA lesions and late stent failures. We observed no significant differences in target lesion related outcomes between patients with and without NA during additional 4 years of follow-up. However, in view of the selection of TLR-free patients throughout 5 years and the relatively small number of patients with NA in our study, further prospective investigations are required for definitive conclusions on the clinical impact of NA.

Study limitations

Our study needs to be interpreted in light of some limitations. First, only selected patients free from TL-related events were considered eligible for angiographic and OCT long-term evaluation. Thus, the generalizability of our findings may be limited. Second, the sample size was relatively small. This limits secondary analyses focusing on predictors of NA as well as the evaluation of the clinical impact of NA. However, the findings related to our primary hypothesis are statistically robust and mechanistically plausible. Third, we investigated the occurrence of NA in early generation DES that are no longer used in clinical practice. It remains to be shown if our findings apply to new generation DES, although new generation everolimus-eluting stents have been reported to have a similar propensity to develop NA as early generation DES in a recent ex vivo histological analysis. Although OCT has been validated against histology for the assessment of atherosclerotic plaque composition and phenotype, we are unaware of a dedicated validation study for the diagnosis of in-stent NA. Whilst the assessment of calcifications is not expected to be the cause of misinterpretations, the differentiation between in-stent fibroatheroma and macrophage accumulations, artefacts (e.g. tangential drop out), fibrin accumulations surrounding stent struts, hypersensitivity reaction (T-lymphocyte and eosinophil infiltration), granulation tissue or the penetration of necrotic core from the original plaque appears more challenging and might be the source of misdiagnosis and a reason for NA over-reporting. Serial QCA was performed one single projection, which may result in an underestimation of angiographic lesion progression. The use of similar projections for serial QCA analyses, however, prevented an overestimation of the observed angiographic lesion progression.

Conclusions

The formation of in-stent NA is closely associated with progression of native coronary atherosclerosis, suggesting similarities in the pathophysiologic mechanisms of these two entities. These findings may have important clinical implications for the development and implementation of strategies to prevent NA among patients undergoing PCI.

Supplementary material

Supplementary material is available at European Heart Journal online.

Authors’ contributions

L.R. and S.W. conceived the study. M.T., S.B. and L.R. did the OCT analysis. M.T. and T.Z. did the angiographic analysis. S.Z. and P.J. performed the statistical analysis and interpreted the findings in collaboration with L.R., S.W., M.T., and all other authors. M.T. and L.R. wrote the first draft of the manuscript, which was critically revised for important intellectual content by S.W. and all authors.

Funding

This study was supported by research grants from Bern University Hospital and the Swiss National Science Foundation (Grant Nos. 33CM30-124112 and 33CM30_140336).

Conflict of interest: L.R. has received speaker fees and an unrestricted research grant from St. Jude Medical. S.W. has received research contracts to the institution from Biotronik and St. Jude, and speaker fees from Astra Zeneca, Abbott, and Eli Lilly.

Table 4 Clinical events up to 5 years angiographic follow-up

<table>
<thead>
<tr>
<th></th>
<th>Patients with NA (N = 14)</th>
<th>Patients without NA (N = 74)</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-TVRA</td>
<td>10 (71.4%)</td>
<td>32 (43.2%)</td>
<td>3.28 (0.94–11.42)</td>
<td>0.062</td>
</tr>
<tr>
<td>Non-TLR</td>
<td>11 (78.6%)</td>
<td>33 (44.6%)</td>
<td>4.56 (1.17–17.69)</td>
<td>0.028</td>
</tr>
<tr>
<td>Non-TLR TVR</td>
<td>1 (7.1%)</td>
<td>5 (6.8%)</td>
<td>–</td>
<td>1.000</td>
</tr>
<tr>
<td>Any revasculariz</td>
<td>11 (78.6%)</td>
<td>37 (50.0%)</td>
<td>3.67 (0.95–14.22)</td>
<td>0.060</td>
</tr>
<tr>
<td>Any MI</td>
<td>0 (0%)</td>
<td>2 (2.70%)</td>
<td>–</td>
<td>1.000</td>
</tr>
</tbody>
</table>

No. of events (%) are reported. Median follow-up time was 1933 days (IQR: 1847–2012). Odds ratios and P-values from logistic regression model. For each patient, clinical events were included until and including the day of 5 years imaging follow-up. If <5 events, P-values from Fisher’s exact test.

aNon-TVR or TVR excluding TLR.

bNon-TLR or TVR including TLR.
Neoatherosclerosis and native coronary artery disease progression

References


