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# Non-culprit MACE-rate in LRP: The influence of optimal medical therapy using DAPT and statins

Mick P.L. Renkens [a], Gary S. Mintz [b], Rebecca Torguson [c], Carlo Di Mario [d], Tim ten Cate [e], Ziad A. Ali [f,g], Varinder Singh [h], William Skinner [i], Andre Artis [j], Hector M. Garcia-Garcia [b], Robbert J. de Winter [a], Joanna J. Wykrzykowska [k,*], Ron Waksman [b]

[a] Department of Cardiology, Amsterdam University Medical Center, Amsterdam, Netherlands
[b] Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC, USA
[c] The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[d] Structural Interventional Cardiology, Department of Clinical & Experimental Medicine, Careggi University Hospital, Florence, Italy
[e] Department of Cardiology, Radboud University Medical Center, Nijmegen, Netherlands
[f] DeMatteis Cardiovascular Institute, St. Francis Hospital and Heart Center, Roslyn, NY, USA
[g] Clinical Trials Center, Cardiovascular Research Foundation, New York, NY, USA
[h] Department of Cardiology, Northwell Health, New York, NY, USA
[i] Department of Cardiology, Central Baptist Hospital, Lexington, KY, USA
[j] Department of Cardiology, Methodist Hospital, Merrillville, IN, USA
[k] Department of Cardiology, University Medical Center Groningen, Groningen, Netherlands

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ABSTRACT

*Background/Purpose:* The Lipid Rich Plaque (LRP) study demonstrated the association between coronary plaque lipid content and outcomes. In this LRP substudy, we assessed the impact of optimal medical therapy (OMT) on the occurrence of non-culprit major adverse cardiac events (NC-MACE). Advanced intracoronary imaging modalities are able to identify patients with vulnerable coronary lesion morphology associated with future events.
*Methods/Materials:* A total of 1270 patients who underwent cardiac catheterization for suspected coronary artery disease (CAD) with evaluable $maxLCBI_{4mm}$ in non-culprit vessels and known medical therapy after discharge were followed for 2 years. OMT was defined as the use of a statin and dual antiplatelet therapy (DAPT).
*Results:* Among the 1270 patients included in this substudy, 1110 (87.7%) had PCI for an index event, and 1014 (80%) patients received OMT. Estimated cumulative incidence functions of NC-MACE did not differ significantly between patients treated with or without OMT (log-rank $p$-value = 0.876). In patients labeled high risk ($maxLCBI_{4mm} > 400$), cumulative incidence function also did not differ between patients treated with vs without OMT (log-rank $p$-value = 0.19).
*Conclusions:* In the current LRP analysis, we could not identify a beneficial effect of OMT in the reduction of NC-MACE rate, even in patients with high-risk plaques during 24-month follow-up.



## 1. Introduction

Coronary artery disease (CAD) accounts for 1.8 million deaths annually worldwide, corresponding to 19% of all deaths in men and 20% of all deaths in women, often as a result of myocardial infarction (MI) or its subsequent clinical complications. [1,2] MI is caused by rupture of an unstable fibrous cap and, to a lesser extent, by superficial erosion of the tunica intima. Atheromas with large amounts of lipid, so called lipid-rich plaques, and thin fibrous caps are strongly associated with MI and are often defined as unstable vulnerable plaques. [3,4]

Intravascular ultrasound (IVUS) with near-infrared spectroscopy (NIRS) is able to determine lipid content in coronary arteries and, thus, to identify these vulnerable lipid-rich plaques. Earlier results published by our group in the Lipid Rich Plaque (LRP) study, conducted in patients with suspected CAD undergoing cardiac catheterization with possible ad hoc percutaneous coronary intervention (PCI), demonstrated that patients with non-culprit lesions containing a large lipid

*Abbreviations:* CAD, Coronary artery disease; DAPT, Dual antiplatelet therapy; IVUS, Intravascular ultrasound; LCBI, Lipid Core Burden Index; LRP, Lipid Rich Plaque study; MI, Myocardial infarction; NC-MACE, Non-culprit-related major adverse cardiac events; NIRS, Near-infrared spectroscopy; OMT, Optimal medical treatment; PCI, Percutaneous coronary intervention.

* Corresponding author at: Interventional Cardiologist, University Medical Center Groningen, Department of Cardiology, Hanzeplein 1, 30.001, 9700 RB Groningen, the Netherlands.
*E-mail address:* j.j.wykrzykowska@umcg.nl (J.J. Wykrzykowska).

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core are at significantly increased risk for developing future non-culprit-related major adverse cardiac events (NC-MACE). [5] A quantitative maximum 4-mm Lipid Core Burden Index ($maxLCBI_{4mm}$), determined by NIRS-IVUS, was able to successfully categorize patients and lesions at risk for NC-MACE (adjusted HR 3.39, 95% CI:1.85–6.20).

In past decades, improvements in invasive treatment strategies as well as in primary and secondary prevention have led to significant decline in case fatality and mortality attributed to MI. Nevertheless, registry studies have illustrated that 18% of patients suffering an MI experience a recurrent event within the first year after the index MI. [6] It has been estimated that this could be more than halved if secondary prevention measures were more rigorously implemented. Furthermore, the results of the SYNTAX trial support this estimation, as optimal medical therapy (OMT) was an independent predictor of survival and was associated with a significant reduction in mortality and in the composite endpoint of death, MI, and stroke during 5-year follow-up. [7]

Therefore, in this sub-analysis of the LRP study, we aimed to determine whether OMT had an effect on the occurrence of future NC-MACE in our patient population. We hypothesized that the absence of OMT at discharge was associated with an increased rate of NC-MACE, especially in patients with lesions with large lipid cores.

## 2. Materials and methods

### 2.1. Study design and participants

Overall, 1563 patients from 44 participating medical centers in Europe (Italy, Latvia, Netherlands, Slovakia, and UK) and the USA were enrolled in the prospective LRP study. [5] All enrolled patients had cardiac catheterization for known or suspected CAD with possible ad hoc PCI. Among them, 1552 patients had evaluable $maxLCBI_{4mm}$. For this substudy, patients were formally included if $maxLCBI_{4mm}$ was evaluable, if two-year follow-up for MACE was completed, and if information on pharmacological treatment for CAD at discharge was registered in the study electronic case report form(eCRF). Patients were considered eligible for follow-up if they had interpretable NC segment NIRS-IVUS data, excluding (by randomization) 50% of the patients having plaques with $maxLCBI_{4mm} < 250$. During follow-up, no data on medical therapy were collected for these excluded patients. All patients provided informed consent before catheterization, and the LRP study was approved by the institutional review or ethics boards of all participating centers.

### 2.2. Definition of optimal medical therapy

Information on medical treatment at discharge was extracted from eCRF collected during the LRP study. These data contained information on medical treatment of individual patients at the time of the index event and at discharge. Medical therapy was at the discretion of the treating physicians. OMT was defined as use of dual antiplatelet therapy (DAPT) and a statin at discharge considering that the study population primarily (97%) comprised patients with non-ST-elevation MI, unstable angina, and stable angina with positive stress tests.

### 2.3. NIRS-IVUS imaging

In addition to unmasked NIRS-IVUS imaging of culprit vessels/lesions as a part of routine management and treatment (i.e., PCI), non-culprit vessel territories were also scanned by NIRS-IVUS imaging but were masked to the physicians taking care of the patients. All NIRS-IVUS images were submitted to the core laboratory (MedStar Cardiovascular Research Network NIRS/IVUS Core Laboratory, Washington, DC, USA) for analysis using validated NIRS-IVUS offline analysis software (QIVUS version 3.0.16.0, Medis Medical Imaging Systems, Leiden, Netherlands). The NIRS-IVUS system (TVC Imaging System, Model TVC-MC-8, Infraredx, a Nipro Company, Burlington, MA, USA) incorporated mechanical 40-MHz IVUS rotating at 960 rpm (16 fps) and 0.5 mm/s pullback, acquiring 160 NIRS spectra per second. The system returned a spatial map of the probability of lipid-core plaque and quantified as the maximum Lipid Core Burden Index over any specified distance of 4 mm ($maxLCBI_{4mm}$). Details have been published previously. [5]

### 2.4. Outcomes

The primary endpoint of this study was the occurrence of NC-MACE during a follow-up period of 24 months comparing patients treated with and without OMT. As part of the LRP study, NC-MACE comprised cardiac death, cardiac arrest, non-fatal MI, acute coronary syndrome, revascularization by coronary artery bypass grafting or PCI, and hospital readmission for angina with >20% diameter stenosis progression. All reported NC-MACE were adjudicated by the independent clinical events committee at both the patient and plaque levels (for hierarchical primary endpoint evaluation). The secondary endpoint in this sub-analysis was the difference in NC-MACE occurrence between patients labeled as high risk ($maxLCBI_{4mm} > 400$) in the LRP study, again stratified by OMT.

### 2.5. Statistical analysis

To assess for differences in baseline medical therapy, on a level of statistical significance of 0.05, the chi-square test was used for counts/proportions; and Student's *t*-test was used for continuous variables. For primary and secondary endpoint evaluation, the Kaplan-Meier estimator was used to estimate the cumulative incidence functions (CIF, i.e., estimates of the hazard functions) in both treatment arms with known observation status, time to censoring, and treatment arm for each individual patient. The differences in CIF between the two treatment arms were analyzed by log-rank tests.

## 3. Results

In this sub-analysis, 1270 (99.9%) patients with evaluable $maxLCBI_{4mm}$, two-year follow-up, and known medical therapy at discharge were included (Fig. 1). One patient was excluded as pharmacological treatment was not registered at discharge and could not be traced. Enrolled patients had a follow-up of 692 ± 129 days. Overall demographic and baseline characteristics are summarized in Table 1. The median age was 64 years, with 614 patients (48.4%) aged ≥65 years old; 388 (31%) were women; and body mass index (BMI) was 30.2 ± 6.52 kg/m$^2$. Overall, 463 (36.6%) patients had diabetes mellitus, of whom 161 (13%) were treated with insulin; 686 (55%) had a history of smoking; and hypertension (1018 patients) and hyperlipidemia (1012) were present in most patients (80% for both).

At baseline, 929 (73%) patients were treated with statins, 525 (41%) with DAPT, 434 (34%) with aspirin only, and 57 (4.5%) with an adenosine diphosphate inhibitor only. At discharge, 1014 (80%) patients received OMT. Differences in patient characteristics are summarized in Table 1. OMT and no-OMT treatment arms differed in age (63.6 ± 10.3 years vs. 66.0 ± 9.9 years, $p < 0.001$), proportions of chronic kidney disease (6.7% vs. 13%, $p < 0.001$), dialysis (1.1% vs. 5.9%, $p < 0.001$), and dyslipidemia (82.7% vs. 71.1%, $p < 0.001$). However, there was no significant difference in total cholesterol and low-density lipoprotein levels, although high-density lipoprotein levels did differ significantly between patients receiving OMT and no-OMT (44.19 ± 14.93 mg/dl vs. 47.02 ± 16.34 mg/dl, respectively, $p = 0.03$). Furthermore, while there was no difference in prior MIs, more patients receiving OMT at discharge had prior PCI than did patients not receiving OMT (47.2% vs. 35.7%, $p < 0.001$).

Medical therapy status during 2 year follow-up is summarized in Table 2. At the time of enrollment, 1110 (87%) patients had a PCI; and

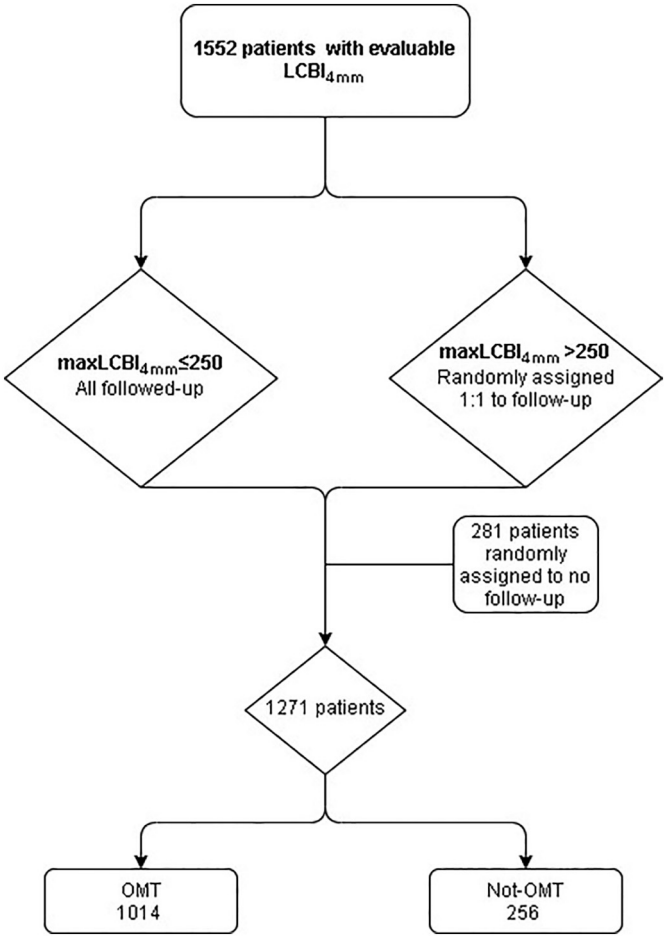


**Fig. 1.** Flowchart of patient enrollment.

973 (87.7%) of these patients received OMT at discharge. In contrast, 40 (25%) of patients who did not undergo PCI received OMT. At discharge, there was a significant difference in use of antiplatelet therapy (aspirin only 0% vs. 39%, DAPT 100% vs. 34%) and use of statins (100% vs. 56%, all $p < 0.001$) between treatment arms.

Finally, there were no significant differences in cumulative NC-MACE rate in patients treated with vs. without OMT ($p = 0.876$, Fig. 2A). This was on both a patient level (Figs. 2A, 2B, and 2C) and on a plaque level (Supplementary Figs. 1 and 2). NC-MACE however, differed significantly in both the OMT and Not-OMT treated patient between when defined by $maxLCBI_{4mm} \leq 400$ and $> 400$ (Supplementary Figs. 3 and 4).

**Table 1**
Baseline characteristics.

| | Total ($n = 1270$) | OMT ($n = 1014$) | Non-OMT ($n = 256$) | $p$-Value[$] |
|---|---|---|---|---|
| Age (years) | 64.04 ± 10.29 | 63.6 ± 10.34 | 66.0 ± 9.9 | <0.001 |
| >65 | 614 (48.4%) | 466 (46%) | 148 (57.8%) | <0.001 |
| BMI | 30.19 ± 6.52 | 30.18 ± 6.27 | 30.23 ± 7.43 | 0.914 |
| Male | 882 (69.4%) | 728 (71.8%) | 154 (60.2%) | <0.001 |
| Female | 388 (30.6%) | 286 (28.2%) | 102 (42.2%) | <0.001 |
| Diabetes | 463 (36.6%) | 375 (37.1%) | 88 (43.5%) | 0.438 |
| Requiring insulin | 161 (13.0%) | 122 (12.3%) | 39 (15.4%) | 0.193 |
| Smoking history | 686 (55.0%) | 542 (54.4%) | 144 (57.4%) | 0.392 |
| Current smoker | 281(22.5%) | 231 (23.2%) | 50 (19.9%) | 0.271 |
| Hypertension | 1018 (80.4%) | 816 (90.8%) | 202 (78.9%) | 0.497 |
| Chronic renal insufficiency | 101 (8%) | 68 (6.7%) | 33 (12.9%) | 0.001 |
| Hyperlipidaemia | 1012 (80.3%) | 830 (82.7%) | 182 (71.1%) | <0.001 |
| Total cholesterol (mg/dL) | 163.47 ± 45.58 | 162.39 ± 45.97 | 168.72 ± 43.44 | 0.122 |
| LDL (mg/dL) | 91.67 ± 40.37 | 91.09 ± 41.14 | 94.54 ± 36.31 | 0.352 |
| HDL (mg/dL) | 44.67 ± 15.2 | 44.19 ± 14.93 | 47.02 ± 16.34 | 0.039 |
| Triglycerides (mg/dL) | 152.33 ± 127.54 | 151.93 ± 125.85 | 154.22 ± 135.85 | 0.843 |
| Previous MI | 293 (23.4%) | 244 (24.4%) | 49 (19.5%) | 0.104 |
| Previous PCI | 568 (44.9%) | 477 (47.2%) | 91 (35.7%) | <0.001 |
| PCI at index | 1110 (87.5%) | 973 (96.1%) | 137 (53.5%) | <0.001 |

Proportions listed are means ± standard deviations or total counts with percentages.
[$] $p$-Values were calculated by use of the chi-square test for counts/proportions; and Student's t-test for continuous variables.

**Table 2**
Pharmacological treatment at baseline and discharge.

| Baseline | OMT (n = 1014) | No-OMT (n = 256) | $p$ Value[$] |
|---|---|---|---|
| Antiplatelet therapy | | | |
| DAPT | 474 (46.7%) | 51 (19.9%) | <0.001 |
| Aspirin | 799 (78.8%) | 160 (62.5%) | <0.001 |
| ADPI | 502 (49.5%) | 80 (31.3%) | <0.001 |
| Clopidogrel | 352 (34.7%) | 64 (25.0%) | 0.003 |
| Prasugrel | 70 (6.9%) | 9 (3.5%) | 0.045 |
| Ticagrelor | 80 (7.9%) | 6 (2.3%) | 0.002 |
| Any statin | 794 (78.3%) | 135 (52.7%) | <0.001 |
| Combination drug – simvastatin + Ezetimibe | 6 (0.6%) | 1 (0.4%) | 0.698 |
| Discharge | | | |
| PCI at index | 973 (96.1%) | 137 (53.5%) | <0.001 |
| Antiplatelet therapy | | | |
| DAPT | 1014 (100%) | 87 (34.0%) | <0.001 |
| Aspirin | 1014 (100%) | 160 (73.0%) | <0.001 |
| Aspirin monotherapy | 0 (0.0%) | 101 (39.0%) | – |
| ADPI | 1014 (100%) | 127 (50.0%) | <0.001 |
| Clopidogrel | 701 (69%) | 91 (35.0%) | <0.001 |
| Prasugrel | 140 (14%) | 15 (6%) | <0.001 |
| Ticagrelor | 173 (17%) | 21 (8.2%) | <0.001 |
| Any statin | 1014 (100%) | 143 (56%) | <0.001 |

[$] $p$-Values were calculated by use of the chi-square test for counts/proportions; and Student's t-test for continuous variables.

## 4. Discussion

Based on LCBI measures, the LRP study demonstrated the ability of NIRS-IVUS to assess the risk for NC-MACE in patients undergoing cardiac catheterization. The main findings of this sub-analysis of the LRP substudy are as follows: 1) The overall proportion of patients receiving OMT at discharge was relatively low, 1014 (80%), especially in patients who were not treated with PCI, 40 (25%). 2) We were not able to demonstrate an effect of OMT on the reduction of NC-MACE. 3) CIFs did not differ between the OMT and no-OMT treatment arms, even in the high-risk group of patients with $maxLCBI_{4mm} > 400$ (Fig. 2B).

Large plaque burden (>70%), thin-cap fibroatheroma lesions, and high lipid content in non-flow-limiting lesions have been associated with a higher MACE rate. [5,8–12] As demonstrated by the SYNTAX trial, OMT has proven to be pivotal in patients with complex CAD requiring revascularization. Lack of OMT was associated with adverse clinical outcomes, including death, MI, and stroke. Our patient cohort was very comparable with the patient cohort from the SYNTAX trial with similar proportions of risk factors and multivessel disease. [7] In the current LRP substudy, however, we were not able to show an effect of OMT on the reduction of NC-MACE. A total of 1110 (87%) patients underwent PCI; among them, 1014 (80%) patients received OMT at discharge, while those who did not receive OMT were treated with DAPT only (52%), statins only (32%), or no pharmacological therapy. This proportion of patients not receiving OMT was quite high, especially in comparison with other studies of vulnerable plaques and vulnerable patients. [8,9,11–13] It is likely that patients not receiving OMT at discharge also were not properly educated or treated beyond discharge, resulting

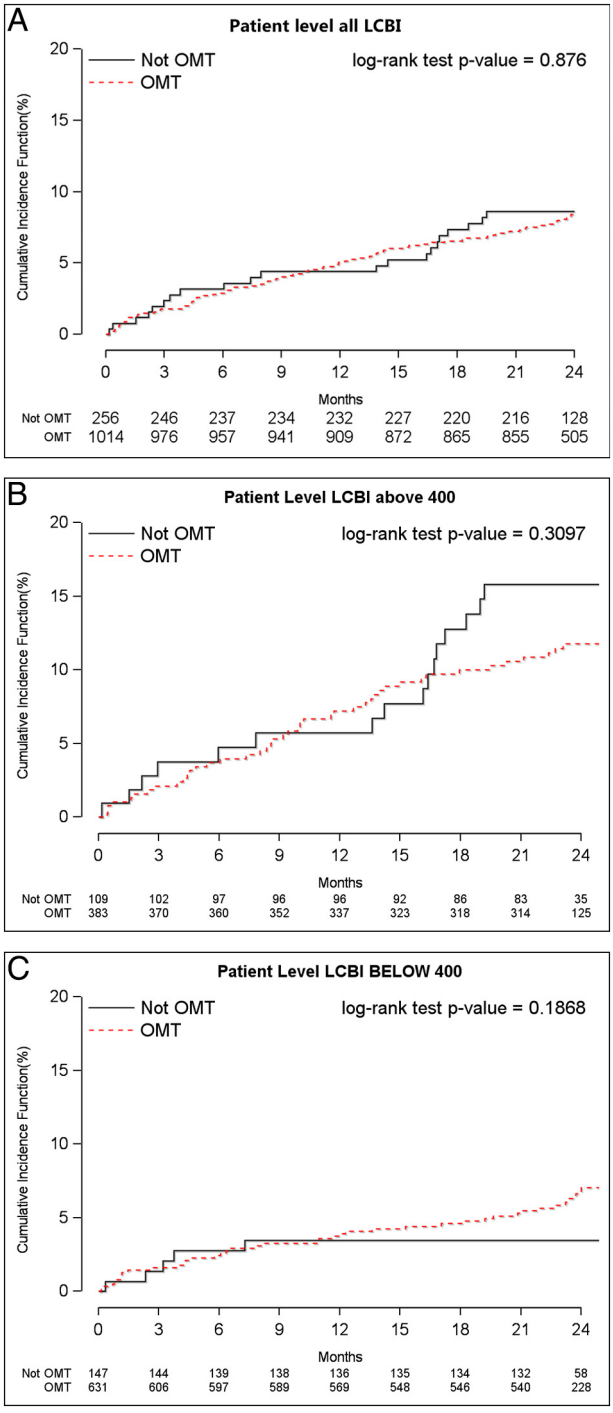


**Fig. 2.** Cumulative incidence functions for non-culprit MACE on a patient level defined by OMT A) in all patients on a patient level, B) in patients with maxLCBI$_{4mm}$ > 400 on a patient level, and C) in patients with maxLCBI$_{4mm}$ ≤ 400 on a patient level. LCBI = Lipid Core Burden Index; MACE = major adverse cardiovascular events; OMT = optimal medical therapy.

in a higher risk of suboptimal secondary prevention and poor adherence to medical therapy. [14] CIFs did not differ between the OMT and no-OMT treatment arms. Similarly, in a subgroup analysis of patients stratified by maxLCBI$_{4mm}$ above and below 400, the CIFs of the OMT versus no-OMT treatment arms did not differ.

However, diversion of cumulative incidences of NC-MACE seemed to occur toward the end of follow-up in high-risk patients (Fig. 2B). This might implicate a longer-term beneficial effect of OMT in this high-risk group of patients. An increase in events might be attributed to changes in antiplatelet therapy regimes (i.e., cessation of DAPT), particularly in the OMT treatment arm, as the majority of patients (96.1%) had PCI vs. 53.5% in the no-OMT treatment group. Sorrentino et al. found that, based on 4000 real-world patients treated with second-generation drug-eluting stents, DAPT disruption after PCI due to non-compliance or bleeding was associated with a significant increased risk of MACE within 2 years after PCI. [15]

The PROSPECT I and II natural history studies looked at NC-MACE occurrence in patients presenting with acute coronary syndromes treated with PCI for culprit lesions at baseline/index. [9,11] In PROSPECT I, 697 patients were followed for a median of 3.4 years; the MACE rate was 20.4%, 12.9% attributable to culprit lesions and 11.6% to NC-MACE. [9] Interestingly, only 1% of patients suffered from MI, with no cardiac deaths attributable to non-culprit vessels. Therefore, an increase in MACE rate was explained by an increase in symptoms (i.e., angina and unstable angina) and not acute thrombotic events. In PROSPECT II, the MACE rate was 13.2% during median follow-up of 3.7 years in 805 patients; the NC-MACE rate was 8%. In PROSPECT II, maxLCBI$_{4mm}$ ≥ 325 and large plaque burden >70% were both individually associated with an increased risk for NC-MACE. [11] In PROSPECT ABSORB, a randomized trial embedded in PROSPECT II, 182 patients with ≥1 non-flow-limiting lesion and ≥ 65% plaque burden were randomly assigned to PCI with the Absorb Bioresorbable Vascular Scaffold (Abbott, Abbott Park, Illinois, USA) plus OMT vs. OMT alone. OMT consisted of high intensity statins with limited use of PCSK9-inhibitors. No statistical differences were found between treatment arms in target lesion failure or MACE (4% in BVS vs 11% OMT, *p*-value 0.12). [10] Compared to the PROSPECT studies, our patient cohort had a higher proportion in cardiovascular risk factors (higher BMI and more diabetes mellitus, hypertension, hyperlipidemia, and previous MI/PCI) T); and patients from PROSPECT were treated more aggressively with antiplatelet therapy and statin regimens compared to patients from LRP. The high proportion of risk factors and unknown adherence to OMT might explain the relatively high MACE rates in the LRP population. Together with the possibly not-representative low NC-MACE rate in the no-OMT treatment arm, this might also explain a lack of significant difference in events in the OMT versus no-OMT group in this sub-study.

## 5. Limitations

The number of patients treated without OMT was quite low; therefore, the NC-MACE rates might also be relatively low and not representative. Also, follow-up (24 months) may have been too short to demonstrate a significant effect.

Furthermore, as this analysis was not prespecified, it comes with several inherent limitations. Underpowering may be present for answering the current research question in this study cohort. Adherence to medical therapy (DAPT and statins) and other elements for secondary prevention in CAD were not tracked. In addition, the therapeutic effect on risk factor management (serum low-density lipoprotein levels, blood glucose, and blood pressure) was not evaluated during the follow-up period. Also, the contemporary role of other vulnerable coronary plaque characteristics determined on intravascular imaging modalities was not evaluated in this study.

## 6. Conclusions

In this LRP substudy, we were not able to establish a beneficial effect of OMT. Future research should, therefore, focus on OMT at baseline (optimal antiplatelet therapy, optimal diabetic control), patient adherence during follow-up (i.e., statin effect on lipid spectrum levels), and lifestyle interventions.

For accurate assessment of the effect of OMT on NC-MACE rate a holistic view on treatment of coronary artery disease with revascularization and secondary prevention by OMT and considering plaque sealing

based may be driven by risk factors on a patients level and on a vessel level is pivotal.

## Clinical trial registration

The Lipid-Rich Plaque Study (LRP), https://clinicaltrials.gov/ct2/show/NCT02033694, NCT02033694

## Disclosures

Ron Waksman, Carlo Di Mario, Hector Garcia-Garcia, Rebecca Torguson were Principal Investigator, European Principal Investigator, Responsible Officer Core Laboratory NIRS-IVUS and angiographic analysis, Worldwide Study Coordinator of the Lipid Rich Plaque study, sponsored by Infraredx-Nipro, Bedford, MA, USA.

## Declaration of interest

Gary Mintz reports honoraria from Boston Scientific and Philips.

Carlo Di Mario is the recipient of research grants (through the Department of Clinical & Experimental Medicine of the University of Florence) from AMGEN, Behring, Chiesi, Daiichi-Sanyo, Edwards, Medtronic, and Shockwave.

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Ron Waksman reports serving on the advisory boards of Abbott Vascular, Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, and Pi-Cardia Ltd.; being a consultant for Abbott Vascular, Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd., and Transmural Systems; receiving grant support from AstraZeneca, Biotronik, Boston Scientific, and Chiesi; serving on the speakers bureaus of AstraZeneca and Chiesi, and being an investor in MedAlliance and Transmural Systems.

All other authors report no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2021.07.015.

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