SUPPLEMENTAL MATERIAL

Supplemental Methods

Biomechanical modeling of plaque structural stress

Plaque geometry was constructed from VH-IVUS images using an in-house developed MATLAB code (proprietary code, MATLAB R2020a, MathWorks, Inc, Natick, Massachusetts, USA). Each VH-IVUS frame was segmented into its individual components, and a 5% circumferential shrinkage applied to generate a zero-pressure condition as in vivo data were recorded during diastole. A 65µm layer of fibrous tissue was introduced during mesh generation to account for the limited axial resolution of VH-IVUS to detect a fibrous cap. The vessel wall and all plaque components were assumed to be hyper-elastic, non-linear, isotropic, incompressible, and piecewise homogeneous. The modified Mooney-Rivlin model was used to describe the material property of each component:

\[ W = c_1 (I_1 - 3) + D_1 \left[ e^{D_2 (I_1 - 3)} - 1 \right] + \kappa (J - 1) \]

where \( I_1 = J^{-2/3} I_1 \) with \( I_1 \) being the first strain invariant of the unimodular component of the left Cauchy-Green deformation tensor. \( J = \text{det}(F) \) and \( F \) is the deformation gradient. \( \kappa \) is the Lagrangian multiplier for the incompressibility. \( c_1, D_1 \) and \( D_2 \) are material parameters derived from direct material testing results. In this study, the following values were used: arterial wall, \( c_1=0.14 \) kPa, \( D_1=3.83 \) kPa, \( D_2=18.80 \) kPa; fibrous tissue, \( c_1=0.19 \) kPa, \( D_1=5.77 \) kPa, \( D_2=18.22 \) kPa; necrotic core, \( c_1=0.05 \) kPa, \( D_1=4.89 \) kPa, \( D_2=5.43 \) kPa and dense calcification, \( c_1=1.15 \times 10^5 \) kPa, \( D_1=7.67 \times 10^4 \) kPa, \( D_2=2.84 \times 10^{-8} \) kPa.\(^{1,2}\) The motion of each atherosclerotic component is governed by kinetic equations as:

\[ \rho v_{i,tt} = \sigma_{ij,j} (i, j = 1, 2) \]
where \([v_t]\) and \([\sigma_{ij}]\) are the displacement vector and stress tensor, respectively, \(\rho\) is the density of each component, and \(t\) is time.

The entire plaque geometric model was meshed using 9-node quadrilaterals, generating approximately 10,000 elements and 40,000 nodes per model. Displacement and strain were assumed to be large. There was no relative movement at the interface of atherosclerotic components and the relative energy tolerance was set to be 0.005. Two adjacent points located on the outer wall were fixed to prevent rigid body displacement. Maximum principal stress was used to characterize the mechanical loading within the plaque structure (PSS) in the peri-luminal region (0.2mm maximum depth from the luminal contour). Mean PSS was calculated as the mean value of PSS experienced by all the luminal nodes. Dynamic loading conditions were standardized to 120/70mmHg. Pressure at the outer boundary was set to zero. All simulations were performed using ADINA 9.5 (ADINA R&D, Inc., USA) software.

**Additional measures (Figure SI):**

- **Lumen aspect ratio** = maximum diameter of ellipse (or lumen major axis)/minimum diameter of ellipse (or lumen minor axis), i.e., lower (improved) aspect ratio describes a rounder lumen, and a value of 1 indicates a perfectly circular lumen.

- **Lumen curvature**:\(^{3,4}\) curvature at point a (in Figure SI) was computed using the radius (as \(r_a\)) of the circle determined by point a and two adjacent points (bottom right figure) on both sides, i.e. curvature = \(1/r_a\). Curvature value was computed for all points in the lumen, and the maximum lumen curvature value (Lumen Curvature\(_{\text{max}}\)) is used in data analysis. The minimum lumen curvature value (Lumen Curvature\(_{\text{min}}\)) is also computed for lumen irregularity calculation.
• **Lumen irregularity**\(^5\) = Lumen Curvature\(_{\text{max}}\) – Lumen Curvature\(_{\text{min}}\)

• **Lumen roughness:** reflects the lumen surface evenness in respect to curvature, and calculated using the following formula, with smaller values representing more round or even surface and a perfect round lumen shape will have roughness being 1. Method adapted from.\(^6\)

\[
\text{Roughness}_{\text{Curvature}} = \sqrt{\frac{1}{2\pi r} \sum r_a^2 \Delta l}
\]

(\(r\) is the radius of the circle best fitting the lumen contour; \(r_a\) is defined as above in lumen curvature calculation; and \(\Delta l\) is the length between point \(a\) and one adjacent point.)

**Assessment of analyst variability**

The reproducibility of matching between baseline and follow-up VH-IVUS frames by 2 analysts was examined in 6 vessels that had both baseline (\(n= 573\) frames) and follow-up (\(n= 623\) frames). The 2 analysts reviewed the VH-IVUS data and separately identified the location of follow-up frames in the 2mm segments defined in the baseline frames. To report the intra-observer variability the 1\(^{st}\) analyst performed the analysis twice. The \(\kappa\) test of concordance was used to assess agreement. A good overall agreement was noted for the estimation of the two analysts with the intra-observer variability being 0.733 and the inter-observer variability being 0.701. The reproducibility of lumen curvature, irregularity, and roughness assessment was examined on 2 randomly selected vessels (77 frames) by testing the intraclass correlation coefficient (ICC); this achieved good to excellent absolute agreement: lumen curvature, ICC = 0.787; lumen irregularity, ICC = 0.72; lumen roughness, ICC = 0.712.
**Statistical analysis of patient demographics**

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and discrete variables as absolute numbers (percentage). Normality tests were performed for all variables using quantile-quantile plots, and Kolmogorov-Smirnov/Shapiro-Wilks test where appropriate. Student’s t-test or one-way ANOVA were used for normally distributed continuous variables. Non-normally distributed variables were analyzed using Mann-Whitney U test or Kruskal-Wallis test for independent samples, and Wilcoxon signed-rank test for paired samples. Chi-square test ($\chi^2$) or Fisher’s exact test was used for discrete variables where appropriate. We identified a number of potential clinically important confounding factors (age as continuous variable, gender, hypertension, smoking status, diabetes, family history of coronary artery disease, and prior statin use), and these were added in the multivariable model as fixed effects to examine our main study finding.
### Supplemental Tables

#### Table S1. Trial groups, inclusion and exclusion criteria

|                          | Control | Atorvastatin | Rosuvastatin |
|--------------------------|---------|--------------|--------------|
| **Treatment**            | Aspirin, low-intensity statin, β-blocker | Atorvastatin 80mg | Rosuvastatin 40mg |
| **Trial registration**   | NCT01230892 | NCT00576576 | NCT00962416 |
| **Patient number**       | n= 18  | n= 20        | n= 22        |
| **Follow-up period**     | 12 months | 6 months  | 13 months  |

#### Inclusion criteria

| Presentation             | Stable angina or NSTEMI | Stable angina or ACS | STEMI |
|--------------------------|-------------------------|----------------------|-------|
| **Age**                  | 21 to 79 years          | ≥ 18 years           | 18 to 89 years |
| **Lesion**               | Moderate lesions requiring physiologic assessment | Moderate lesions requiring invasive physiologic evaluation | 2 major proximal arteries suitable for intracoronary imaging |

**Exclusion criteria**

| **Hemodynamic**          | STEMI, cardiogenic shock, hemodynamic instability | Acute MI due to stent thrombosis |
|--------------------------|---------------------------------------------------|---------------------------------|
| **Lesion specific**      | Lesions requiring PCI or CABG | Lesions requiring treatment (stenosis>50%) in 2 major proximal arteries |
| **Other cardiac history**| CABG, severe valvular heart disease | Infarct lesion at site of a previously implanted stent |
| **Treatment**            | Contraindication to β-blockers, CCBs or extended-release nitrate therapy within last 48 hours | On maximum dose of statin |
| **Other comorbidities**  | Creatinine>1.5mg/dL, renal impairment, Liver impairment | Creatinine>1.5mg/dL, Liver disease, Uncontrolled diabetes, Uncontrolled hypertension |
| **Pregnancy**            | - | Pregnancy or planned pregnancy | Female of childbearing potential |
| **Coagulopathy**         | Hematologic disease | INR>1.8, Hematologic disease | Bleeding diathesis/known coagulopathy, Use of warfarin |
| **Other trial**          | - | - | Currently participating in another trial before reaching first endpoint |

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CCB, calcium channel blocker; EF, ejection fraction; INR, international normalized ratio; LDL, low-density lipoproteins; LM, left main stem artery; MACE, major adverse cardiac events; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
### Table S2. Patient demographic and clinical characteristics

|                  | Control (C) n=18 | Atorvastatin (A) n=20 | Rosuvastatin (R) n=22 | P value          |
|------------------|------------------|-----------------------|-----------------------|------------------|
|                  |                  |                       |                       | C vs. A | C vs. R | A vs. R |
| **Age, years**   | 51.0 ±10.2       | 55.9 ± 12.5           | 57.6 ± 9.7            | 0.36    | 0.14    | 0.855   |
| **Male, n (%)**  | 8 (44.4)         | 13 (65)               | 20 (90.9)             | 0.203   | **0.002** | 0.062   |
| **BMI, kg/m²**   | 29.2 ± 5.8       | 31.9 ± 5.9            | 27.2 ± 3.8            | 0.259   | 0.451   | **0.014** |
| **Hypertension, n (%)** | 12 (66.7) | 14 (70)               | 11 (50)               | 0.825   | 0.289   | 0.187   |
| **Current smoking, n (%)** | 1 (5.6) | 5 (25)               | 11 (50)               | 0.184   | **0.004** | 0.096   |
| **Diabetes, n (%)** | 3 (16.7) | 6 (30)               | 2 (9.1)               | 0.454   | 0.642   | 0.123   |
| **Hypercholesterolemia, n (%)** | 12 (66.7) | 17 (85)               | 8 (36.4)              | 0.26    | 0.057   | **0.002** |
| **Family history of CAD, n (%)** | 8 (44.4) | 7 (35)               | 5 (22.7)              | 0.552   | 0.145   | 0.379   |
| **Previous MI, n (%)** | 4 (22.2) | 2 (10)               | 1 (4.5)               | 0.395   | 0.155   | 0.598   |
| **Previous PCI, n (%)** | 5 (27.8) | 4 (20)               | 1 (4.5)               | 0.709   | 0.073   | 0.174   |
| **Presentation** |                  |                       |                       |         |         |         |
| Stable angina, n (%) | 13 (72.2) | 13 (65)               | 0 (0)                 | 0.632   | -       | -       |
| ACS, n (%) | 5 (27.8) | 7 (35)               | 0 (0)                 | 0.632   | -       | -       |
| STEMI, n (%) | 0 (0) | 0 (0)               | 22 (100)              | -       | -       | -       |
| **Prior Medications** |                  |                       |                       |         |         |         |
| Statin, n (%) | 12 (66.7) | 4 (20)               | 1 (4.5)               | **0.008** | <0.001 | 0.174   |
| β-blockers, n (%) | 7 (38.9) | 8 (40)               | 2 (9.1)               | 0.944   | 0.053   | **0.03** |
| Aspirin, n (%) | 13 (72.2) | 13 (65)               | 1 (4.5)               | 0.632   | <0.001  | <0.001  |
| Antiplatelet, n (%) | 5 (27.8) | 3 (15)               | 0 (0)                 | 0.438   | **0.013** | 0.099   |
| ACE inhibitor or ARB, n (%) | 5 (27.8) | 10 (50)               | 5 (22.7)              | 0.162   | 0.714   | 0.065   |
| **Lipid levels** |                  |                       |                       |         |         |         |
| Change in LDL, mg/dL (mean ± SD) | **17.2 ± 35.8** | -47.5 ± 30.5† | **-29.8 ± 38.2‡** | <0.001 | <0.001 | 0.256   |
| Change in HDL, mg/dL (mean ± SD) | 0.4 ± 10.8§ | 1.8 ± 8.5|| | **5.0 ± 8.4¶** | 0.869   | 0.285   | 0.551   |
| **Blood pressure** |                  |                       |                       |         |         |         |
| Change in mean arterial pressure, mmHg (mean ± SD) | -2.6 ± 15.5 | 0.1 ± 16.3 | -2.7 ± 13.3 | 0.852 | 0.999 | 0.853   |

ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

*p=0.031; † p<0.001; ‡ p=0.003; § p=0.877; || p=0.308; ¶ p=0.014.
## Table S3. Baseline VH-IVUS characteristics

| Characteristics, mean ± SE | Control (C) frame n=766 patient=18 | Atorvastatin (A) frame n=1218 patient=20 | Rosuvastatin (R) frame n=1690 patient=22 | P value |
|---------------------------|------------------------------------|------------------------------------------|------------------------------------------|---------|
|                           |                                    |                                          |                                          | C vs. A | C vs. R | R vs. A |
| EEM area, mm²             | 16.71 ± 0.20                      | 16.29 ± 0.14                            | 14.18 ± 0.11                            | 0.902   | **0.028** | **0.033** |
| Lumen area, mm²           | 10.21 ± 0.15                      | 9.11 ± 0.11                             | 7.16 ± 0.06                             | 0.355   | **0.001** | **0.01**  |
| Plaque area, mm²          | 6.50 ± 0.11                       | 7.18 ± 0.08                             | 7.01 ± 0.07                             | 0.304   | 0.663    | 0.515    |
| Plaque burden (%)         | 39.6 ± 0.49                       | 44.4 ± 0.38                             | 48.5 ± 0.29                             | 0.122   | **0.003** | 0.156    |
| NC%                       | 17.7 ± 0.45                       | 18.5 ± 0.34                             | 20.2 ± 0.32                             | 0.823   | 0.327    | 0.421    |
| NC area, mm²              | 0.70 ± 0.03                       | 0.80 ± 0.02                             | 1.00 ± 0.02                             | 0.578   | 0.16     | 0.357    |
| DC%                       | 6.31 ± 0.33                       | 7.40 ± 0.26                             | 8.00 ± 0.23                             | 0.268   | 0.164    | 0.761    |
| DC area, mm²              | 0.23 ± 0.01                       | 0.33 ± 0.01                             | 0.41 ± 0.01                             | 0.107   | 0.052    | 0.532    |
| FT%                       | 65.9 ± 0.72                       | 64.7 ± 0.48                             | 57.9 ± 0.49                             | 0.395   | **0.004** | **0.021** |
| FT area, mm²              | 1.92 ± 0.06                       | 2.39 ± 0.05                             | 2.21 ± 0.03                             | 0.258   | 0.592    | 0.441    |
| FF%                       | 6.90 ± 0.23                       | 8.75 ± 0.23                             | 9.34 ± 0.23                             | 0.093   | 0.198    | 0.667    |
| FF area, mm²              | 0.22 ± 0.01                       | 0.39 ± 0.01                             | 0.33 ± 0.01                             | **0.034** | 0.25     | 0.167    |

Data are mean (SE)

DC, dense calcification; EEM, external elastic membrane; FF, fibrofatty tissue; FT, fibrous tissue; NC, necrotic core; SE, standard error; VH-IVUS, virtual histology intravascular ultrasound
Table S4. Segmental analysis on changes in peak and mean plaque structural stress with different statin regimes and baseline disease severity

|                  | Control                  | Atorvastatin             | Rosuvastatin             |
|------------------|--------------------------|--------------------------|--------------------------|
| **Overall**      | Segment=237              | Segment=374              | Segment=445              |
| ΔPeak PSS, kPa (mean ± SE) | **-8.6 ± 3.6 0.03**      | 6.2 ± 5.9 0.306          | -1.4 ± 1.8 0.446         |
| ΔMean PSS, kPa (mean ± SE)  | **-1.1 ± 1.5 0.481**     | 1.2 ± 1.2 0.34           | -0.5 ± 0.6 0.399         |
| **Baseline PB<40%** | Segment=141              | Segment=165              | Segment=94               |
| ΔPeak PSS, kPa (mean ± SE) | **-16.7 ± 5.0 0.004**    | 9.1 ± 8.0 0.272          | -2.9 ± 3.4 0.405         |
| ΔMean PSS, kPa (mean ± SE)  | **-2.4 ± 1.8 0.2**       | 1.7 ± 1.9 0.368          | 0.2 ± 0.8 0.82           |
| **Baseline PB=40-60%** | Segment=71               | Segment=168              | Segment=269              |
| ΔPeak PSS, kPa (mean ± SE) | **-2.3 ± 4.5 0.608**     | 6.6 ± 5.2 0.224          | -1.2 ± 2.0 0.562         |
| ΔMean PSS, kPa (mean ± SE)  | **-0.7 ± 1.3 0.625**     | 0.8 ± 1.1 0.466          | -1.1 ± 0.6 0.076         |
| **Baseline PB>60%** | Segment=25               | Segment=41               | Segment=82               |
| ΔPeak PSS, kPa (mean ± SE) | **19.4 ± 6.1 0.058**     | -7.2 ± 7.1 0.412         | -2.0 ± 5.7 0.735         |
| ΔMean PSS, kPa (mean ± SE)  | **1.5 ± 3.4 0.681**      | -0.2 ± 1.9 0.936         | -0.2 ± 1.4 0.88           |

PB, plaque burden; PSS, plaque structural stress; SE, standard error.
Table S5. Correlation between changes in peak and mean PSS and plaque geometric and compositional parameters

|                      | ∆PSS peak (kPa) |                      | ∆PSS mean (kPa) |                      |
|----------------------|----------------|----------------------|----------------|----------------------|
|                      | Correlation coefficient (r) | R²   | p         | Correlation coefficient (r) | R²   | p         |
| ∆Lumen area (mm²)    | 0.297          | 0.088                | <0.0001        | 0.584          | 0.34    | <0.0001    |
| ∆Plaque area (mm²)   | -0.16          | 0.026                | <0.0001        | -0.4           | 0.16    | <0.0001    |
| ∆Plaque burden (%)   | -0.261         | 0.068                | <0.0001        | -0.6           | 0.36    | <0.0001    |
| ∆Lumen aspect ratio  | 0.346          | 0.12                 | <0.0001        | 0.026          | 0.0007  | 0.11       |
| ∆NC area (mm²)       | -0.024         | 0.0006               | 0.142          | -0.16          | 0.026   | <0.0001    |
| ∆NC %                | 0.033          | 0.001                | 0.046          | -0.064         | 0.004   | <0.0001    |
| ∆FF area (mm²)       | -0.071         | 0.005                | <0.0001        | -0.116         | 0.014   | <0.0001    |
| ∆FF %                | -0.0046        | 2.1e-5               | 0.78           | -0.051         | 0.003   | 0.002      |
| ∆FT area (mm²)       | -0.151         | 0.023                | <0.0001        | -0.272         | 0.074   | <0.0001    |
| ∆FT %                | -0.061         | 0.004                | 0.0002         | -0.072         | 0.005   | <0.0001    |
| ∆DC area (mm²)       | -0.01          | 0.0001               | 0.52           | -0.33          | 0.11    | <0.0001    |
| ∆DC %                | 0.05           | 0.0026               | 0.0022         | -0.202         | 0.041   | <0.0001    |
| ∆Maximum arc of DC (°) | 0.02         | 0.0004               | 0.21           | -0.417         | 0.17    | <0.0001    |
| ∆Total arc of DC (°) | -0.013         | 0.0002               | 0.44           | -0.428         | 0.18    | <0.0001    |

DC, dense calcium; FF, fibrofatty; FT, fibrous tissue; NC, necrotic core; PSS, plaque structural stress.
Table S6. Peri-MLA analysis on changes in lumen geometric features in plaques with baseline PB>60%

| Characteristics          | Control         |     | High-intensity statin |     |
|--------------------------|-----------------|-----|-----------------------|-----|
|                          | frame =84       | p   | frame =412            | p   |
| ΔCurvature_{max} (mm⁻¹)  | -0.070 ± 0.090  | 0.464 | -0.0773 ± 0.0378      | 0.0513 |
| ΔIrregularity (mm⁻¹)     | -0.113 ± 0.0769 | 0.196 | -0.139 ± 0.0544       | 0.0174 |
| ΔRoughness_{curvature}   | -0.00638 ± 0.00816 | 0.462 | -0.0161 ± 0.00583     | 0.0108 |
| ΔLumen aspect ratio      | -0.010 ± 0.024  | 0.678 | -0.059 ± 0.021        | 0.01 |

MLA, minimal luminal area; PB, plaque burden; SE, standard error.
• Lumen aspect ratio = \( \frac{\text{lumen major axis}}{\text{lumen minor axis}} \)

• Lumen curvature: curvature at point a was computed using the radius (as \( r_a \)) of the circle determined by point a and two adjacent points (\( a_1 \) and \( a_2 \)), i.e. Lumen Curvature = \( 1/r_a \).

• Lumen Irregularity = Lumen Curvature_{max} – Lumen Curvature_{min}

• Roughness_{curvature} = \( \sqrt{\frac{1}{2\pi r} \sum \left( \frac{r}{r_a} \right)^2 \Delta l} \)

- Roughness as a measure of evenness of lumen curvature. \( r \) is the radius of the circle best fitting the lumen contour (i.e. lumen area =\( \pi r^2 \)), \( \Delta l \) is the length between point a and one adjacent point

Figure S1. Definitions of lumen aspect ratio, curvature, irregularity, and roughness
Figure S2. Association between change in PSS and change in lipid levels.
Linear correlation curves for change in peak (left) and mean PSS (right) with change in (A) LDL, (B) HDL. LDL or HDL changes are values for follow-up minus baseline, such that a higher negative value indicates a greater reduction from treatment. HDL = high-density lipoprotein; LDL = low-density lipoprotein; PSS = plaque structural stress.
Figure S3. Correlation between changes in peak PSS and lumen parameters in atorvastatin and rosvastatin groups in plaques with baseline PB>60%.
(A) maximum lumen curvature, (B) lumen irregularity, (C) lumen roughness (D) lumen aspect ratio. These regression slopes between the 2 high-intensity statin groups are similar (p>0.05).
Supplemental References

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