Supplementary data

Supplementary Appendix 1. Methods

Matching procedures

Multiple validation steps were used during the matching process of IVUS and OCT both baseline and at follow-up. Both OCT and IVUS follow-up were matched with baseline IVUS. Matching was performed with all side branches visible in the two imaging modalities, both in longitudinal and circumferential direction. Visible large calcifications were used as control landmarks after matching.

Based on all matched imaging modalities, a luminal area correlation was performed **(Supplementary Figure 1)**.

Rotational matching was checked by creating 2D maps by cutting open the vessel in longitudinal direction of the matched wall thickness and plaque components (IVUS-IVUS: Wall thickness patterns & calcifications, IVUS-OCT: calcifications **(Supplementary Figure 2).**

Subsequently, by fusing the 3D spatial information on the coronary vessel centreline segmented from the CCTA and the lumen contours extracted from the IVUS, a 3D reconstruction was made in MeVisLab (MeVis Medical Solutions AG). The data from the two imaging modalities were matched using large side branches as landmarks, visible in both acquisitions. The regions proximal and distal to the IVUS-derived region of interest, as well as side branches (>1.5 mm) were segmented on the CCTA and scaled and fused with the 3D reconstruction [7]. Of note, for final analysis, only the IVUS-derived region of interest (ROI) was considered.

By using side branches as landmarks, both the analysed OCT data, as well as the segmented IVUS follow-up contours, were matched to the IVUS baseline pullback. Matching was performed in both longitudinal and circumferential directions. The axial adjustment in the matching process has been performed using a dedicated matching software (linear rotational between the two side-branches) QCU-CMS software (Version 4.69; Division of Image Processing, Leiden University Medical Center). All matched and analysed data was mapped

and interpolated on the IVUS-based region of interest (ROI) on the 3D mesh geometry using VMTK (Orobix) and MATLAB (v2017b; Mathworks Inc.). For further analysis, the 3D-ROIs were divided into 1.5 mm segments, which were then further divided into 45 degrees sectors (**Figure 1**). All continuous data for each sector (i.e., OCT lipid plaque) was an average of the mesh data in that sector and has been presented as percentage. Lipid-rich plaque was defined as a region with an inhomogeneous, slowly attenuating signal and an invisible EEM. A lipid-pool was defined as a region with a sudden drop in signal with a diffuse border and an overlying signal rich cap structure. As there were only 124 sectors identified with a lipid pool at baseline (out of the overall 6,936 analysed sectors), the OCT lipid sectors included both the lipid-rich and the lipid pools together.

Supplementary Appendix 2. Results

Changes in plaque area over 12-month follow-up.

Overall, the thin wall artery regions showed significant increase, whereas the thick wall artery regions showed significant decrease in relative plaque area (PA) of the sector (mean Δ PA: 5.0% [95% CI: 4.0–6.7] vs -3.3% [95% CI: -4.7 – -2.0%]; p<0.001). The near-infrared spectroscopy (NIRS)-positive sectors showed significant plaque progression, whereas no significant progression was observed in the NIRS negative sectors (mean ΔPA: 2.9% [95% CI: 1.5–4.4] vs 1.0% [95% CI: -0.1–2.2]; p<0.001) **(Supplementary Figure 3)**.

Plaque progression was more pronounced in the NIRS-positive sectors within the thin wall regions and plaque regression in regions with already established plaques (thick regions) was significantly smaller in the NIRS-positive sectors. In the thin wall regions, the mean ΔPA in NIRS(+) vs NIRS(-) sectors was (7.9% [95% CI: 6.0–9.7]) vs (5.4% [95% CI: 4.2–6.6]), respectively, p<0.001. In the thick wall regions, the mean ΔPA in NIRS(+) vs NIRS(-) sectors was (-2.0% [95% CI: -3.6 – -0.4]) vs (-3.3% [95% CI: -4.5 – -2.1]), p<0.001. **(Supplementary Figure 4)**

Similarly, the thin wall sectors with OCT-detected lipids showed significantly higher plaque growth than the thin wall sectors with no OCT-detected lipids (7.9% [95% CI: 5.4–11]) vs (5.2% [95% CI: 2.7–7.7]). The thin wall NIRS positive sectors, for which the presence of lipid content was confirmed by OCT, showed significant plaque growth (9.3% [95% CI: 6.4–9.3]) (**Supplementary Figure 5**). Analyses adjusted for high-intensity statin use, LDL level and presence of diabetes brought consistent results **(Supplementary Table 5, Supplementary Table 6)**.

Supplementary Table 1. Reasons for sectors exclusions.

Overall sectors:	**9,906 sectors**
Not available OCT data due to e.g., non-analysable frames due to flushing artefacts, matching etc.	2,207 sectors
Not available NIRS data due to e.g., guidewire artefacts	212 sectors
Not available due to calcium (baseline)	391 sectors
Not available due to "artefact" (baseline)	30 sectors
Not available due to calcium (follow-up)	121 sectors
Not available due to artefact (follow-up)	9 sectors
Number of sectors included in the final analysis	**6,936 sectors**

OCT: optical coherence tomography; NIRS: near-infrared spectroscopy

Supplementary Table 2. Positive and negative predictive value of NIRS positive signal vs OCT-detected lipid plaque.

NIRS lipid-rich plaque	OCT-detected lipid plaque	
	PPV	55.9%
	NPV	96.7%

OCT: optical coherence tomography; NIRS: near-infrared spectroscopy; NPV: negative predictive value; PPV: positive predictive value

Supplementary Table 3. Changes in wall thickness (WT) in thin and thick artery regions over 12-month follow-up, categorised according to NIRS detected lipid rich plaque. Analysis adjusted for high-intensity statin use, LDL level and presence of diabetes.

Wall thickness	NIRS	Mean ΔWT (mm)	95% CI		*p*-value
			Lower bound	Upper bound	
Thin wall	NIRS (-)	0.07	0.05	0.09	p<0.001
	NIRS (+)	0.12	0.08	0.14	
Thick wall	NIRS (-)	-0.08	-0.11	-0.06	p<0.001
	NIRS (+)	-0.07	-0.10	-0.05	

ΔWT: change in wall thickness; LDL: low-density lipoproteins; NIRS: near-infrared spectroscopy

Supplementary Table 4. Changes in wall thickness (WT) in thin and thick artery regions over 12-month follow-up, categorised according to NIRS and OCT-detected lipid at baseline. Analysis adjusted for high-intensity statin use, LDL level and presence of diabetes.

Wall thickness	NIRS	OCT- Lipid	Mean ΔWT (mm)	95% confidence interval	
				Lower bound	Upper bound
Thin wall	NIRS (-)	OCT- lipid (-)	0.07	0.04	0.09
	NIRS (-)	OCT- lipid (+)	0.11	0.08	0.13
	NIRS (+)	OCT- lipid (-)	0.08	0.03	0.13
	NIRS (+)	OCT- lipid (+)	0.13	0.07	0.18
Thick wall	NIRS (-)	OCT- lipid (-)	-0.08	-0.10	-0.05
	NIRS (-)	OCT- lipid (+)	-0.09	-0.11	-0.06
	NIRS (+)	OCT- lipid (-)	-0.05	-0.10	-0.004
	NIRS (+)	OCT- lipid (+)	-0.06	-0.11	-0.02

ΔWT: change in wall thickness; LDL: low-density lipoproteins; OCT: optical coherence tomography; NIRS: near-infrared spectroscopy

Supplementary Table 5. Changes in relative plaque area (per sector) in thin and thick artery regions over 12-month follow-up, categorised according to NIRS detected lipid rich plaque. Analysis adjusted for high-intensity statin use, LDL level and presence of diabetes.

Wall thickness	NIRS	Mean ΔPA (%)	95% confidence interval		
			Lower bound	Upper bound	*p*-value
Thin wall	NIRS (-)	5.5	4.1	7.0	p<0.001
	NIRS (+)	8.0	6.0	10.0	
Thick wall	NIRS (-)	-3.2	-4.6	-1.7	p<0.001
	NIRS (+)	-1.8	-3.6	-0.1	

ΔPA: change in relative (sectorial) plaque area; NIRS: near-infrared spectroscopy

Supplementary Table 6. Changes in relative plaque area (per sector) in thin and thick artery regions over 12-month follow-up, categorised according to NIRS and OCT-detected lipid at baseline. Analysis adjusted for high-intensity statin use, LDL level and presence of diabetes.

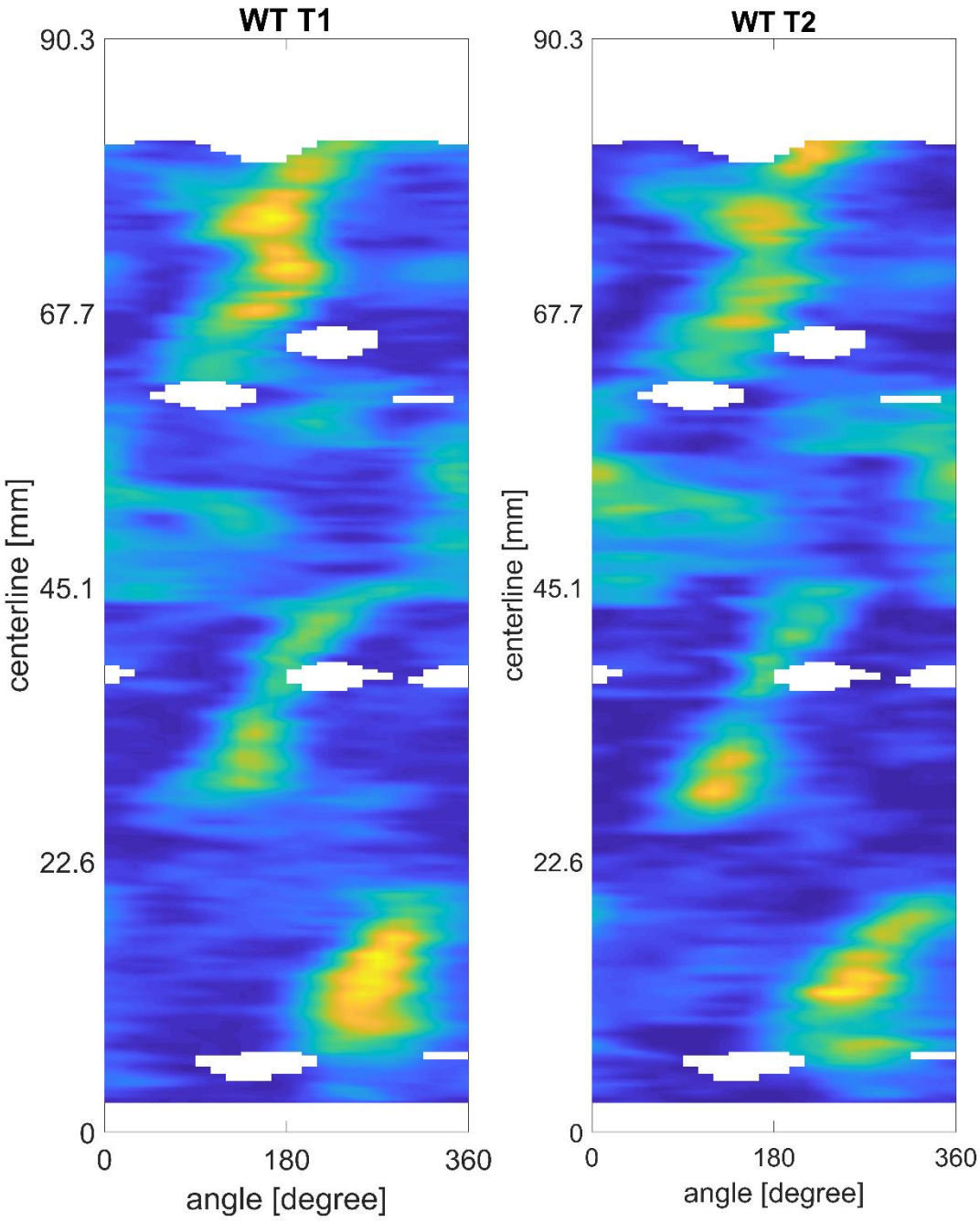
Wall thickness	NIRS	OCT- lipid	Mean ΔPA (%)	95% confidence interval	
				Lower bound	Upper bound
Thin wall	NIRS (-)	OCT-lipid (-)	5.5	4.3	6.7
	NIRS (-)	OCT-lipid (+)	8.2	6.7	9.6
	NIRS (+)	OCT-lipid (-)	6.8	4.1	9.5
	NIRS (+)	OCT-lipid (+)	9.0	5.9	12.1
Thick wall	NIRS (-)	OCT-lipid (-)	-3.2	-0.4	-1.9
	NIRS (-)	OCT-lipid (+)	-2.8	-4.1	-1.5
	NIRS (+)	OCT-lipid (-)	-1.6	-4.3	1.0
	NIRS (+)	OCT-lipid (+)	-1.2	-3.4	-1.0

ΔPA: change in relative (sectorial) plaque area; LDL: low-density lipoproteins; NIRS: near-infrared spectroscopy

Supplementary Figure 1. Overlay of luminal area of IVUS and OCT.

X: axis frame numbers OCT (5 frames per 1 mm); Y: axis luminal area

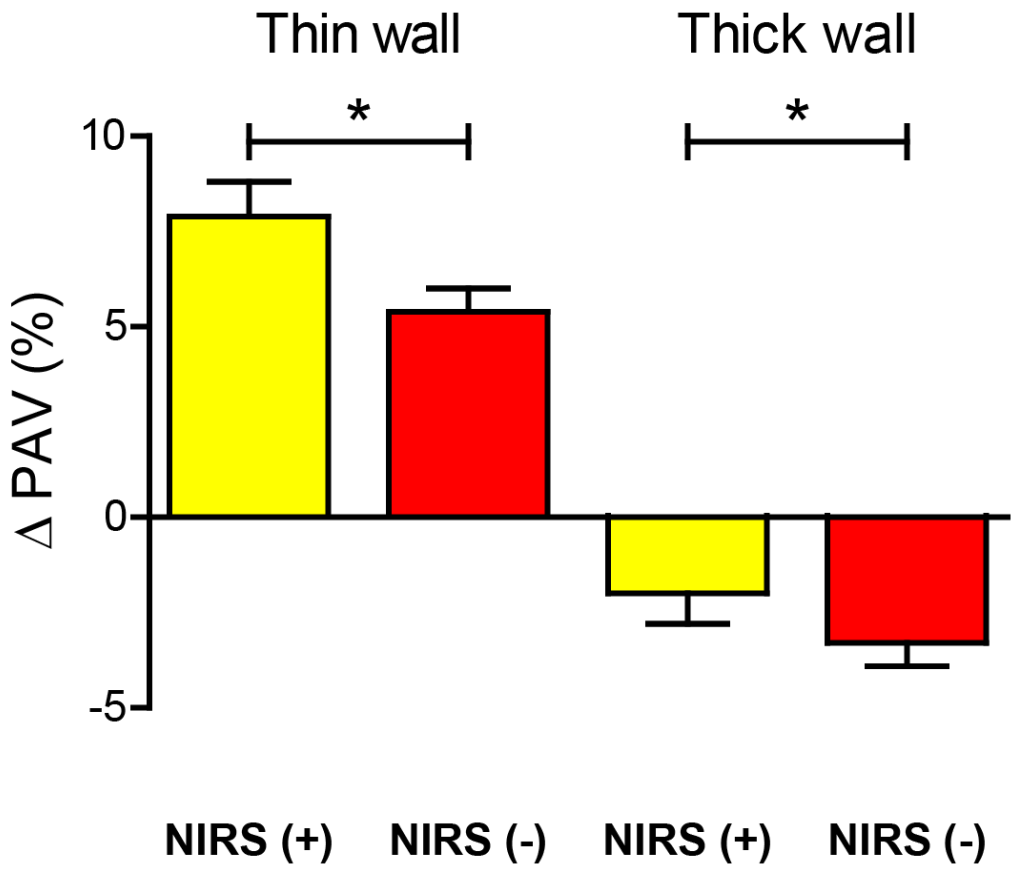
IVUS: intravascular ultrasound; OCT: optical coherence tomography



Supplementary Figure 2. 2D maps of wall thickness IVUS baseline and follow-up, visual check on WT patterns.

White regions in the 2D maps are side branches or calcifications.

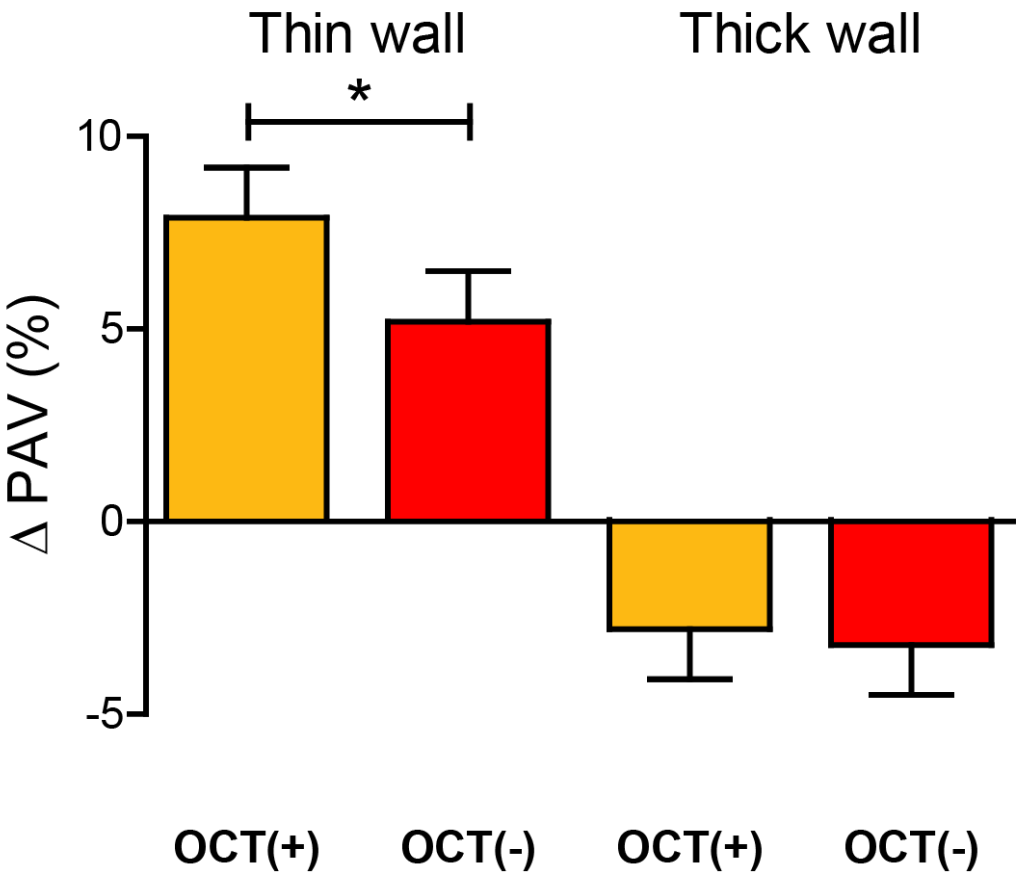
IVUS: intravascular ultrasound



Supplementary Figure 3. Relative plaque area (per sector) progression in thin and thick artery wall sectors as assessed by IVUS at baseline stratified for the presence and absence of NIRS signal.

Yellow: NIRS positive sectors (NIRS[+]); red: NIRS negative sectors (NIRS[-]); thin <0.5 mm wall thickness by IVUS; thick ≥0.5 mm wall thickness. * p<0.001.

IVUS: intravascular ultrasound; NIRS: near-infrared spectroscopy; ΔPAV: Change in relative plaque area

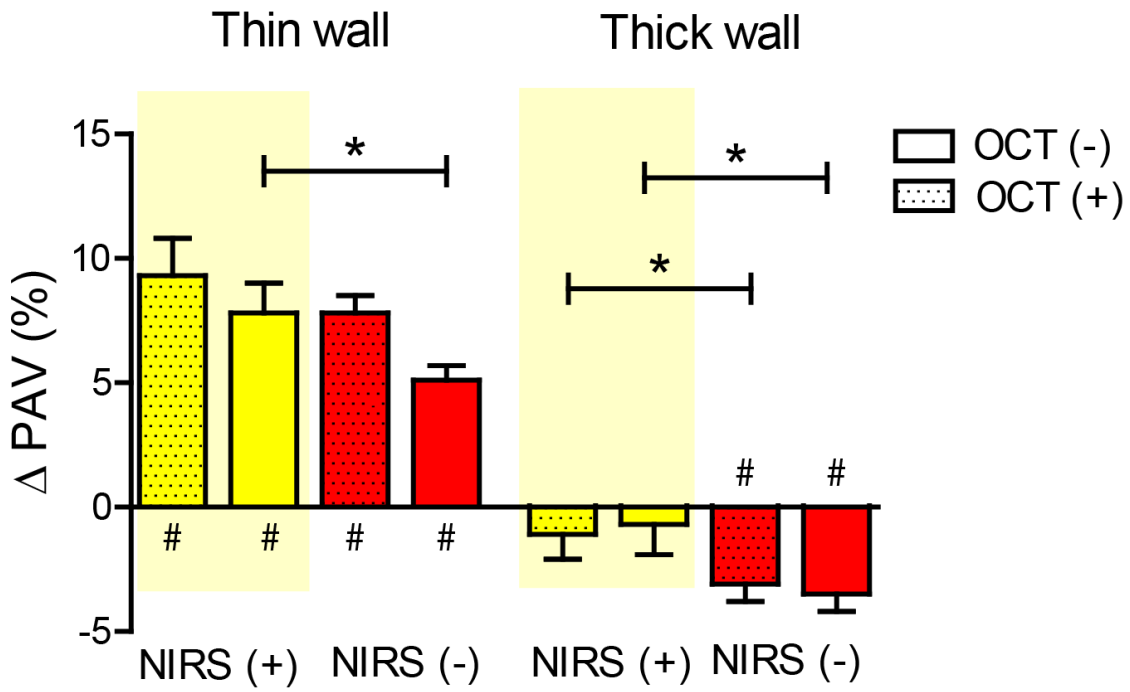


Supplementary Figure 4. Relative plaque area (per sector) progression in thin and thick artery wall sectors as assessed by IVUS at baseline stratified for the presence and absence of OCT-detected lipid plaque.

Yellow: OCT-lipid plaque positive sectors (OCT[+]); red: OCT-lipid plaque negative sectors (OCT[-]); thin <0.5 mm wall thickness by IVUS; thick ≥0.5 mm wall thickness.

* $p<0.001$

IVUS: intravascular ultrasound; OCT: optical coherence tomography; NIRS: near-infrared spectroscopy; ΔPAV: Change in relative plaque area



Supplementary Figure 5. Relative plaque area (per sector) progression in thin and thick wall sectors stratified by NIRS and OCT-detected lipid plaque.

Yellow: NIRS positive sectors (NIRS[+]); red: NIRS negative sectors (NIRS[-]); thin, <0.5 mm wall thickness by IVUS; thick; ≥0.5 mm wall thickness by IVUS. OCT(-) sectors that did not demonstrate lipid on OCT; OCT(+): sectors that demonstrated lipid on OCT;

* $p<0.001$, # $p<0.001$.

IVUS: intravascular ultrasound; OCT: optical coherence tomography; NIRS: near-infrared spectroscopy; ΔPAV: Change in relative plaque area