Supplement Table 1: Baseline clinical and demographic characteristics of participants that withdrew prior to, or completed at least, the 9-month MRI visit.

	Completed < 9 months (n=32)	Completed ≥ 9 months (n=131)	P-value
Sex (% male)	100%	95%	0.3
Race (% white)	81%	88%	0.4
Age (years)	63 ± 7	63 ± 8	1.0
BMI (kg/m^2)	31 ± 6	34 ± 6	0.007
Obesity (%)	50%	72%	0.02
Diabetes duration (years)	5 ± 3	6 ± 4	0.2
Fasting glucose (mg/dl)	156 ± 51	158 ± 48	0.8
Hemoglobin A1c (%)	7.9 ± 1.3	7.9 ± 1.2	1.0
Systolic BP (mmHg)	137 ± 18	137 ± 17	0.8
Diastolic BP (mmHg)	83 ± 12	82 ± 12	0.5
History of hypertension (%)	88%	92%	0.5
History of CVD (%)	13%	24%	0.2
Smoking (%)	22%	16%	0.4
Statins (%)	78%	82%	0.6
Fasting triglycerides (mg/dl)	143 ± 59	174 ± 105	0.04
Fasting cholesterol (mg/dl)	158 ± 35	152 ± 35	0.4
HDL-cholesterol (mg/dl)	45 ± 9	43 ± 10	0.3
LDL-cholesterol (mg/dl)	86 ± 28	76 ± 27	0.08

Data are means ± SD or percentages, P-values indicate between-group comparison by Student's t-test (for continuous variables) or by Chi-square test (for categories). BP; blood pressure; CVD, cardiovascular disease.

Supplement Table 2: Change in cardiovascular risk factors after 3 months of randomization in participants that withdrew prior to, or completed at least, the 9-month MRI visit.

	Completed < 9 months (n=25)	Completed ≥ 9 months (n=131)	P-value
Hemoglobin A1c (%)	-0.5 (-0.8, 0.7)	-0.7 (-1.3, 0)	0.2
Body weight (kg)	-0.1 (-2.3, 0.7)	-1.4 (-3.6, 0.4)	0.01
Systolic BP (mmHg)	-2 (-11, 9)	-8 (-17, 2)	0.06
Diastolic BP (mmHg)	-1 (-3, 5)	-2 (-10, 4)	0.2
Heart rate (bpm)	9 (0, 13)	6 (-1, 12)	0.4
Fasting glucose (mg/dl)	-12 (-34, 14)	-23 (-51, 6)	0.6
Fasting triglycerides (mg/dl)	7 (-29, 39)	6 (-26, 29)	0.8
Fasting cholesterol (mg/dl)	-8 (-23, 0)	-11 (-27, 2)	0.4
HDL-cholesterol (mg/dl)	-3 (-6, -1)	-1 (-5, 1)	0.9
LDL-cholesterol (mg/dl)	-14 (-22, 5)	-9 (-21, 3)	0.4

Data are medians (interquartile range). P-values indicate between-group comparison by mixed models (3-month values adjusted for baseline and treatment assignment). BP; blood pressure.

Supplement Table 3: Related or probably related adverse events by treatment group. All p>0.05.

Event type*	Exenatide Number (%)	Placebo Number (%)
Gastrointestinal	23 (21%)	5 (9%)
Nausea	10 (9%)	3 (6%)
Nausea only	5	2
Nausea & vomiting	5	1
Dyspepsia	6 (6%)	0
Diarrhea	7 (6%)	0
Constipation	7 (6%)	2 (4%)
Allergic reaction	6 (6%)	1 (2%)
Injection site reaction	3	1
Rash	3	0
Hypoglycemia	5 (5%)	0
Headache	4 (4%)	0
Increased creatinine	4 (4%)	0
Other Dyspnea, erectile dysfunction, leg cramps	3 (3%)	0

*Multiple side effects may be present in the same participant

Supplement Table 4: Comparison of diabetes, hypertension and statin medication use at baseline and during the study. Shown are numbers (%) of participants using ≤1, 2 or ≥3 medications for diabetes, 0, 1 or ≥ 2 medication for hypertension, and any statin use. P-values indicate.

	No.	Group	Baseline	3 months	9 months	18 months
Diabetes	≤ 1	Exenatide	44 (41%)	42 (41%)	39 (44%)	39 (46%)
		Placebo	22 (41%)	21 (40%)	16 (39%)	12 (32%)
	2	Exenatide	41 (38%)	41 (40%)	34 (39%)	32 (38%)
		Placebo	18 (33%)	21 (40%)	15 (37%)	16 (43%)
	≥ 3	Exenatide	23 (21%)	19 (19%)	15 (17%)	14 (16%)
		Placebo	14 (26%)	11 (21%)	10 (24%)	9 (24%)
Insulin		Exenatide	44 (41%)	33 (32%)	27 (31%)	26 (31%)
		Placebo	31 (57%)	30 (57%)†	18 (43%)	14 (37%)
Metformin		Exenatide	93 (86%)	83 (81%)	69 (78%)	66 (78%)
		Placebo	42 (78%)	42 (79%)	35 (83%)	32 (84%)
Sulfonylureas		Exenatide	50 (46%)	44 (43%)	37 (42%)	34 (40%)
		Placebo	26 (48%)	25 (47%)	19 (45%)	15 (39%)
Other*		Exenatide	12 (11%)	10 (10%)	9 (10%)	9 (11%)
		Placebo	6 (11%)	6 (11%)	5 (12%)	6 (16%)
Hypertension	0	Exenatide	15 (14%)	14 (14%)	12 (14%)	13 (16%)
		Placebo	8 (15%)	5 (9%)	6 (14%)	4 (11%)
	1	Exenatide	40 (37%)	38 (37%)	34 (39%)	31 (37%)
		Placebo	19 (35%)	21 (40%)	14 (33%)	11 (31%)
	≥ 2	Exenatide	54 (50%)	50 (49%)	42 (48%)	40 (48%)
		Placebo	27 (50%)	27 (51%)	22 (52%)	21 (58%)
Statins		Exenatide	87 (81%)	82 (80%)	73 (83%)	69 (82%)
		Placebo	45 (83%)	45 (85%)	34 (83%)	31 (86%)

*DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors or PPAR-γ agonists, small numbers of each; †$p<0.05$ exenatide vs. placebo.

Supplement Table 5: Association of percent changes in plaque volume with percent changes in risk factors and vascular function in the whole group (adjusted for treatment arm) and by treatment arm. Data are beta-estimates (SE); *p<0.05 for association; p-value for interaction indicates a difference in the association between the treatment arms.

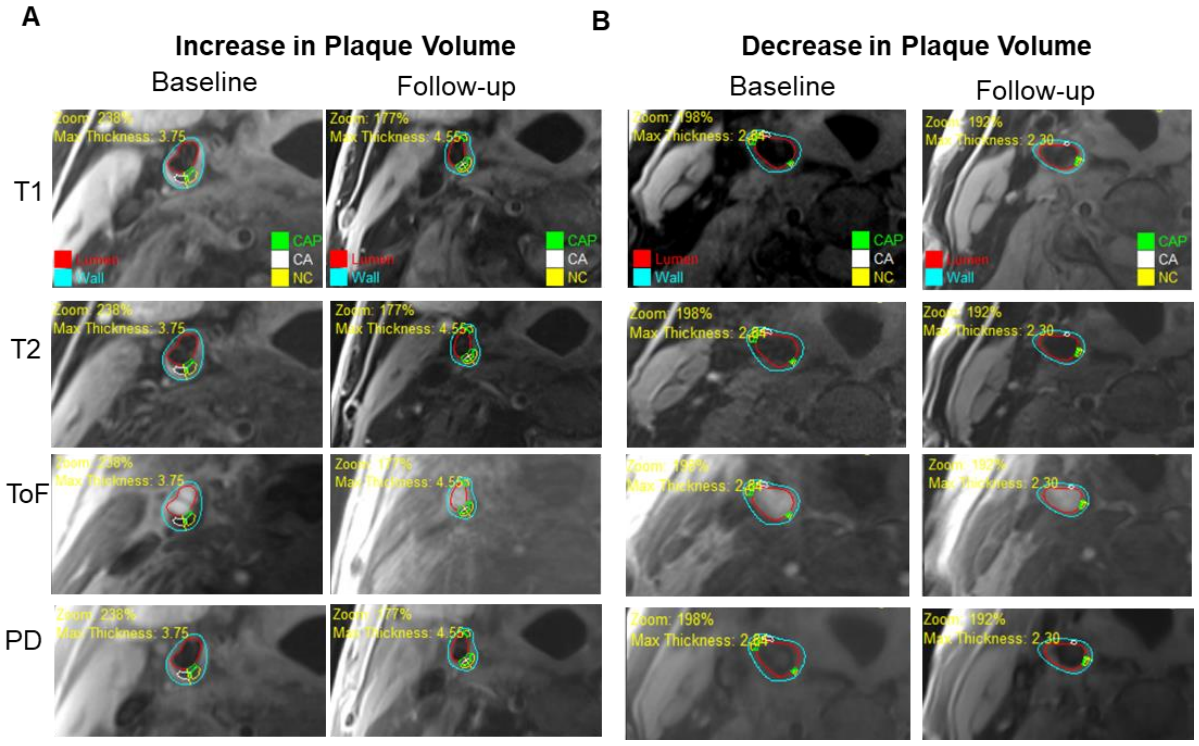
	All	Exenatide	Placebo	P-value for interaction
Hemoglobin A1c	0.18 (0.06)*	0.24 (0.07)*	-0.14 (0.12)	**0.03**
Body weight	0.50 (0.19)*	0.63 (0.23)*	0.12 (0.30)	0.2
Heart rate	0.08 (0.06)	0.11 (0.08)	0.03 (0.08)	0.5
Systolic BP	0.08 (0.07)	0.13 (0.09)	-0.02 (0.10)	0.3
Diastolic BP	0.08 (0.07)	0.15 (0.09)	-0.13 (0.11)	0.09
Total cholesterol	0.02 (0.05)	0.01 (0.07)	0.06 (0.07)	0.6
HDL cholesterol	0.09 (0.09)	0.12 (0.11)	-0.01 (0.15)	0.6
LDL cholesterol	-0.01 (0.02)	-0.02 (0.03)	0.03 (0.04)	0.4
Meal glucose†	0.07 (0.03)*	0.10 (0.04)*	-0.01 (0.05)	0.15
Meal triglycerides†	0.01 (0.03)	0.00 (0.03)	0.07 (0.06)	0.5
Fasting RHI	-0.02 (0.03)	-0.01 (0.04)	-0.07 (0.07)	0.5
Meal RHI	0.06 (0.05)	0.07 (0.06)	0.03 (0.08)	0.7

†Area under the curve, calculated by trapezoid method.

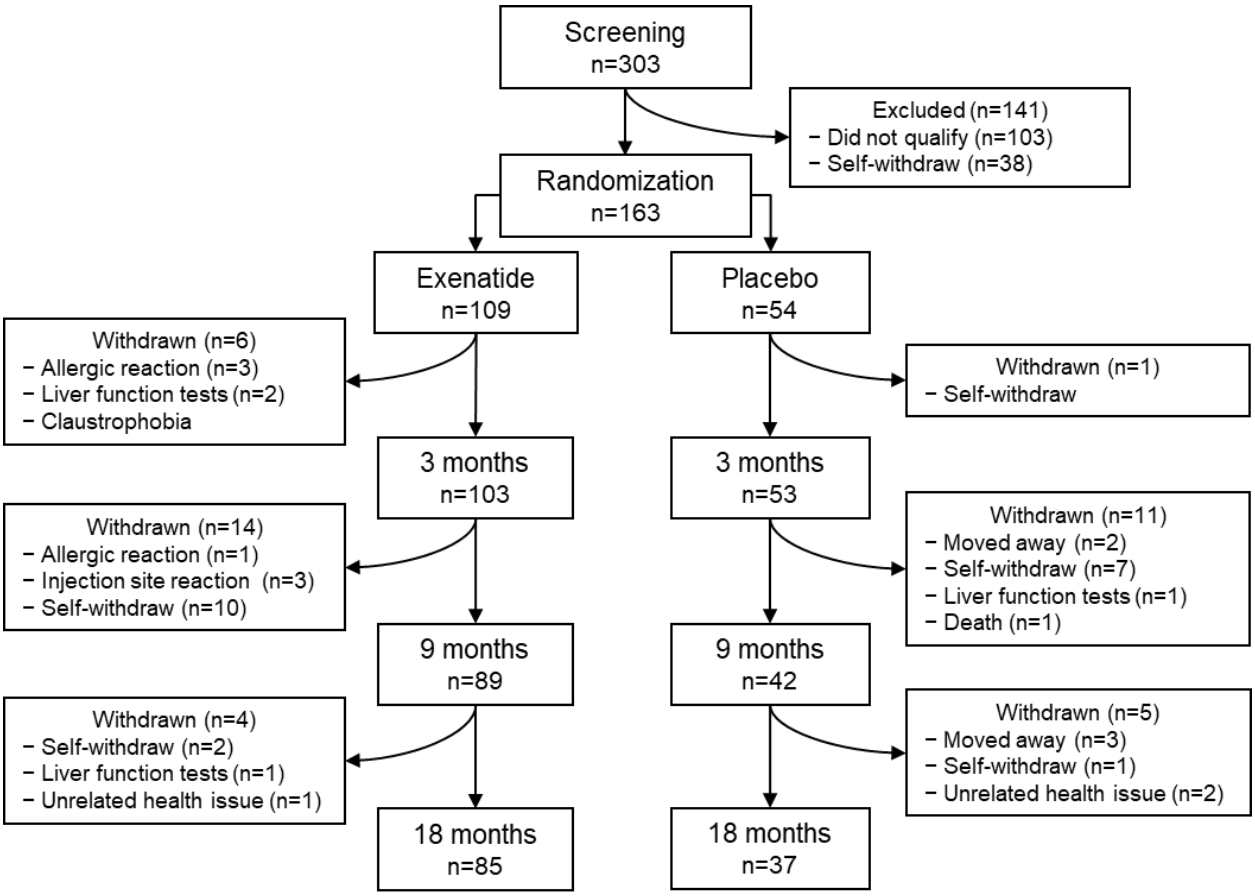
Supplement Table 6: Change in normalized plaque volume after exenatide (% change from baseline to last available visit) according to cardiovascular risk factors and plaque volume at baseline. Data are medians (25th, 75th percentile).

Baseline characteristic	Median	Low (≤ Median)	High (> Median)	P-value
Age (years)	66	-0.9 (-5.1, 3.4)	-1.2 (-5.1, 5.2)	0.9
Body mass index (kg/m^2)	34	0.3 (-3.9, 4.3)	-1.1 (-5.2, 3.4)	0.9
Diabetes duration (years)	5.5	-0.9 (-5.1, 5.2)	-1.2 (-5.4, 3.9)	0.5
Hemoglobin A1c (%)	7.5	-1.2 (-5.6, 4.3)	0.7 (-3.6, 4.6)	0.8
Systolic BP (mmHg)	135	-0.9 (-6.0, 4.3)	-1.0 (-3.1, 4.5)	0.6
Diastolic BP (mmHg)	81	-1.6 (-5.5, 2.1)	1.1 (-2.0, 5.9)	0.2
LDL-cholesterol (mg/dl)	71	-0.9 (5.4, 4.0)	-1.1 (-5.1, 4.3)	0.3
HDL-cholesterol (mg/dl)	40	-0.6 (-5.3, 3.9)	-1.1 (-5.1, 4.5)	0.4
Plaque volume (mm^3/slice)	81	0.3 (-1.9, 6.6)	-1.6 (-5.6, 3.4)	0.13

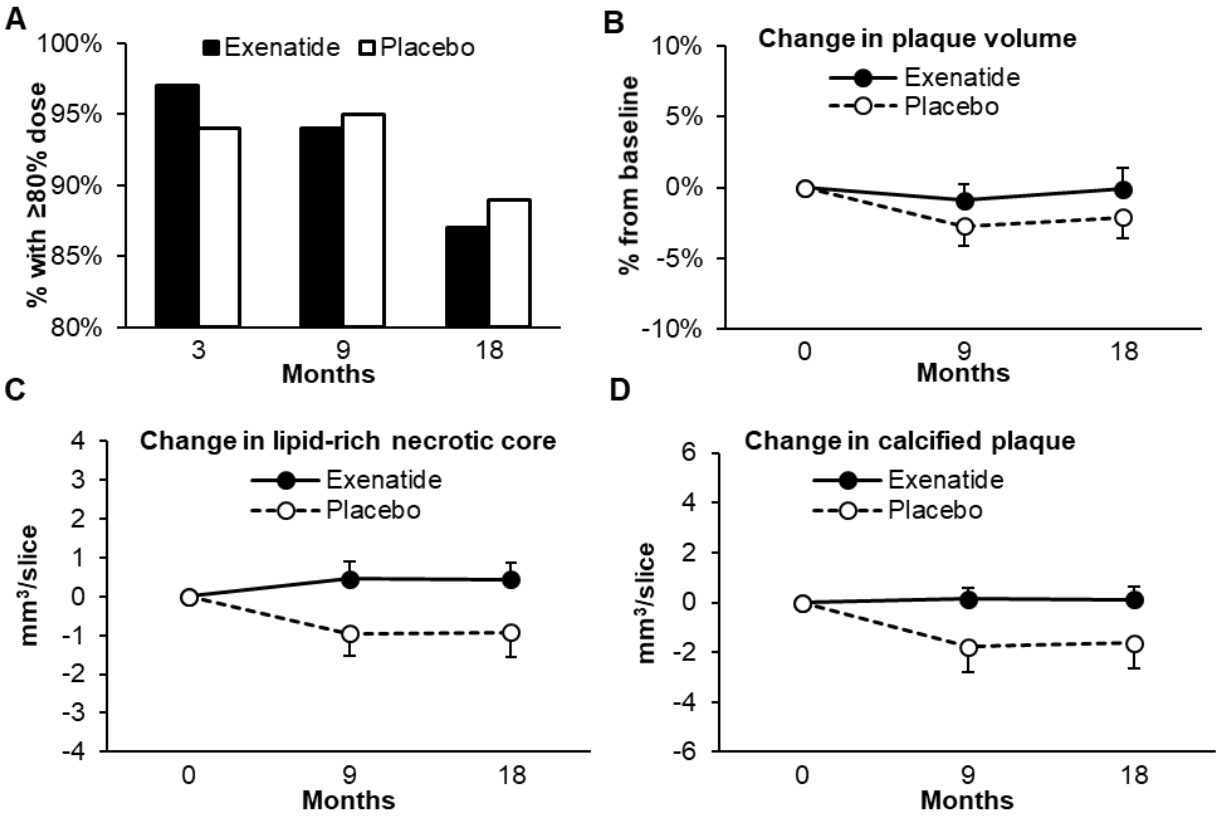
Supplement Figure 1: Representative T1/T2/time of flight (ToF)/proton density (PD) weighted single slice images at flow divider in study participants with increased plaque volume (**panel A**) and decreased plaque volume (**Panel B**) during the study. CAP, fibrous cap; CA, calcified plaque; NC, lipid-rich necrotic core.



Supplement Figure 2: Study flow



Supplement Figure 3: Compliance with study medication (A) and the effect of exenatide once-weekly and placebo on carotid plaque volume (B, p=0.05) and plaque components (C-D) in participants with ≥80% self-reported compliance taking the study medication and completing the 18 months treatment (per-protocol). Data are means ± S.E; n=72, exenatide; n=30, placebo; all p>0.05.



Supplement Figure 4: Association between plasma exenatide levels at last available visit with corresponding changes in metabolic and vascular outcomes. Dotted line indicates therapeutic plasma concentration of exenatide (50 pg/ml). Assay quantification range was 20-500 pg/ml. All p-values for Spearman correlation were >0.05.