Supplementary Online Content

Hauser TH, Salastekar N, Schaefer EJ, et al; Effect of targeting inflammation with salsalate: the TINSAL-CVD randomized clinical trial on progression of coronary plaque in overweight and obese patients using statins. *JAMA Cardiol*. Published online May 25, 2016. doi:10.1001/jamacardio.2016.0605.

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Supplemental Background

Mechanistic Evidence of Salicylate Anti-Inflammatory Effects

Acetylsalicylic acid (aspirin) inhibits cyclooxygenase (COX) enzymes even at low doses by covalent transacetylation[1], and is commonly used at for antiplatelet effects and pain relief. Salicylates, including non-acetylated salicylates which do not inhibit COX, have multiple potential mechanisms of action, including anti-inflammatory effects by inhibition of nuclear factor-κB (NF-κB)[2-4], mitochondrial dehydrogenases[5], heat shock protein[6], and nuclear factor of activated T cells (NFAT)-dependent transcription factors[7], and cellular kinases including IkappaB kinase[4], ribosomal S6 kinase[8], p38 mitogen-activated protein[9], and insulin receptor substrate-1[10]. Salicylates also stimulate adenosine monophosphate–activated protein kinase[11], and inhibit 11-β hydroxysteroid dehydrogenase type 1 in adipose tissue[12].

Salsalate is a dimer of salicylate that is hydrolyzed to salicylate and absorbed in the duodenum. It has been marketed for decades for the relief of pain and inflammation associated with arthritis. In preclinical models of vascular injury and repair using carotid artery balloon catheter injury, salsalate decreases intimal-medial ratio and upregulated expression of aortic endothelial nitric oxide synthase, mitochondrial antioxidant manganese superoxide dismutase and reduced serum interleukin-6 with concomitant down regulation of NFκB subunit p65, and vascular endothelial growth factor[13]. Salsalate likewise reduces oxidative stress and protein expression of NADPH oxidase p47 in human endothelial cells[14]. However, effects of salsalate on endothelial function in humans *in vivo* remains controversial, and has been suggested to improve, remain unchanged, or worsen[14-17]. Salsalate significantly down regulates NF-κB, which controls transcription of DNA regulating production of multiple cytokines and chemokines, surface proteins and receptors, transcription factors and others, that have been associated with incident

or progression of atherosclerosis[18]. The mechanistic hypothesis underlying this clinical trial is that reductions across many inflammatory factors might combine to clinically reduce atherosclerotic plaque progression.

Supplemental Methods

Additional Inclusion Criteria

In addition to criteria provided in main text, participants needed liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) below 3 times upper limits of normal; normal thyroid function (on stable dose replacement therapy was acceptable); and women with child bearing potential must have had a negative pregnancy test and use contraception throughout the study. Those with type 2 diabetes needed screening fasting glucose <11.1 mmol/L (200 mg/dl), without insulin, thiazolidinedione, or glucagon-like peptide-1 receptor agonist class agents.

Additional Exclusion Criteria:

Unstable angina; significant obstructive disease (>70%) in left main coronary artery, ostial LAD or three-vessel disease by MDCTA; more than one vascular territory involved with reversible defect (multiple defects) or large reversible defects of the anterior wall on nuclear or echocardiographic imaging during stress testing; significant heart failure (NYHA class III and IV); current atrial fibrillation or Wolf-Parkinson-White (WPW) syndrome; prior hemorrhagic stroke; allergy to aspirin; beta-blocker in subjects with resting heart rate above 65 bpm; uncontrolled hypertension (systolic blood pressure (BP) above 160 mm Hg and/or diastolic BP > 100 mm Hg; history of asthma only if unable to tolerate beta-blockers; allergy to iodinated contrast material or shellfish, or nitroglycerin; unwilling to refrain from medicine for erectile dysfunction within 72

hours prior to MDCTA; BMI above 35 kg/m^2 (if female) and above 40 kg/m^2 (if male) and/or body weight above 159 kg (350 lbs); use of drugs for weight loss within three months of screening; prior gastric bypass surgery; surgery within 30 days of screening; history of acquired immune deficiency syndrome or human immunodeficiency virus (HIV) ; poor mental function or history of dementia/ Alzheimer's Disease or on medications used for treatment of dementia or any other reason to expect patient difficulty in complying with the requirements of the study; type 1 diabetes; use of continuous oral corticosteroid treatment (more than 2 weeks), or patients requiring corticosteroids within 3 months; peptic ulcer or gastritis within 5 years; positive stool guaiac; hemoglobin 2 standard deviations below normal; thrombocytopenia (2 standard deviations below normal); known bleeding disorder; use of warfarin compounds; history of malignancy, except subjects who have been disease-free for greater than 5 years, or whose only malignancy has been basal or squamous cell skin carcinoma; history of drug or alcohol abuse, or current weekly alcohol consumption above 14 units/week; daily use of NSAIDS (including salsalate) for arthritis; use of uricosuric agents; chronic, severe tinnitus; urine albumin-to-creatinine ratio above 300 mcg albumin/mg creatinine; history of significant chronic rheumatologic or other chronic inflammatory disease.

Low dose (81-325 mg) aspirin use was not a contraindication to enrollment in the trial and continued use was encouraged, unless contra-indicated.

Laboratory Assays run at Boston Heart Diagnostics

The following assays were run at Boston Heart Diagnostics, in the CAP-accredited, CLIA-certified clinical laboratory in Framingham, Massachusetts, all using automated, standardized, high throughput methods with coefficient of variation below 5%. Lipids were all measured using enzymatic colormetric assay; lipoprotein A, apolipoprotein B, high sensitivity CRP, fibrinogen,

using immunoturbimetric assays; adiponectin using immunoassay-competitive principle. Insulin was measured using immunoassays; myeloperoxidase was measured using one-step enzyme immunoassay; and serum amyloid A was measured using a nephelometer and latex kits from Siemens Healthcare Diagnostics, Inc. (Newark, DE).

Image acquisition and reconstruction

Imaging was performed at a single site using a 320-row detector scanner (Aquilion-ONE, Toshiba Medical Systems, Otawara, Japan) with x-ray tube focal spot size 1.4 x 1.6 mm, gantry rotation time 350 milliseconds, and temporal resolution 175 milliseconds for half-scan reconstructions with a spatial resolution of $0.45mm^3$. Metoprolol was administered orally for heart rate control 1-2 hours prior to imaging, and intravenously as needed in 5mg doses (up to three) at 15-minute intervals for heart rate <65 beats-per-minute. Sublingual nitroglycerin was given five minutes before coronary MDCTA.

Coronary artery calcium (CAC) images were acquired using unenhanced prospective ECG triggering at 120kVp and 300mA, with scanned volume starting 1.5cm below the carina through the base of the heart. Images were reconstructed using a sharp kernel (FC5, Toshiba) into 3mm slices with 0.5mm overlap.

Coronary MDCTA was performed with prospective ECG gating and intravenous administration of 90-100ml of iohexol (Omnipaque-350, GE Healthcare, Princeton, NJ) at 5ml/s, during a breath hold. Image acquisition was triggered at a threshold of 280HU in the descending aorta, with tube voltage 120kVp, and current 400-580mA, adjusted according to the participant's BMI. The heart was scanned from 15mm above the left main coronary artery to 15mm below the heart's

base. For heart-rate above 65 beats-per-minute acquisition exposure time was adjusted from 166ms to 266ms. MDCTA data was reconstructed at 60-85% of the R-R interval at 5% intervals, with slice thickness of 0.5mm at 0.25mm intervals.

Calculations

Estimated creatinine clearance (CrCL) calculated using Cockcroft-Gault (CG) (eCrCLCG (ml/min)) = [(140 – age) x weight (kg)]/[SCr(mg/dl) x 72] x [0.85 if female]) [19].

Estimated glomerular filtration rate (eGFR):

The CKD-EPI creatinine equation [20] calculated by $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [× 1.018 if female] [× 1.159 if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of Scr/κ or 1, and max is the maximum of Scr/κ or 1 .

Serious Adverse Event Definition

Adverse events were defined as serious if they resulted death, were life-threatening, required hospitalization (initial or prolonged), resulted in disability or permanent damage, a congenital anomaly or birth defect, or required intervention to prevent permanent impairment or damage, or other important medical event that might jeopardize the patient (http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm, accessed August 1, 2015).

Trial modifications

Two changes occurred in May, 2009, after trial commencement. The original trial was designed with three arms comparing salsalate, placebo, and a lifestyle intervention. The lifestyle

intervention was separated into a unique trial (ClinicalTrials.gov Identifier:NCT01624727) due to enrollment challenges and the primary analysis plan was changed from total non-calcified plaque per-patient to a per-segment plaque analysis. The per-segment plaque analysis was chosen because of extensive coronary calcification present in most study subjects precluded evaluation of many segments, as heavily calcified segments result in significant image artifact and segments with 'calcium bloom' type artifact were pre-specified to be excluded. Therefore analysis was restricted to those coronary segments that could be reliably analyzed in accordance with the original MDCTA analysis plan and additional data that plaque dynamics are influenced by factors which vary by location[21-23].

Role of the funding source

Funding was from the National Heart, Lung, and Blood Institute of the National Institutes of Health. Caraco Pharmaceutical Laboratories (Detroit, Michigan) initially donated drug, which was switched in 2012 to Amneal Pharmaceuticals (Hauppauge, NY) due to limitations of product supply. Specialized assays were performed by Boston Heart Diagnostics (Framingham, MA). No private company had roles in trial design, conduct, data analysis, or manuscript preparation.

Additional Analyses and Results

Four additional analyses were performed. The first was a plaque-length adjusted analysis where all components of plaque volume were divided by segment length to determine plaque density by component. The second was a per-subject analysis instead of per-segment. The third was a per-protocol analysis for those adhering to >3.0 g/d for over 80% of the study duration, which included 144 participants. These included 62 out of the 84 participants (73.8%) whose final images were analyzed in the salsalate treated group and 82 out of the 90 participants (91.1%) in the placebo group. Similar to the primary results, there was no difference in change in total

non-calcified plaque volume or the fatty or fibrous components between salsalate and placebo in any of these sensitivity analyses (**Supplemental Tables-2-4**). Finally, as diabetes is associated with more inflammation and salsalate improves glycemia in patients with diabetes,[24,25] analysis was performed within the subgroup of subjects with diabetes. Again, there was no difference in change in plaque components between treatment groups (**Supplemental Table-5**).

Handling of Missing Data – Sensitivity Analyses

Assessment of the primary endpoint of this trial involved completion and analysis of coronary MDCTA at baseline and 30 months. Because there were no interim assessments of the primary endpoint, any participant who either did not complete the study or had MDCTA data that was not adequate for analysis resulted in missing data.

We performed a sensitivity analysis on the effect of missing data using data from all 257 randomized study subjects. We used the Markov chain Monte Carlo method to perform multiple imputation (5 imputations) and calculated revised parameter estimates and P-values based on the imputed data. This analysis showed no impactful difference from our analysis without missing data. Our primary analysis without imputing the missing data calculated a difference in non-calcified plaque in the two study arms of -0.84 (95% CI -11.1 to 9.4, P=0.872); the estimate with imputed values was -0.74 (95% CI -11.4 to 10.0, P=0.890).

To determine how different the missing data would need to be from the non-missing data to result in a statistically significant different result, we repeated the analysis assuming 0.5, 0.75 and 1 standard deviation unit increases in non-calcified plaque in the placebo group, and assuming 0.5, 0.75, and 1 standard deviation unit decreases in non-calcified plaque in the salsalate-assigned treatment group **(Supplemental Table 6)**. These analyses show that there

would need to be at least a 0.75 standard deviation unit shift to approach statistical significance.

Such a large difference from the non-missing data is implausible.

Post Hoc Analysis of Trial Power:

A *post hoc* analysis was performed to evaluate the power of the trial. The observed difference in non-calcified plaque volume between treatment groups was 0.8mm^3 with a pooled standard deviation of 53.8mm^3. Based on these results and assuming a variance inflation factor of 1.06, this trial had 80% power to detect a 12.1mm^3 difference (6% of 210mm^3, the average baseline non-calcified plaque volume) with a 0.05 type-1 error. The power to detect an 8.4mm^3 difference (4% change from baseline value, the *a priori* meaningful change) was 50%. The number of subjects randomized in a 1:1 ratio required to have a 80%power to detect the observed difference of 0.8mm^3 would be 150,509.

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eAppendix 2. Additional TINSAL-CVD Study Team in Alphabetical Order Providing Current

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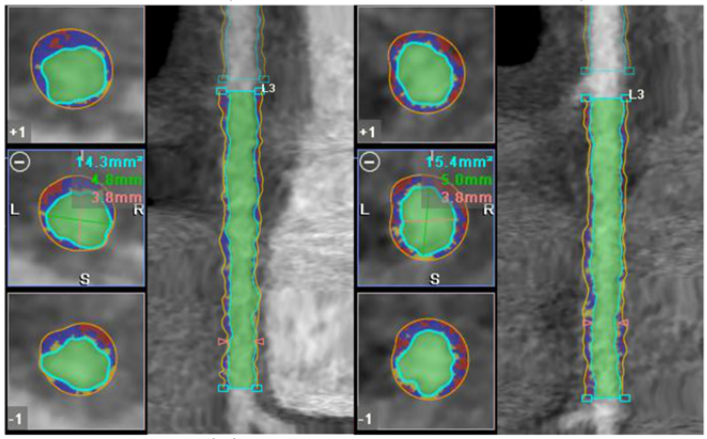
eFigure. Coronary Artery Segment Plaque Assessment Demonstrating [A] Progression and [B] Regression Over 30-Months

A. Coronary Artery Segment with Plaque Progression

Baseline	
Length (mm)	47.6
Diameter stenosis (%)	29
Total plaque volume (mm^3)	528
Fatty plaque volume (mm^3)	142
Fibrous plaque volume (mm^3)	301
Calcified plaque volume (mm^3)	85

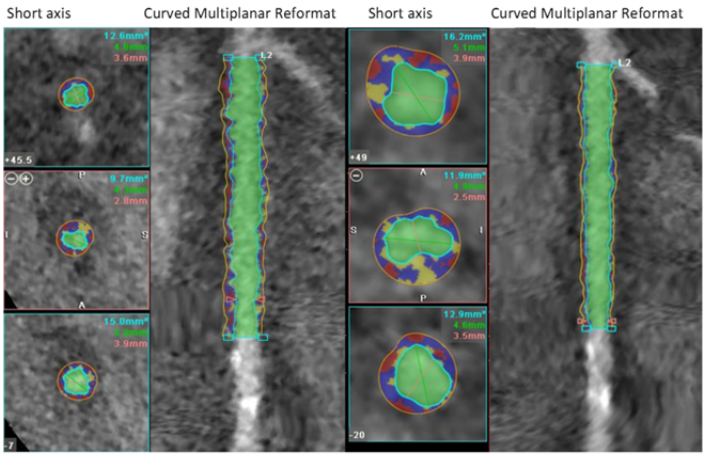
End of Study	
Length (mm)	47.6
Diameter stenosis (%)	28
Total plaque volume (mm^3)	658
Fatty plaque volume (mm^3)	191
Fibrous plaque volume (mm^3)	311
Calcified plaque volume (mm^3)	157



B. Coronary Artery Segment with Plaque Regression

Baseline	
Length (mm)	51.2
Diameter stenosis (%)	26
Total plaque volume (mm^3)	840
Fatty plaque volume (mm^3)	274
Fibrous plaque volume (mm^3)	403
Calcified plaque volume (mm^3)	162

End of Study	
Length (mm)	51.3
Diameter stenosis (%)	28
Total plaque volume (mm^3)	532
Fatty plaque volume (mm^3)	203
Fibrous plaque volume (mm^3)	292
Calcified plaque volume (mm^3)	37



eTable 1. Primary Endpoint Plaque Volume in Salsalate Versus Placebo Results for the Intention to Treat (ITT) Population (Per Plaque Analysis)

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Non-calcified	213 ± 150	0 (-7, 7)	206 ± 147	0 (-8, 7)	-1 (-11, 9)	0.87
Fatty	80 ± 56	1 (-2, 4)	75 ± 52	0 (-3, 4)	0 (-5, 4)	0.88
Fibrous	134 ± 97	0 (-5, 4)	132 ± 98	-1 (-6, 4)	-1 (-7, 6)	0.84
Calcified	35 ± 44	13 (8, 18)	40 ± 49	8 (2,13)	-5 (-13, 2)	0.17
Total	248 ± 177	13 (4, 22)	246 ± 181	7 (-2, 16)	-6 (-19, 7)	0.35

eTable 2. Secondary Analysis Plaque Density in Salsalate Versus Placebo Results for the Intention to Treat (ITT) Population (Per Plaque Analysis)

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Non-calcified	7.4 ± 2.8	-0.1 (-0.3,0.2)	7.7 ± 3.1	-0.1 (-0.4, 0.1)	-0.1 (-0.5,0.3)	0.66
Fatty	2.7 ± 1.0	0.0 (-0.1, 0.1)	2.8 ± 1.1	-0.0 (-0.1, 0.1)	-0.0 (-0.2, 0.1)	0.73
Fibrous	4.7 ± 1.9	-0.1 (-0.2,0.1)	4.9 ± 2.2	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.2)	0.66
Calcified	1.4 ± 1.7	0.4 (0.2, 0.6)	1.6 ± 1.8	0.3 (0.1, 0.5)	-0.1 (-0.4, 0.1)	0.30
Total	8.8 ± 3.9	0.4 (0.1, 0.7)	9.3 ± 4.4	0.2 (-0.2, 0.5)	-0.2 (-0.7, 0.2)	0.32

Plaque density is calculated from plaque volume corrected for plaque length.

eTable 3. Plaque Volume and Plaque Density in Salsalate Versus Placebo Results for the Intention to Treat (ITT) Population (Per Subject Analysis)

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Plaque Volume						
Non-calcified	822 ± 578	0 (-29, 28)	781 ± 469	-3 (-32, 26)	-3 (-43, 38)	0.90
Fatty	307 ± 209	3 (-10, 16)	283 ± 164	2 (-11, 16)	-1 (-20, 18)	0.93
Fibrous	516 ± 372	-3 (-21, 14)	498 ± 312	-5 (-24, 13)	-2 (-27, 24)	0.88
Calcified	134 ± 122	50 (28, 71)	151 ± 137	26 (4, 49)	-23 (-54, 8)	0.14
Total	956 ± 674	48 (13, 84)	932 ± 577	24 (-12, 60)	-24 (-75, 26)	0.35
Plaque Density						
Non-calcified	7.2 ± 1.7	-0.0 (-0.3, 0.2)	7.7 ± 2.3	-0.1 (-0.4, 0.1)	-0.1 (-0.4, 0.3)	0.67
Fatty	2.7 ± 0.7	0.0 (-0.1, 0.1)	2.8 ± 0.8	0.0 (-0.1,0.1)	-0.0 (-0.2, 0.2)	0.90
Fibrous	4.5 ± 1.2	0.0 (-0.2, 0.1)	4.9 ± 1.7	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.2)	0.57
Calcified	1.2 ± 1.1	0.5 (0.3, 0.7)	1.5 ± 1.2	0.3 (0.1, 0.5)	-0.2 (-0.5, 0.1)	0.19
Total	8.4 ± 2.5	0.5 (0.2, 0.8)	9.2 ± 3.3	0.2 (-0.1, 0.5)	-0.3 (-0.7, 0.2)	0.25

Sum of all plaques within an individual participant.

eTable 4. Plaque Volume and Plaque Density in Salsalate Versus Placebo Results for the Per Protocol Analyses

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Plaque Volume (Per Plaque Analysis)						
Non-calcified	219 ± 156	0 (-8, 8)	216 ± 153	-3 (-12, 6)	-3 (-15, 9)	0.64
Fatty	81 ± 58	1 (-3, 4)	77 ± 54	0 (-4, 4)	-1 (-6, 4)	0.72
Fibrous	138 ± 100	-1 (-6, 4)	138 ± 102	-2 (-8, 3)	-2 (-9, 6)	0.62
Calcified	36 ± 45	13 (7, 19)	43 ± 52	8 (1,14)	-6 (-15, 3)	0.21
Total	255 ± 183	14 (4, 23)	259 ± 191	5 (-6, 16)	-8 (-23, 6)	0.25
Remodeling Index	78 ± 20	-1 (-4, 2)	77 ± 22	0 (-4, 3)	1 (-4, 5)	0.75
Stenosis	33 ± 18	-1, (-4,1)	32 ± 17	1 (-2, 4)	3 (-1, 7)	0.19
Plaque Density (Per Plaque Analysis)						
Non-calcified	7.4 ± 2.8	-0.0 (-0.3, 0.2)	8.0 ± 3.2	-0.2 (-0.5, 0.1)	-0.2 (-0.6, 0.3)	0.42
Fatty	2.7 ± 1.0	0.0 (-0.1, 0.1)	2.8 ± 1.1	-0.1 (-0.2, 0.1)	-0.1 (-0.3, 0.1)	0.42
Fibrous	4.7 ± 1.9	-0.1 (-0.2, 0.1)	5.1 ± 2.3	-0.2 (-0.4, 0.1)	-0.1 (-0.4, 0.2)	0.48
Calcified	1.4 ± 1.7	0.5 (0.2, 0.7)	1.8 ± 2.0	0.3 (0.1, 0.5)	-0.1 (-0.5, 0.2)	0.37
Total	8.8 ± 3.9	0.4 (0.1, 0.7)	9.8 ± 4.6	0.1 (-0.3, 0.5)	-0.3 (-0.8, 0.2)	0.22
Plaque Volume (Per Subject Analysis)						
Non-calcified	831 ± 589	0 (-31, 31)	817 ± 488	-10 (-46, 26)	-10 (-57, 38)	0.69
Fatty	309 ± 214	3 (-11, 17)	292 ± 166	1 (-15, 17)	-2 (-24, 20)	0.85
Fibrous	523 ± 379	-3 (-23, 16)	525 ± 328	-11 (-33, 11)	-8 (-37, 22)	0.62

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Calcified	137 ± 127	52 (28, 76)	165 ± 147	30 (3, 58)	-21 (-58, 15)	0.25
Total	968 ± 689	51 (13, 89)	982 ± 606	20 (-24, 64)	-31 (-89, 26)	0.28
Plaque Density (Per Subject Analysis)						
Non-calcified	7.2 ± 1.7	-0.0 (-0.3, 0.2)	8.0 ± 2.4	-0.2 (-0.5, 0.1)	-0.2 (-0.6, 0.2)	0.39
Fatty	2.7 ± 0.7	0.0 (-0.1, 0.1)	2.8 ± 0.8	-0.1 (-0.2, 0.1)	-0.1 (-0.2, 0.1)	0.61
Fibrous	4.5 ± 1.2	-0.0 (-0.2, 0.2)	5.1 ± 1.8	-0.2 (-0.4, 0.1)	-0.1 (-0.4, 0.1)	0.36
Calcified	1.2 ± 1.1	0.5 (0.3, 0.7)	1.7 ± 1.3	0.3 (0.1, 0.6)	-0.2 (-0.5, 0.1)	0.24
Total	8.5 ± 2.5	0.5 (0.1, 0.8)	9.6 ± 3.5	0.1 (-0.3, 0.5)	-0.4 (-0.9, 0.2)	0.16

The per protocol analysis was performed on all participants taking 3.0 g/d of salsalate or identical placebo for over 80% of the study duration.

eTable 5. Plaque Volume and Plaque Density in Salsalate Versus Placebo Results for the Participants With Type 2 Diabetes

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Plaque Volume (Per Plaque Analysis)						
Non-calcified	196 ± 117	3 (-9, 15)	228 ± 140	-3 (-16, 11)	-6 (-24, 13)	0.55
Fatty	76 ± 46	2 (-3, 8)	84 ± 51	-2 (-8, 4)	-4 (-13, 4)	0.31
Fibrous	121 ± 73	1 (-7, 8)	144 ± 92	0 (-9, 9)	-1 (-13, 11)	0.89
Calcified	34 ± 41	10 (1, 20)	41 ± 43	4 (-7, 15)	-6 (-20, 8)	0.37
Total	231 ± 144	14 (-2, 30)	269 ± 164	1 (-17, 20)	-13 (-37, 12)	0.30
Remodeling Index	82 ± 19	-6 (-12, 1)	75 ± 22	0 (-8, 7)	5 (-4, 15)	0.27
Stenosis	30 ± 15	3 (-3, 9)	32 ± 18	3 (-4, 10)	0 (-9, 10)	0.97
Plaque Density (Per Plaque Analysis)						
Non-calcified	7.6 ± 2.5	-0.1 (-0.6, 0.4)	8.5 ± 3.7	-0.3 (-0.8, 0.3)	-0.2 (-0.9, 0.6)	0.64
Fatty	2.9 ± 0.9	0.0 (-0.2, 0.2)	3.1 ± 1.2	-0.1 (-0.9, 0.1)	-0.2 (-0.5, 0.2)	0.33
Fibrous	4.7 ± 1.8	-0.1 (-0.4, 0.2)	5.4 ± 2.6	-0.1 (-0.5, 0.2)	0.0 (-0.5, 0.5)	0.98
Calcified	1.5 ± 1.9	0.4 (-0.0, 0.7)	1.9 ± 2.1	0.2 (-0.3, 0.6)	-0.2 (-0.7, 0.4)	0.50
Total	9.1 ± 4.0	0.3 (-0.3, 0.8)	10.4 ± 5.4	-0.1 (-0.8, 0.6)	-0.4 (-1.2, 0.5)	0.44
Plaque Volume (Per Subject Analysis)						
Non-calcified	652 ± 447	10 (-36, 56)	851 ± 378	-9 (-65, 47)	-19 (-92, 55)	0.61
Fatty	252 ± 167	7 (-13, 56)	315 ± 119	-8 (-32, 17)	-15 9-47, 17)	0.34
Fibrous	400 ± 283	2 (-27, 32)	536 ± 263	-1 (-37, 35)	-3 (-50, 44)	0.89

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline ± SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Calcified	113 ± 75	33 (2, 64)	154 ± 112	18 (-20, 56)	-15 (-65, 34)	0.53
Total	765 ± 549	43 (-15, 100)	1005 ± 474	9 (-61, 79)	-34 (-125, 58)	0.46
Plaque Density (Per Subject Analysis)						
Non-calcified	7.2 ± 1.8	0.1 (-0.4, 0.5)	8.4 ± 2.7	-0.2 (-0.7, 0.4)	-0.2 (-0.9, 0.5)	0.55
Fatty	2.8 ± 0.6	0.1 (-0.1, 0.3)	3.1 ± 0.8	-0.1 (-0.4, 0.1)	-0.2 (-0.5, 0.1)	0.20
Fibrous	4.4 ± 1.3	-0.0 (-0.3, 0.3)	5.3 ± 1.9	-0.0 (-0.4, 0.3)	-0.0 (-0.5, 0.5)	0.98
Calcified	1.4 ± 1.8	0.5 (0.1, 0.9)	1.6 ± 1.2	0.2 (-0.3, 0.7)	-0.3 (-0.9, 0.3)	0.28
Total	8.6 ± 3.3	0.6 (-0.0, 1.2)	10.0 ± 3.8	0.0 (-0.7, 0.7)	-0.5 (-1.4, 0.4)	0.24

eTable 6. Sensitivity Analyses Using Markov Chain Monte Carlo Method

Imputations using Markov chain Monte Carlo	Estimate of the effect of treatment group (95% CI)	P-value
Missing Placebo - Units of standard deviation added to missing data		
+ 0.50 SD	7.38 (-4.720, 19.40)	0.224
+ 0.75 SD	12.09 (-0.17, 24.36)	0.053
+ 1.00 SD	13.52 (1.83, 25.22)	0.024
Missing Salsalate - Units of standard deviation subtracted from missing data		
- 0.50 SD	7.99 (-4.63, 20.62)	0.203
- 0.75 SD	11.51 (1.71, 21.31)	0.021
- 1.00 SD	17.66 (6.76, 28.57)	0.002

Note: Outcome was change in segment plaque volume and explanatory variables included baseline segment plaque volume and treatment group. Diabetes status was used as random effect and randomization was stratified on this variable. Auto-regressive covariance structure was used.

eTable 7. Baseline and Change From Baseline of Clinical and Laboratory Parameters by Treatment Group (SI Units)

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline±SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline±SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Clinical Parameters						
Body Mass Index (BMI) (kg/m^2)	31.4±2.9	0.1 (-0.1, 0.3)	31.7±3.1	0.2 (0.0, 0.5)	0.1(-0.2, 0.5)	0.46
Systolic Blood Pressure (mmHg)	129.6±13.0	2.8 (0.8, 4.8)	125.7±12.3	3.0 (0.9, 5.1)	0.2 (-2.7, 3.2)	0.88
Diastolic Blood Pressure (mmHg)	75.0±8.0	-0.5 (-1.6, 0.6)	74.2±7.9	-1.4 (-2.5,-0.2)	-0.9 (-2.4, 0.7)	0.29
Chemistry Profile						
Sodium (mmol/L)	139.1±2.1	0.6 (0.4, 0.9)	139.1±2.4	1.8 (1.5, 2.0)	1.1 (0.8, 1.5)	<.0001
Potassium (mmol/L)	4.3±0.4	0.2 (0.1, 0.2)	4.3±0.4	0.1 (0.1, 0.1)	-0.1 (-0.1, 0.0)	0.03
Chloride (mmol/L)	103.8±2.6	0.4 (0.1, 0.7)	103.5±2.5	0.9 (0.7, 1.2)	0.5 (0.2, 0.9)	0.005
Bicarbonate (mmol/L)	24.8±2.3	0.9 (0.7, 1.2)	25.1±2.3	0.5 (0.3, 0.8)	-0.4 (-0.7, 0.0)	0.03
Anion Gap (mmol/L)	24.0±8.2	-0.7 (-0.9, -0.5)	24.7±8.8	0.3 (0.1, 0.5)	1.0 (0.7, 1.3)	<.0001
Albumin (g/L)	44.1±2.7	0.4 (0.1, 0.6)	43.8±2.0	-1.1 (-1.4, -0.9)	-1.5 (-1.9, -1.2)	<.0001
AST* (U/L)	24.0±8.2	-0.9 (-1.7, -0.1)	24.7±8.8	0.8 (-0.1, 1.7)	1.8 (0.5, 3.2)	0.01
ALT* (U/L)	26.4±11.5	-0.6 (-1.6, 0.4)	27.1±11.9	-1.1 (-2.1, -0.1)	-0.5 (-2.0,1.0)	0.48
Alkaline Phosphatase (U/L)	65.1±18.6	-0.3 (-1.7, 1.2)	65.0±16.2	-1.4 (-2.9, 0.1)	-1.1 (-3.2, 0.9)	0.28
Total Bilirubin* (µmol/L)	12.6±5.4	-0.9 (-1.3, 0.4)	12.5±5.3	-3.2 (-3.6, -2.9)	-2.6 (-3.1, -2.1)	<.0001
Blood Urea Nitrogen (mmol/L)	6.2±1.7	0.2 (0.0, 0.3)	6.5±1.6	0.1 (0.0, 0.3)	-0.1 (-0.3, 0.2)	0.67
Uric Acid (µmol/L)	386.2±79.9	-2.1 (-14.4, 10.2)	369.1±80.9	-99.4 (-112.0, -86.8)	-97.3 (-114.9, -79.6)	<.0001
Markers of Glycemia						
Glucose (mmol/L)	5.7±1.7	0.0 (-0.1, 0.1)	5.7±1.2	-0.4(-0.5, -0.3)	-0.3 (-0.5, -0.2)	<.0001

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline±SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline±SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Hemoglobin A1c (mmol/mol)[†]	43±9.0	-0.2 (-1.2, 0.8)	42±6.7	-0.4 (-1.6, 0.7)	-0.2 (-1.7, 1.2)	0.73
Adiponectin* (ug/mL)	6.6 ± 3.2	0.3 (0.0, 0.6)	6.8±3.8	1.9 (1.4, 2.3)	1.5 (0.9, 2.1)	<.0001
Insulin* (pmol/L)	113.8±72.1	5.4 (-4.4, 16.0)	116.3±88.0	20.9 (8.9, 34.0)	14.7 (-0.8, 32.2)	0.06
Renal						
Serum Creatinine* (µmol/L)	86.2±16.6	4.3 (3.0, 5.7)	82.2±14.5	6.6 (5.3, 7.9)	2.3 (0.6, 4.2)	0.01
eGFR (CKD-EPI)* (ml/min/1.73m^2)	83.45±15.06	-2.1 (-3.4, -0.8)	85.63±12.50	-2.0 (-3.3, -0.8)	0.0 (-1.8, 1.9)	0.98
Urine Microalbumin/Creatinine Ratio* (u/dL)	10.4±16.9	-1.8 (-3.0, -0.3)	13.4±33.5	13.4 (9.4, 18.1)	18.9 (12.5, 26.8)	<.0001
Complete Blood Count						
Total White Blood Cells (10^9/L)	6.7±1.8	-0.1 (-0.3, 0.1)	6.5±1.6	-0.7 (-0.9, -0.5)	-0.6 (-0.9, -0.4)	<.0001
Hemoglobin (g/L)	147.6±11.5	-2.5(-3.7, -1.3)	148.8±10.2	-0.1 (-1.3, 1.1)	2.4 (0.7, 4.1)	0.01
Hematocrit (Proportion of 1.0)	0.438±0.033	-0.005 (-0.008, -0.001)	0.441±0.030	0.003 (0.000, 0.007)	0.008 (0.003, 0.013)	0.002
Absolute Neutrophils (cells/uL)	4107.0±1275.9	-28.0 (-152.4, 96.4)	4063.5±1187.9	-336.0 (-467.9, -204.1)	-308.0 (-489.4, -126.6)	0.001
Absolute Lymphocytes (cells/uL)	1835.0±730.6	-52.7 (-156.8, 51.5)	1704.9±544.9	-305.0 (-414.9, -195.1)	-252.3 (-404.1, -100.6)	0.001
Absolute Monocytes (cells/uL)	521.4±145.5	-15.3 (-29.4, -1.1)	515.8±152.7	-37.7 (-52.5, -22.9)	-22.5 (-42.9, -2.0)	0.03
Lipids						
Apolipoprotein B (g/L)	0.77±0.21	0.02 (0.00, 0.05)	0.78±0.17	0.05 (0.02, 0.07)	0.02 (-0.01, 0.06)	0.21
Total Cholesterol (mmol/L)	3.8±0.8	0.1 (0.0, 0.1)	3.9±0.7	0.1 (0.0, 0.2)	0.1 (-0.1, 0.2)	0.24
HDL Cholesterol (mmol/L)	1.06±0.31	0.03 (0.00, 0.06)	1.07±0.30	0.02 (-0.01, 0.05)	-0.01 (-0.05, 0.03)	0.70
LDL Cholesterol (mmol/L)	2.12±0.67	0.01 (-0.08, 0.09)	2.17±0.51	0.12 (0.03, 0.21)	0.11 (-0.01, 0.23)	0.07
Lipoprotein A* (g/L)	0.38±0.35	0.00 (-0.01, 0.02)	0.37±0.34	0.01 (0.00, 0.03)	0.01 (-0.01, 0.03)	0.33
Triglycerides* (mmol/L)	1.61±0.82	-0.03 (-0.12, 0.07)	1.54±0.74	-0.17 (-0.26, -0.08)	-0.15 (-0.27, -0.02)	0.03

	Placebo		Salsalate		Difference in Mean Change	
Variable	**Mean value at Baseline±SD**	**Mean change from Baseline (95%CI)**	**Mean value at Baseline±SD**	**Mean change from Baseline (95%CI)**	**Difference in the mean change (95%CI)**	**P value for difference in the mean change**
Markers of Inflammation						
High-sensitivity C-reactive protein* (mg/L)	2.0±3.8	-0.1 (-0.4, 0.1)	2.2±3.7	-0.1 (-0.4, 0.2)	0.0 (-0.3, 0.5)	0.84
Fibrinogen (µmol/L)	13.1±3.9	-0.3 (-0.8, 0.2)	12.5±3.2	-0.8 (-1.4, -0.3)	-0.5 (-1.3, 0.2)	0.15
Myeloperoxidase* (pmol/L)	515.4 ± 566.1	-81.8 (-119.0, -41.2)	526.8 ± 605.8	-78.4 (-118.9, -33.8)	6.3 (-58.9, 80.6)	0.86
Serum Amyloid A* (mg/L)	6.5 ± 8.1	-0.4 (-0.8, 0.2)	7.7 ± 15.4	-0.5 (-1.1, 0.2)	0.0 (-0.9, 0.9)	0.94

**Log transformed*

† *Diabetes status used as fixed effect with no random effects*

eTable 8. Serious Adverse Events Occurring After Randomization by Treatment Assignment

	Total	Salsalate		Placebo	
Body System	**Number of Events**	**Number of events**	**Number of participants**	**Number of events**	**Number of participants**
Cardiac (total)	33	15	13	18	19
Ischemia	22	12	10	10	9
Arrhythmia: Atrial	4	1	1	3	2
Arrhythmia: Ventricular	1	0	0	1	1
Atrial-Ventricular Block	3	1	1	2	2
Congestive Heart Failure	1	0	0	1	1
Endocarditis	1	1	1	0	0
ICD Lead Revision	1	0	0	1	1
Atypical chest pain/unclear etiology	8	2	2	6	6
Vascular *	5	3	3	2	2
Pulmonary	5	2	2	3	3
Musculoskeletal	9	5	5	4	4
Gastrointestinal	11	4	4	7	6
Hepatobiliary	2	1	1	1	1
Genitourinary (total)	5	5	5	0	0
Nephrolithiasis	2	2	2	0	0
Elevated Urinary Albumin	1	1	1	0	0
Kidney Failure	1	1	1	0	0
Urinary Tract Infection	1	1	1	0	0
Infections	5	3	3	2	1
Neoplasms	3	1	1	2	2
Dermatologic	1	1	1	0	0
General Etiology †	5	3	3	2	2
Total Events	**92***	**45**		**47**	
Total Unique Participants			**33**		**32**

* Vascular events were DVT with or without pulmonary emboli, or pulmonary embolism secondary to atrial fibrillation (which occurred in the Placebo group).

† General Etiology events include dizziness (2), syncopal episodes (2), and weakness (1), all of which were resolved without specific intervention. Abbreviations: Implantable cardioverter-defibrillator (ICD).

eTable 9. Cardiac Events by Treatment Assignment

	Total		Salsalate		Placebo	
Cardiac Event/Procedure*	**Number of Events**	**Number of Participants†**	**Number of Events**	**Number of Participants**	**Number of Events**	**Number of Participants†**
Atrial Arrhythmia	19	12	12	10	7	2
Myocardial Infarction	2	2	2	2	0	0
Cardiac Catheterization	32	27	14	12	18	15
Revascularization	21	18	12	10	9	8
PCI	*16*	*13*	*9*	*7*	*7*	*6*
CABG	*5*	*5*	*3*	*3*	*2*	*2*
No intervention	11	10	2	2	9	8
Device Implantation	3	3	1	1	2	2
Cardioversion	2	2	0	0	2	2
Ischemic CVA	1	1	1	1	0	0
Death	0	0	0	0	0	0
Total	**59**		**30**		**29**	
Total unique participants		**41**		**22**		**19**

*Includes serious and non-serious adverse events.

†The number of participants is the number of unique participants per category.

Abbreviations: Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG), Cerebrovascular Accident (CVA)

eTable 10. Adverse Events Reported by 5% of Total Cohort and Numerically More in Salsalate Than Placebo Treated Group

	Total		Salsalate		Placebo	
Event	**Number of Events**	**Number of Participants**	**Number of Events**	**Number of Participants**	**Number of Events**	**Number of Participants**
Tinnitus	53	48	39	35	14	13
Dizziness	31	30	18	17	13	13
Constipation	25	24	16	15	9	9
Depressive disorder	28	28	16	16	12	12
Upper Respiratory Infection	158	118	90	64	68	54
Dyspnea on exertion	36	36	21	21	15	15
Mouth sores	21	21	13	13	8	8