Original Investigation

Effect of Targeting Inflammation With Salsalate
The TINSAL-CVD Randomized Clinical Trial on Progression of Coronary Plaque in Overweight and Obese Patients Using Statins

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IMPORTANCE Inflammation may contribute to pathological associations among obesity, diabetes mellitus, and cardiovascular disease.

OBJECTIVE To determine whether targeting inflammation using salsalate compared with placebo reduces progression of noncalcified coronary artery plaque.

DESIGN, SETTING, AND PARTICIPANTS In the Targeting Inflammation Using Salsalate in Cardiovascular Disease (TINSAL-CVD) trial participants were randomly assigned between September 23, 2008, and July 5, 2012, to 30 months of salsalate or placebo in addition to standard, guideline-based therapies. Randomization was computerized and centrally allocated, with patients, health care professionals, and researchers masked to treatment assignment. Participants were overweight and obese statin-using patients with established, stable coronary heart disease.

INTERVENTIONS Salsalate (3.5 g/d) or placebo orally over 30 months.

MAIN OUTCOMES AND MEASURES The primary outcome was progression of noncalcified coronary artery plaque assessed by multidetector computed tomographic angiography. Secondary outcomes were other measures of safety and efficacy.

RESULTS Two hundred fifty-seven participants were randomized to salsalate (n = 129) or placebo (n = 128). Their mean (SD) age was 60.8 (7.0) years, and 94.0% (236 of 251) were male. One hundred ninety participants (89 in the salsalate group and 101 in the placebo group) completed the study. Compared with baseline, there was no increase in noncalcified plaque volume in the placebo-treated patients and no difference in change between the salsalate and placebo groups (mean difference, −1 mm^3; 95% CI, −11 to 9 mm^3; $P = .87$). Salsalate treatment decreased total white blood cell, lymphocyte, monocyte, and neutrophil counts and increased adiponectin levels without change in C-reactive protein levels. Fasting glucose, triglycerides, uric acid, and bilirubin levels were decreased in the salsalate group compared with the placebo group, while hemoglobin levels were increased. Urinary albumin levels increased, with tinnitus and atrial arrhythmias more common, in the salsalate group compared with the placebo group.

CONCLUSIONS AND RELEVANCE Salsalate when added to current therapies that include a statin does not reduce progression of noncalcified coronary plaque volume assessed by multidetector computed tomographic angiography in statin-using patients with established, stable coronary heart disease. The absence of progression of noncalcified plaque volume in the placebo group may limit interpretation of the trial results.

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Obesity-related subacute chronic inflammation may contribute to pathogenesis of atherosclerosis, diabetes mellitus, and other metabolic diseases.[1,2] Innate and acquired immune mechanisms participate in inflammatory cell adhesion and movement across endothelium into smooth muscle, formation of fatty streaks, plaque progression, and, ultimately, lesion rupture and thrombosis, resulting in clinical events that include myocardial infarction, stroke, and cardiovascular death. Higher leucocyte counts are associated with increased coronary heart disease (CHD) event rates.[3] Cardiovascular risk associated with increased C-reactive protein (CRP) levels is comparable to that associated with total cholesterol level or blood pressure.[4] Whether anti-inflammatory drugs reduce progression of established coronary artery plaque lesions remains unknown.

Salicylates are among the oldest drugs in clinical practice, treating pain and inflammation using plant extracts dating over 3500 years.[5] Molecular mechanisms and clinical applications are still being identified, but multiple potential pathways for the anti-inflammatory effects of salicylates have been identified.[2,6] Salsalate is a prodrug dimer of salicylates marketed for relief of arthritic pain. Recent studies demonstrate that salsalate improves glycemia and metabolic risk profiles in prediabetes[7,8] and type 2 diabetes mellitus.[6,9] We hypothesized that targeting inflammation using salsalate would reduce progression of coronary atherosclerosis in overweight and obese persons. This hypothesis was tested in Targeting Inflammation Using Salsalate in Cardiovascular Disease (TINSAL-CVD) by evaluating whether salsalate compared with placebo reduces progression of noncalcified coronary artery plaque assessed by multidetector computed tomographic angiography (MDCTA) in patients receiving statins with stable, established CHD.

Key Points

Question Does targeting inflammation using salsalate slow progression of coronary artery plaque over 30 months compared with placebo?

Findings In this randomized clinical trial of overweight and obese patients with established coronary heart disease, salsalate when added to current therapies that include a statin does not reduce progression of noncalcified coronary plaque volume over 30 months compared with placebo. Increases in albuminuria were seen.

Conclusion In overweight and obese patients with established, clinically stable coronary heart disease receiving good medical care that includes statins, noncalcified coronary plaque volume does not change over 30 months and is not altered with salsalate treatment.

Methods

Trial Design and Conduct

The TINSAL-CVD investigation was a double-masked, randomized (1:1), placebo-controlled, parallel clinical trial conducted at Joslin Diabetes Center and Beth Israel Deaconess Medical Center, Boston, Massachusetts, with participation of investigators from 5 academic private cardiology practice sites (H.L.G., Benjamin Lowenstein, MD, Giulia L. Sheftel, MD, Jon Cronin, MD, and Michael Dansinger, MD). The trial was approved by the institutional review board at each institution and by the US Food and Drug Administration (IND75909). Written informed consent was obtained from all participants. The primary hypothesis was that salsalate is superior to placebo over 30 months in slowing progression of noncalcified coronary artery plaque as assessed by MDCTA in patients with stable CHD receiving statins. Secondary outcomes included changes in other cardiometabolic health variables between groups. Enrollment was between September 23, 2008, and July 5, 2012, and the last patient visit occurred December 11, 2014. Randomization was computer allocated in permuted blocks of 8, stratified by the presence or absence of diabetes mellitus. Codes were securely maintained by the website manager (G.M.W.).

The trial protocol (Supplement 1) included a screening visit, pretreatment baseline visit, and on-treatment assessments at 6 weeks and 3, 6, 9, 12, 18, 24, and 30 months, with each visit following an overnight fast. Multidetector computed tomographic angiography was performed before treatment (baseline) and repeated at 30 months (end of treatment). Salsalate was administered at 3.5 g daily or as tolerated, divided into 2 daily doses. Adverse events were assessed by questionnaires at follow-up visits. Clinical laboratory evaluations were performed at Quest Diagnostics (Cambridge, Massachusetts). Participants, investigators, clinical staff, and steering committee members were masked to treatment assignment. Standard-of-care dosing of lipid-lowering, hypertensive, and diabetes medications were at the discretion of health care professionals.

Participants

Eligible participants had stable, established coronary artery disease (including previous myocardial infarction [≥6 months prior], coronary artery bypass surgery [>12 months prior] or angioplasty, stable angina, or evidence of CHD on prior imaging), an abnormal exercise tolerance test result, or ischemia by nuclear imaging, deemed by the patients' clinical cardiologist not to require current intervention by the patient's clinical cardiologist. Additional inclusion criteria were age 21 to 75 years, body mass index (calculated as weight in kilograms divided by height in meters squared) exceeding 27 and less than 35 in women or less than 40 in men, a stable regimen of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor (statin) dosing, and an estimated creatinine clearance (Cockcroft-Gault[10] equation) of at least 60 mL/min/1.73 m^2 (to convert creatinine clearance to milliliters per second per meter squared, multiply by 0.0167). Participants had at least 1 evaluable segment with plaque on baseline MDCTA (eAppendix 1 in Supplement 2 contains the full inclusion and exclusion criteria).

Study Drug

Salsalate (500 mg) and identical placebo tablets were shipped to participants by PBM Plus, Inc (Milford, Ohio). Participants were instructed to take 7 tablets orally each day, divided into 2 doses of 3 tablets and 4 tablets, respectively. Titration downward was permitted to maintain maximal tolerable doses.

Image Acquisition and Reconstruction

Imaging was performed at a single site using a 320-row detector scanner (Aquilion-ONE; Toshiba Medical Systems). Coronary calcium measurement and MDCTA were performed using standard protocols conforming to the manufacturer's recommendations and best practices (eAppendix 1 in Supplement 2 contains image acquisition details and references).

Coronary Segment Plaque Analysis

The Agatston[11] scoring method was used for total calcification measurement (InSight; NeoImagery Technologies). MDCTA images underwent 3-dimensional reconstruction. Multiplanar reconstructed images were used for coronary segment plaque volume analysis (SUREPlaque, version 6.3.2; Vital Images).

Assessment of full interpretable segment lengths rather than discrete plaque measures was performed to permit identification of any new plaque formation that may occur over time. Segments with significant calcification imparting "calcium bloom" artifact, length of 5 mm or less, prior revascularization, motion artifact, or image degradation were excluded. Analysis was performed independently by 2 readers (N.S., M.C., and other TINSAL-CVD study team members). Branches or focal calcification served as definitive reference points to select the exact same segment for a second determination at 30 months (eFigure in Supplement 2). Segment plaque volume and lumen diameter were analyzed using semiautomated software (SUREPlaque, version 6.3.2; Vital Images). Noncalcified plaque within segments was further subclassified based on Hounsfield unit (HU) densities as fatty (−100 to 49 HU), fibrous (50-149 HU), or calcified (150-1300 HU) plaque. Remodeling index was calculated by the ratio of plaque volume at the most diseased site compared with the least diseased site within the 10 mm of vessel proximal to the plaque.

Statistical Analysis

The primary outcome was change in volume of noncalcified plaque at final compared with baseline assessment. Initial sample size was estimated based on MDCTA data showing a mean (SD) 24% (13%) reduction in coronary plaque volume with new statin therapy in 27 patients,[12] the only longitudinal study using MDCTA coronary plaque assessments at the time. We assumed that a 4% reduction in segment plaque volume (one-sixth that for statins) would represent minimal importance. Randomization of 278 participants with 20% dropout would provide 111 individuals per arm for the primary end point. Assuming a mean of 1.7 measurable segments per participant—with a 0.24 intraindividual correlation[13] (providing a variance inflation factor of 1.06 to account for lack of independence within the same individual[14])—would provide 80% power with a type I error of 0.05 to detect a 4% difference in segment plaque volume between groups. Enrollment was stopped after 257 participants were randomized because they had a mean (SD) of 3.8 (1.2) segments per patient. We analyzed data following intent-to-treat principles, with individuals analyzed by assigned treatment regardless of drug adherence. A per-protocol analysis for those adhering to more than 3.0 g/d for more than 80% of the study duration, a sensitivity analysis for missing data, and a post hoc analysis for trial power were also performed. For normally distributed continuous outcomes, including change in segment volume of noncalcified plaque, we estimated the mean group differences using linear mixed models with baseline value, time, and treatment group as fixed effects and diabetes status and intercept as random effects unless otherwise noted. Models evaluating per-individual outcomes and those in the subgroup with diabetes mellitus included only fixed effects. Natural log transformations were used for variables with log-normal distributions. Baseline characteristics are provided as the mean (SD) or median (interquartile range), and changes from baseline are provided with 95% CIs. Statistical tests report 2-sided *P* values, and values less than .05 were considered significant. Analyses were performed using statistical software (SAS, version 9.3; SAS Institute Inc).

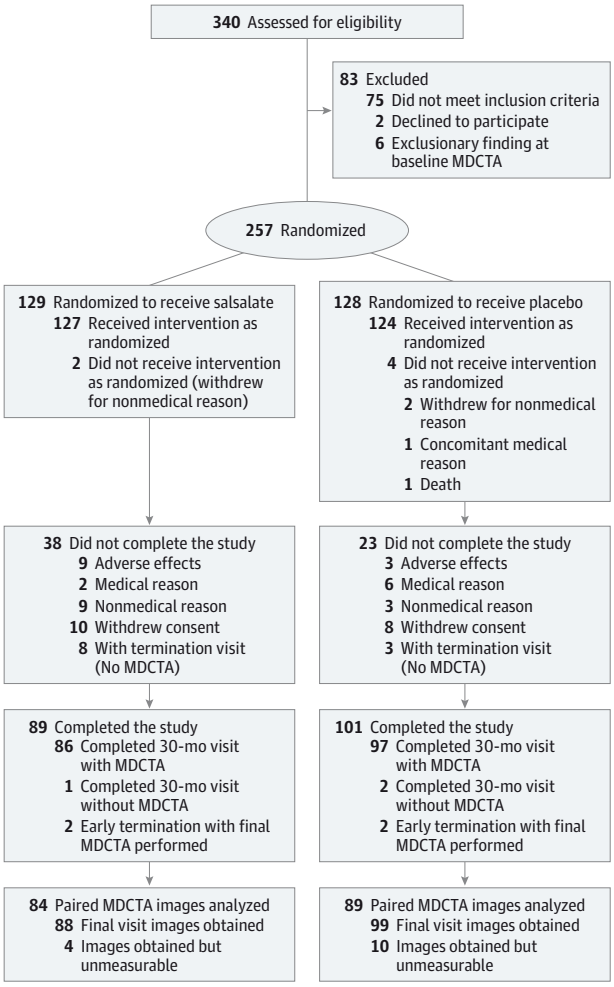
Results

Demography and Study Adherence

Of 340 persons screened, 265 underwent baseline MDCTA evaluation, and 257 with 1 or more evaluable segments were randomly allocated to salsalate (n = 129) or placebo (n = 128). Six participants did not take the study drug (2 in the salsalate group and 4 in the placebo group) (**Figure 1**). Groups were similar in baseline characteristics (**Table 1**). The median coronary calcium score was 542 Agatston units, 62.5% (157 of 251) had prior myocardial infarction, 67.3% (169 of 251) had coronary stenting, 23.1% (58 of 251) had previous coronary artery bypass surgery, 23.5% (59 of 251) had type 2 diabetes mellitus, and 98.8% (248 of 251) were using statins (mean [SD] duration of statin use, 5.8 [5.5] years). One hundred ninety participants completed the study, and 173 (84 in the salsalate group and 89 in the placebo group) with at least 1 segment evaluable at baseline and end-of-study MDCTA were included in the analysis for the primary end point. Safety findings were reported for all participants. Withdrawals after randomization, with reasons, are summarized in Figure 1. Two participants in each group had early termination, with MDCTA performed at 24 months.

Expected visits were 98.7% (1663 of 1685) completed, with a suggestion of greater withdrawal in the salsalate group compared with the placebo group (31.0% [40 of 129] vs 21.1% [27 of 128], respectively; *P* = .06 by log-rank test), which tended to occur within 6 months, with similar rates for the remaining 24 months. The study drug was permanently stopped for medical issues in 26 participants (13 in the salsalate group and 13 in the placebo group), including those who withdrew consent for medical issues and those who remained in the trial while off the study drug. A numerically higher proportion of participants in the salsalate group compared with the placebo group reduced the dosage for tolerability (*P* = .19). Among those assigned to salsalate, the mean (SD) salicylates level obtained before morning dosing was 69.4 (3.3) μg/L (to convert salicylates level to micromoles per liter, multiply by 7.24). No participants were unmasked during the trial.

Figure 1. Consolidated Standards of Reporting Trials Diagram



The flow of patients in the study is shown. All data are presented through trial completion or point of withdrawal. MDCTA indicates multidetector computed tomographic angiography.

Primary Outcome

There were 318 evaluable segments in 84 participants randomized to salsalate (mean [SD], 3.8 [1.7] segments per individual), with a mean (SD) segment length of 27.2 (14.9) mm. There were 343 evaluable segments in 89 participants randomized to placebo (mean [SD], 3.9 [1.8] segments per individual), with a mean (SD) segment length of 29.0 (15.0) mm. Among the 661 evaluable segments, measured segments were located in the left main (49 [7.4%]), left anterior descending (230 [34.8%]), left circumflex (143 [21.6%]), and right (239 [36.2%]) coronary arteries or their major branches. More than 1 segment could be measured in each coronary artery for each patient. Among 173 participants, 26 (15.0%) had noncalcified segments measured in 1 vessel, 66 (38.2%) in 2 vessels, 61 (35.3%) in 3 vessels, and 20 (11.6%) in 4 vessels. These values are not equal to the number of significantly diseased vessels because lesions with heavy calcium, motion artifact, or bypass were not quantified. Only 92 of 661 (13.9%) measured segments were found to contain more than 50% stenosis.

There was no difference in change in total noncalcified plaque volume (mean difference, −1 mm^3; 95% CI, −11 to 9 mm^3; P = .87) or the fatty or fibrous components between the salsalate group and the placebo group (**Figure 2** and eTable 1 in Supplement 2). Most important, no overall progression in these plaque components was seen within either group. Although calcified plaque volume increased, there was no difference between groups. Likewise, total coronary calcium score increased, but there was no difference between groups (**Figure 3**A).

There was no change in remodeling index or maximal diameter stenosis in either treatment group and no difference between groups (P = .31 and P = .81, respectively). These results are summarized in **Table 2** and Figure 3B and C.

Four additional end point analyses, a sensitivity analysis for missing data, and a post hoc analysis of trial power were performed (eTables 2-6 in Supplement 2). Plaque length-adjusted analysis, per-individual analysis, per-protocol analysis, and analysis in the subgroup with diabetes mellitus all showed no difference in change in total noncalcified plaque volume or the fatty or fibrous components between the salsalate group and the placebo group.

Other Measures of Safety and Efficacy

Changes in multiple metabolic variables are summarized in Table 2 (eTable 7 in Supplement 2 lists SI units). Compared with baseline, there was no difference between groups in changes in weight, systolic or diastolic blood pressure, or levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipoprotein A, and apolipoprotein B. Triglycerides lowering was greater in the salsalate group compared with the placebo group. Lower total white blood cell, neutrophil, lymphocyte, and mononuclear cell counts (in the setting of increased hemoglobin levels and hematocrit) occurred in the salsalate group compared with the placebo group, without development of leukopenia, neutropenia, lymphopenia, or monocytopenia in any participant. Adiponectin levels increased, whereas other markers and mediators of inflammation, including high-sensitivity CRP, fibrinogen, myeloperoxidase, and serum amyloid A levels, did not differ between groups. Fasting glucose levels were reduced more in the salsalate group than the placebo group, as were uric acid and bilirubin levels.

Adverse Events

Serious adverse events were generally balanced between groups (eTable 8 in Supplement 2), although diverse types of renal events occurred solely in the salsalate group, including nephrolithiasis (n = 2), significant albuminuria (n = 1), acute kidney injury (n = 1), and urinary tract infection (n = 1). Cardiac events, both serious and nonserious, are listed in eTable 9 in Supplement 2. First ischemic cardiac events (myocardial infarction, ischemic stroke, and revascularization) were numerically but not statistically higher in the salsalate group compared with the placebo group (11 in the salsalate group vs 8 in the placebo group, P = .36). There were no deaths after randomization. All nonserious adverse events occurring in more

Table 1. Baseline Characteristics of the Study Cohort and by Treatment Group

Characteristic[a]	Total (N = 251)	Salsalate (n = 127)	Placebo (n = 124)
Demographic Characteristics			
Age, mean (SD), y	60.8 (7.0)	61.5 (6.8)	60.1 (7.2)
Male sex, No. (%)	236 (94.0)	118 (92.9)	118 (95.2)
White race/ethnicity, No. (%)	235 (93.6)	124 (97.6)	111 (89.5)
Inclusion Criteria (May Have >1), No. (%)			
Previous myocardial infarction	157 (62.5)	78 (61.4)	79 (63.7)
Previous coronary artery bypass graft	58 (23.1)	27 (21.3)	31 (25.0)
Angioplasty or stent	169 (67.3)	90 (70.9)	79 (63.7)
Abnormal exercise tolerance test result	96 (38.2)	50 (39.4)	46 (37.1)
Stable angina	98 (39.0)	56 (44.1)	42 (33.9)
Catheterization report showing coronary artery disease	215 (85.7)	111 (87.4)	104 (83.9)
Significant noncalcified plaque	27 (10.8)	17 (13.4)	10 (8.1)
Cardiovascular Risk Factors			
No. of components of metabolic syndrome, mean (SD)	3.2 (1.2)	3.3 (1.2)	3.3 (1.2)
Hypertension, No. (%)	169 (67.3)	87 (68.5)	82 (66.1)
Type 2 diabetes mellitus, No. (%)	59 (23.5)	27 (21.3)	32 (25.8)
Dyslipidemia, No. (%)	238 (94.8)	118 (92.9)	120 (96.8)
Ever smoked, No. (%)	57 (22.7)	26 (20.5)	31 (25.0)
Parental history of coronary heart disease, No. (%)[b]	128 (51.0)	64 (50.4)	64 (51.6)
Clinical Assessments, Mean (SD)			
Weight, kg	96.1 (12.5)	94.9 (11.9)	97.3 (13.0)
Waist circumference, cm	107.5 (8.7)	107.2 (8.7)	107.9 (8.9)
Heart rate, beats/min	61.0 (9.4)	60.8 (10.4)	61.3 (8.4)
Medications, No. (%)			
Diabetes therapies	47 (18.7)	21 (16.5)	26 (21.0)
Statin class agents	248 (98.8)	126 (99.2)	122 (98.4)
Antihypertensive agents	229 (91.2)	117 (92.1)	112 (90.3)
Antianginal agents	54 (21.5)	28 (22.0)	26 (21.0)
Aspirin	246 (98.0)	124 (97.6)	122 (98.4)
Nonaspirin platelet aggregation inhibitor	75 (29.9)	37 (29.1)	38 (30.6)
Imaging Characteristics			
Coronary calcium score, median (interquartile range), Agatston units	542 (218-1052)	545 (218-1048)	542 (219-1065)
No. of coronary segments per patient, mean (SD)	3.8 (1.8)	3.8 (1.7)	3.9 (1.8)
Mean segment length, mean (SD), mm	28.1 (15.0)	27.2 (14.9)	29.0 (15.0)

[a] Among randomized participants who took at least 1 dose of study medication.

[b] Parental history of coronary heart disease reported below the age of 55 years for fathers and 65 years for mothers.

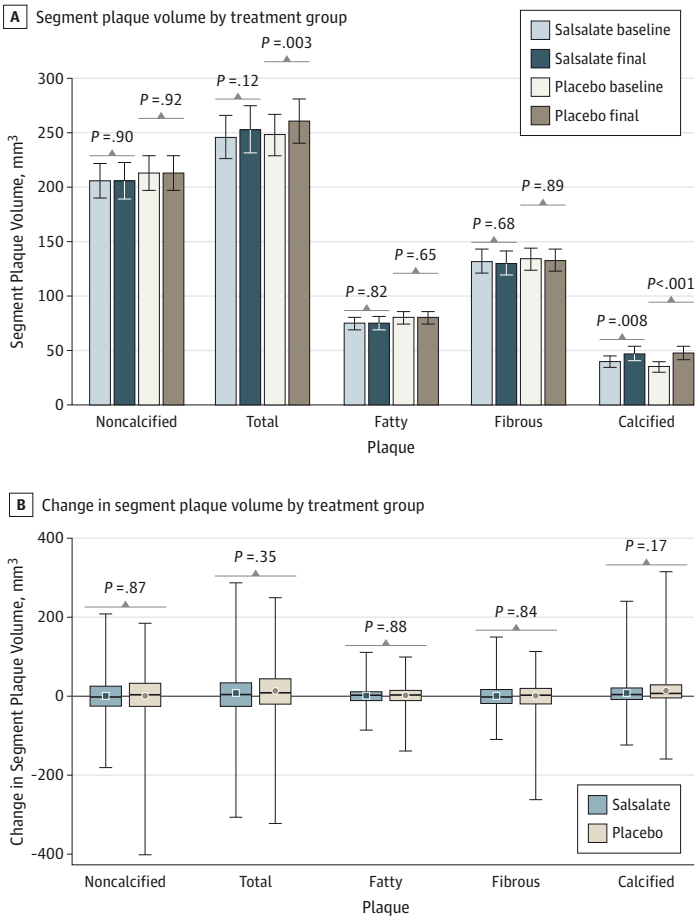
than 5% of the trial population and numerically more in the salsalate group than in the placebo group are listed in eTable 10 in Supplement 2. Atrial arrhythmia in 10 salsalate patients and 2 placebo patients (eTable 9 in Supplement 2) and tinnitus in 35 salsalate patients and 13 placebo patients (eTable 10 in Supplement 2) were the only nonserious adverse events occurring at rates 2-fold higher in the salsalate group compared with the placebo group.

Safety signals included increased anion gap, urinary albumin, and lactate dehydrogenase levels and decreased sodium and albumin levels, with no change in alanine transaminase or aspartate transaminase levels (Table 2). Although creatinine levels increased more in the salsalate group than in the placebo group, the estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration derived[15]) did not differ between groups. Only one safety alert was sent for a salicylates level exceeding 300 µg/L.

Discussion

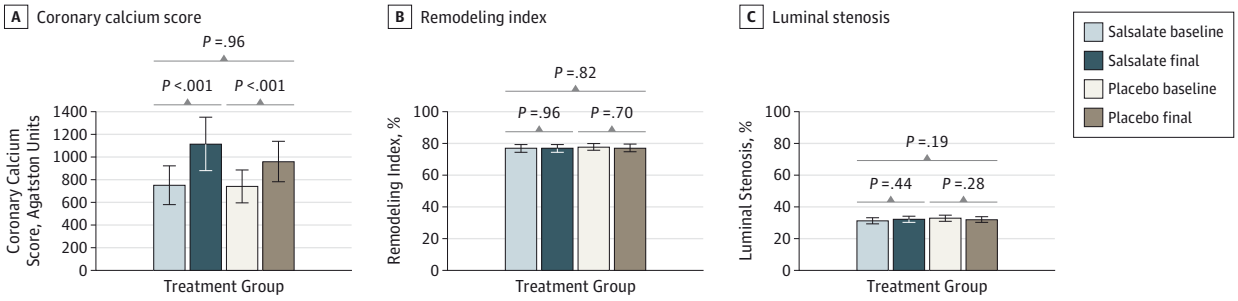
This study tested the hypothesis that targeting inflammation using salsalate would reduce progression of noncalcified coronary plaque volume in overweight and obese patients with stable, established CHD receiving statins. We found no difference in rates of progression of noncalcified coronary segment plaque volume between the salsalate group and the placebo group. However, we also found no progression of noncalcified plaque in the placebo group as assessed by MDCTA in the setting of good medical care, including 98.8% (248 of 251) statin use, blood pressure control, and antiplatelet therapy. The ability to halt atherosclerotic progression with current therapies may underlie falling cardiovascular event rates seen in cardiovascular outcome trials and nationally.[16] We did not anticipate and did not observe salsalate inducing regression of

Figure 2. Coronary Artery Segment Plaque Volume, Assessed at Baseline and 30 Months, for Noncalcified Plaque, Total Plaque, Fatty Plaque, Fibrous Plaque, and Calcified Plaque in the Salsalate and Placebo Groups



A, The means (95% CIs) are shown. *P* values represent the difference in segment plaque volume from baseline to final assessment within each treatment group. B, Changes in segment plaque volume are presented as box and whisker plots, with the top and bottom of the whisker representing the maximum and minimum observations, respectively. Box boundaries represent the interquartile range (75% and 25% boundaries, respectively), the line within the box represents the median, and the square in the salsalate and circle in the placebo represents the mean.

Figure 3. Coronary Calcium Score, Remodeling Index, and Luminal Stenosis, Assessed at Baseline and 30 Months



The means (95% CIs) in the salsalate and placebo groups are shown. *P* values evaluating the difference between baseline and 30-month assessments within the salsalate and placebo groups and the difference in change between the 2 groups are shown.

established lesions. Given the small changes in noncalcified plaque volume and large physiological variance, we can exclude an effect difference for progression of noncalcified plaque volume of greater than 6% between the salsalate group and the placebo group. Ongoing cardiovascular outcome trials may show whether residual cardiovascular risk can be favorably influenced using alternative anti-inflammatory strategies.[17,18]

Inflammation mediates multiple adverse effects on arterial biology to drive atherothrombosis. In primary and secondary cardiovascular prevention populations, inflammation assessed by high-sensitivity CRP levels is strongly related to recurrent event rates.[4] The possibility that anti-inflammatory agents, and aspirin in particular, may have clinical benefits in preventing cardiovascular disease in patients with high CRP

Table 2. Baseline Values and Change From Baseline for Clinical and Laboratory Variables by Treatment Group

Variable	Placebo		Salsalate		Difference in Mean Change	
	Value at Baseline, Mean (SD)	Mean (95% CI) Change From Baseline	Value at Baseline, Mean (SD)	Mean (95% CI) Change From Baseline	Difference (95% CI)	*P* Value
Clinical Variables						
Body mass index[a]	31.4 (2.9)	0.1 (−0.1 to 0.3)	31.7 (3.1)	0.2 (0.0 to 0.5)	0.1 (−0.2 to 0.5)	.46
Systolic blood pressure, mm Hg	129.6 (13.0)	2.8 (0.8 to 4.8)	125.7 (12.3)	3.0 (0.9 to 5.1)	0.2 (−2.7 to 3.2)	.88
Diastolic blood pressure, mm Hg	75.0 (8.0)	−0.5 (−1.6 to 0.6)	74.2 (7.9)	−1.4 (−2.5 to −0.2)	−0.9 (−2.4 to 0.7)	.29
Chemistry Profile						
Sodium, mEq/L	139.1 (2.1)	0.6 (0.4 to 0.9)	139.1 (2.4)	1.8 (1.5 to 2.0)	1.1 (0.8 to 1.5)	<.001
Potassium, mEq/L	4.3 (0.4)	0.2 (0.1 to 0.2)	4.3 (0.4)	0.1 (0.1 to 0.1)	−0.1 (−0.1 to 0.0)	.03
Chloride, mEq/L	103.8 (2.6)	0.4 (0.1 to 0.7)	103.5 (2.5)	0.9 (0.7 to 1.2)	0.5 (0.2 to 0.9)	.005
Bicarbonate, mEq/L	24.8 (2.3)	0.9 (0.7 to 1.2)	25.1 (2.3)	0.5 (0.3 to 0.8)	−0.4 (−0.7 to 0.0)	.03
Anion gap, mEq/L	24.0 (8.2)	−0.7 (−0.9 to −0.5)	24.7 (8.8)	0.3 (0.1 to 0.5)	1.0 (0.7 to 1.3)	<.001
Albumin, g/dL	4.4 (0.3)	0.0 (0.0 to 0.1)	4.4 (0.2)	−0.1 (−0.1 to −0.1)	−0.2 (−0.2 to −0.1)	<.001
Aspartate aminotransferase, U/L[b]	24.0 (8.2)	−0.9 (−1.7 to −0.1)	24.7 (8.8)	0.8 (−0.1 to 1.7)	1.8 (0.5 to 3.2)	.01
Alanine aminotransferase, U/L[b]	26.4 (11.5)	−0.6 (−1.6 to 0.4)	27.1 (11.9)	−1.1 (−2.1 to −0.1)	−0.5 (−2.0 to 1.0)	.48
Alkaline phosphatase, U/L	65.1 (18.6)	−0.3 (−1.7 to 1.2)	65.0 (16.2)	−1.4 (−2.9 to 0.1)	−1.1 (−3.2 to 0.9)	.28
Total bilirubin, mg/dL[b]	0.7 (0.3)	0.0 (−0.1 to 0.0)	0.7 (0.3)	−0.2 (−0.2 to −0.2)	−0.2 (−0.2 to −0.1)	<.001
Serum urea nitrogen, mg/dL	17.5 (4.8)	0.5 (0.1 to 1.0)	18.3 (4.5)	0.4 (−0.1 to 0.8)	−0.1 (−0.8 to 0.5)	.67
Uric acid, mg/dL	6.5 (1.3)	0.0 (−0.2 to 0.2)	6.2 (1.4)	−1.7 (−1.9 to −1.5)	−1.6 (−1.9 to −1.3)	<.001
Markers of Glycemia						
Glucose, mg/dL	103.3 (30.9)	−0.9 (−2.7 to 0.9)	102.1 (21.1)	−6.8 (−8.5 to −5.1)	−5.9 (−8.2 to −3.7)	<.001
Glycated hemoglobin, % of total hemoglobin[c]	6.1 (0.8)	−0.0 (−0.1 to 0.1)	6.1 (0.6)	−0.0 (−0.2 to 0.1)	−0.0 (−0.2 to 0.1)	.73
Adiponectin, μg/mL[b]	6.6 (3.2)	0.3 (0.0 to 0.6)	6.8 (3.8)	1.9 (1.4 to 2.3)	1.5 (0.9 to 2.1)	<.001
Insulin, μIU/mL[b]	16.4 (10.4)	0.8 (−0.6 to 2.3)	16.7 (12.7)	3.0 (1.3 to 4.9)	2.1 (−0.1 to 4.6)	.06
Renal						
Serum creatinine, mg/dL[b]	1.0 (0.2)	0.0 (0.0 to 0.1)	0.9 (0.2)	0.1 (0.1 to 0.1)	0.0 (0.0 to 0.0)	.01
Estimated glomerular filtration rate (CKD-EPI), mL/min/1.73 m^2	83.5 (15.1)	−2.1 (−3.4 to −0.8)	85.6 (12.5)	−2.0 (−3.3 to −0.8)	0.0 (−1.8 to 1.9)	.98
Ratio of urine microalbumin to creatinine, μg/mg[b]	10.4 (16.9)	−1.8 (−3.0 to −0.3)	13.4 (33.5)	13.4 (9.4 to 18.1)	18.9 (12.5 to 26.8)	<.001
Complete Blood Count						
Total white blood cells, /μL	6.7 (1.8)	−0.1 (−0.3 to 0.1)	6.5 (1.6)	−0.7 (−0.9 to −0.5)	−0.6 (−0.9 to −0.4)	<.001
Hemoglobin, g/dL	14.8 (1.2)	−0.2 (−0.4 to −0.1)	14.9 (1.0)	0.0 (−0.1 to 0.1)	0.2 (0.1 to 0.4)	.01
Hematocrit, %	43.8 (3.3)	−0.5 (−0.8 to −0.1)	44.1 (3.0)	0.3 (0.0 to 0.7)	0.8 (0.3 to 1.3)	.002
Absolute neutrophils, /μL	4107.0 (1275.9)	−28.0 (−152.4 to 96.4)	4063.5 (1187.9)	−336.0 (−467.9 to −204.1)	−308.0 (−489.4 to −126.6)	.001
Absolute lymphocytes, /μL	1835.0 (730.6)	−52.7 (−156.8 to 51.5)	1704.9 (544.9)	−305.0 (−414.9 to −195.1)	−252.3 (−404.1 to −100.6)	.001
Absolute monocytes, /μL	521.4 (145.5)	−15.3 (−29.4 to −1.1)	515.8 (152.7)	−37.7 (−52.5 to −22.9)	−22.5 (−42.9 to −2.0)	.03

(continued)

Table 2. Baseline Values and Change From Baseline for Clinical and Laboratory Variables by Treatment Group (continued)

Variable	Placebo		Salsalate		Difference in Mean Change	
	Value at Baseline, Mean (SD)	Mean (95% CI) Change From Baseline	Value at Baseline, Mean (SD)	Mean (95% CI) Change From Baseline	Difference (95% CI)	*P* Value
Lipids						
Apolipoprotein B, mg/dL	76.7 (21.0)	2.5 (0.1 to 4.8)	78.0 (16.5)	4.6 (2.2 to 7.1)	2.2 (−1.2 to 5.6)	.21
Total cholesterol, mg/dL	147.2 (30.4)	2.0 (−1.7 to 5.6)	149.1 (26.2)	5.1 (1.2 to 9.0)	3.1 (−2.2 to 8.4)	.24
High-density lipoprotein cholesterol, mg/dL	41.1 (11.8)	1.1 (0.0 to 2.3)	41.2 (11.5)	0.8 (−0.4 to 2.0)	−0.3 (−2.0 to 1.3)	.70
Low-density lipoprotein cholesterol, mg/dL	81.7 (25.9)	0.3 (−2.9 to 3.5)	83.6 (19.8)	4.6 (1.1 to 8.0)	4.3 (−0.4 to 9.0)	.07
Lipoprotein A, mg/dL[b]	37.9 (35.0)	0.4 (−0.9 to 1.7)	36.9 (34.3)	1.3 (0.0 to 2.7)	0.9 (−0.9 to 2.8)	.33
Triglycerides, mg/dL[b]	142.2 (72.9)	−2.7 (−10.9 to 6.1)	135.9 (65.6)	−15.4 (−22.9 to −7.4)	−13.1 (−23.5 to −1.7)	.03
Markers of Inflammation						
High-sensitivity C-reactive protein, mg/L[b]	2.0 (3.8)	−0.1 (−0.4 to 0.1)	2.2 (3.7)	−0.1 (−0.4 to 0.2)	0.0 (−0.3 to 0.5)	.84
Fibrinogen, mg/dL	444.7 (132.9)	−10.6 (−27.5 to 6.3)	425.2 (109.9)	−28.5 (−46.5 to −10.6)	−17.9 (−42.6 to 6.7)	.15
Myeloperoxidase, pmol/L[b]	515.4 (566.1)	−81.8 (−119.0 to −41.2)	526.8 (605.8)	−78.4 (−118.9 to −33.8)	6.3 (−58.9 to 80.6)	.86
Serum amyloid A, mg/L[b]	6.5 (8.1)	−0.4 (−0.8 to 0.2)	7.7 (15.4)	−0.5 (−1.1 to 0.2)	0.0 (−0.9 to 0.9)	.94

Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

SI conversation factors: To convert absolute lymphocytes level to $\times 10^9$/L, multiply by 0.001; absolute monocytes level to $\times 10^9$/L, multiply by 0.001; absolute neutrophils level to $\times 10^9$/L, multiply by 0.001; alanine aminotransferase level to microkatals per liter, multiply by 0.0167; albumin level to grams per liter, multiply by 10; alkaline phosphatase level to microkatals per liter, multiply by 0.0167; anion gap level to millimoles per liter, multiply by 1.0; apolipoprotein B level to grams per liter, multiply by 0.01; aspartate aminotransferase level to microkatals per liter, multiply by 0.0167; bicarbonate level to millimoles per liter, multiply by 1.0; chloride level to millimoles per liter, multiply by 1.0; cholesterol levels (total, HLD, or LDL) to millimoles per liter, multiply by 0.0259; C-reactive protein level to nanomoles per liter, multiply by 9.524; creatinine level to micromoles per liter, multiply by 88.4; fibrinogen level to micromoles per liter, multiply by 0.0294; glucose level to millimoles per liter, multiply by 0.0555; glycated hemoglobin level to proportion of total hemoglobin, multiply by 0.01; hematocrit level to proportion of 1.0, multiply by 0.01; hemoglobin level to grams per liter, multiply by 10.0; insulin level to picomoles per liter, multiply by 6.945; lipoprotein A level to micromoles per liter, multiply by 0.0357; potassium level to millimoles per liter, multiply by 1.0; serum urea nitrogen level to millimoles per liter, multiply by 0.357; sodium level to millimoles per liter, multiply by 1.0; total bilirubin level to micromoles per liter, multiply by 17.104; total white blood cell count level to $\times 10^9$/L, multiply by 0.001; triglycerides level to millimoles per liter, multiply by 0.0113; and uric acid level to micromoles per liter, multiply by 59.485.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Log transformed.

[c] Diabetes status is used as a fixed effect with no random effect.

levels was first noted within the Physicians' Health Study,[19] although the effect may have been due to platelet inhibition at the aspirin dosing used. Statins have pleotropic effects and lower both low-density lipoprotein cholesterol and CRP levels.[20] It is possible that inflammatory risk was maximally influenced by the use of statins in all participants. Anti-inflammatory mechanisms differ between statins (which do not lower white blood cell counts) and salicylates (which did not lower high-sensitivity CRP levels), but effects may not be additive. Lowering of total white blood cell, neutrophil, lymphocyte, and monocyte counts provides evidence for anti-inflammatory properties of salsalate and has previously been demonstrated in type 2 diabetes mellitus.[6] This finding does not appear to be a bone marrow toxic effect because hemoglobin levels and hematocrits increased. Rates of infection were not higher. While higher leukocyte counts are associated with increased hazard of CHD events and monocyte-derived macrophages are the predominant inflammatory cell type in atherosclerotic plaque,[1,3] lowering of circulating concentrations did not affect plaque volume in the setting of existing disease and high levels of compliance with established guidelines for treatment of CHD. Uric acid crystals promote activation of the leucine-rich repeat and pyrin domain-containing protein 3 inflammasome and interleukin 1β secretion.[21] Although we found decreases in white blood cell counts and adiponectin and uric acid levels, no difference occurred between groups in additional markers and mediators of inflammation, including levels of high-sensitivity CRP, fibrinogen, myeloperoxidase, and serum amyloid A. However, point estimates were numerically decreased within the salsalate group.

Adiponectin and high-density lipoprotein cholesterol levels are highly correlated in the general population, although precise mechanisms underlying this association remain incompletely understood.[22] We demonstrated increased adiponectin levels, without change in high-density lipoprotein cholesterol levels, in the salsalate group, suggesting mechanistic uncoupling of this association.

Multidetector computed tomographic angiography permits assessment of coronary artery plaque, with quantification of total plaque and plaque subcomponent volumes. Segment analysis permits detection of new plaques or progression of existing plaques within evaluable vessels.[23] Leukotriene inhibition may reduce new plaque formation,[24]

and progression of noncalcified coronary plaques is slowed by statins across multiple studies,[12,25-28] together demonstrating that serial MDCTA evaluation of coronary plaques allows assessment of interval change in the plaque morphology. Statin studies have generally shown reductions in noncalcified plaque volume in patients with newly identified CHD in whom statin therapy has been recently initiated, typically at high doses. To our knowledge, effects on more advanced disease have not previously been evaluated, and kinetics of plaque change over time have not been clearly assessed. Our participants were receiving statin treatment at enrollment, most for many years. We demonstrated no further regression or progression of noncalcified plaque in our statin-treated cohorts. It is possible that regression of plaque due to statin use had already occurred before study entry or is attenuated in patients with advanced disease. Statins increase coronary atheroma calcification,[29] which may underlie increased calcification seen in our cohort, although progression of calcification did not differ between the salsalate group and the placebo group. In addition, our data may help inform power estimates for subsequent imaging studies of patients with advanced CHD.

Overall, there were no clinically meaningful differences in serious and nonserious adverse events between the salsalate and placebo treatment arms. Safety and tolerability findings with salsalate use that were observed in patients with established heart disease are consistent with those observed in patients with type 2 diabetes mellitus and when used for arthritic pain.[6,30] Tinnitus is an established adverse effect of salicylates use.[30] Increased serum creatinine and urinary albumin levels are concerning as an adverse marker of health. Mechanisms underlying increased albuminuria, also seen in type 2 diabetes mellitus,[6] remain unknown. Salsalate use does not change renal prostaglandin levels, which are suppressed by other nonsteroidal anti-inflammatory class agents.[31] The uricosuric effects of salsalate may contribute to glomerular damage or to the numeric increase in nephrolithiasis. Increased atrial arrhythmias have not previously been reported to our knowledge. Mechanisms are unknown, and the finding may be spurious, but caution should be used when prescribing salsalate for pain management in patients at high risk.

Limitations of our study include the short trial duration and small number of patients (which prohibit assessment of cardiovascular outcomes) and the reliance on an imaging surrogate outcome, as well as the prevalence of established advanced CHD, which restricts assessments of effects on early atherosclerotic lesions. Anti-inflammatory properties of statins may confound the ability to demonstrate effects of targeting inflammation using salsalate. Our participants had a mean CRP level of 2.1 mg/L, near the minimum CRP level for enrollment in CHD outcome studies[18,32] targeting inflammation using rosuvastatin calcium or canakinumab (to convert CRP level to nanomoles per liter, multiply by 9.524). Patients with a lower severity of inflammation may have less benefit from anti-inflammatory therapy. Our trial had insufficient women and racial/ethnic minorities to establish whether responses would differ in subgroups. The absence of progression of noncalcified plaque volume in the placebo group limits interpretation of the trial results because it is not possible to fully distinguish lack of ability of MDCTA to detect plaque progression vs the absence of progression in this population receiving high-standard medical care. Studies using combined functional and structural imaging investigations, such as fludeoxyglucose F 18 positron emission tomography–computed tomography (PET-CT), provide evidence of inflammation in the vasculature,[33] particularly in patients with acute coronary syndrome.[34,35] Detailed quantification of coronary artery inflammation using PET-CT is still under development,[33,35] and changes in fludeoxyglucose F 18 uptake in patients with stable CHD have not been reliably demonstrated[36]; thus, PET-CT was not selected as the imaging modality at trial initiation. However, functional imaging may provide different physiological findings.

Conclusions

Salsalate does not reduce progression of noncalcified coronary plaque volume assessed by MDCTA when added to current therapies in patients with established CHD in whom disease is stable. Current statin use, blood pressure control, and high compliance with guideline-directed care are associated with stable noncalcified plaque in those with advanced disease. It remains unknown if salsalate treatment earlier in disease might reduce initiation or progression of initial lesions. Further evidence is needed to support whether targeting inflammation may be a valuable therapeutic intervention for cardiometabolic complications of obesity.

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Group Information: eAppendix 2 in Supplement 1 contains details about the Targeting Inflammation Using Salsalate in Cardiovascular Disease (TINSAL-CVD) Study Team. Additional TINSAL-CVD Study Team members who contributed to the trial are listed below (in alphabetical order).

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TINSAL-CVD Imaging Core Study Team at Beth Israel Deaconess Medical Center: Imaging core collaborators work was performed when employed at Beth Israel Deaconess Medical Center. Current affiliations are Ahmad R. Cheema, MD, Department of Internal Medicine, Icahn School of Medicine at Mount Sinai (internal medicine resident); Huzaifa Haj-Ibrahim, MD, Beth Israel Deaconess Medical Center (general surgery resident); Ali Farzan Jon, MD, Rutgers, The State University of New Jersey (diagnostic radiology resident); and Atif Niaz Khan, MD, Marshfield Clinic (internal medicine and pediatrics resident).

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Invited Commentary

Informative Neutral Studies Matter—Why the Targeting Inflammation With Salsalate in Cardiovascular Disease (TINSAL-CVD) Trial Deserves Our Attention

Paul M Ridker, MD, MPH

Clinical research requires a fundamental state of equipoise allowing the physician responsible for care to state with assurance to a potential trial participant that the best treatment alternative is unknown, that an important but untested hypothesis has been raised in the scientific community, and that the only way to address validity of the hypothesis is to perform a randomized, placebo-controlled clinical trial in which the therapy of interest is determined by random allocation. This covenant between physician and patient is a delicate one because, if true scientific equipoise exists, roughly half of all trials will be neutral. In a survey of 104 contemporary trials funded by not-for-profit agencies between 2000 and 2005, 49% reported evidence favoring new treatments over standard of care, whereas 51% did not.[1] Yet, when a well-conducted trial is based on solid pathophysiologic principles, neutral outcomes can be highly informative.

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In this issue of *JAMA Cardiology*, Hauser et al[2] present primary results from the National Heart, Lung, and Blood Institute–funded Targeting Inflammation Using Salsalate in Cardiovascular Disease (TINSAL-CVD) trial. Salsalate is a nonacetylated prodrug of salicylate that has the capacity to inhibit the nuclear factor-κB signaling pathway and is used in the treatment of inflammatory disorders, such as rheumatoid arthritis. Because inflammation is a major contributor to both atherothrombosis and diabetes mellitus, there has been considerable interest in salsalate as a potential intervention for these disorders. In fact, much of this work has been accomplished by the TINSAL investigators themselves. In 2010, the TINSAL group reported in an initial dose-escalation trial among patients with diabetes mellitus that salsalate modestly reduced glycated hemoglobin levels and led to improvement of other markers of glycemic control.[3] The same group then confirmed this finding for glycated hemoglobin in 2013 in a 12-month trial of 286 patients (TINSAL-T2D), which additionally demonstrated lower levels of circulating leukocyte, neutrophil, and lymphocyte counts.[4] In related work, the TINSAL investigators have also demonstrated that salsalate increases adiponectin levels, while reducing adipose tissue nuclear factor-κB activity in a manner not related to peripheral insulin sensitivity.[5] On the other hand, in these same patients, salsalate had no significant effect on late advanced glycation end products[6] or on flow-mediated endothelial dependent dilation or nitroglycerin-mediated dilation (TINSAL-FMD).[7] These latter data are less consistent with direct anti-inflammatory effects within arteries; therefore, equipoise is clearly present with regard to potential vascular benefits of salsalate.

In this context, the TINSAL-CVD trial[2] sought to address whether salsalate can reduce progression of noncalcified coro-