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The Effects of Salsalate on Glycemic Control in Patients With Type 2 Diabetes:

A Randomized Trial

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Abstract

Background—Salsalate, a nonacetylated prodrug of salicylate, has been shown to decrease blood glucose concentration in small studies.

Objective—To compare the efficacy and safety of salsalate at different doses in patients with type 2 diabetes.

Design—Parallel randomized trial with computer-generated randomization and centralized allocation. Patients and investigators, including those assessing outcomes and performing analyses, were masked to group assignment. (ClinicalTrials.gov registration number: NCT00392678)

Setting—3 private practices and 14 universities in the United States.

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Patients—Persons aged 18 to 75 years with fasting plasma glucose concentrations of 12.5 mmol/L or less (≤225 mg/dL) and hemoglobin A_{1c} (HbA_{1c}) levels of 7.0% to 9.5% treated by diet, exercise, and oral medication at stable doses for at least 8 weeks.

Intervention—After a 4-week, single-masked run-in period, patients were randomly assigned to receive placebo or salsalate in dosages of 3.0, 3.5, or 4.0 g/d for 14 weeks (27 patients each) in addition to their current therapy.

Measurements—Change in HbA_{1c} was the primary outcome. Adverse effects and changes in measures of coronary risk and renal function were secondary outcomes.

Results—Higher proportions of patients in the 3 salsalate treatment groups experienced decreases in HbA_{1c} levels of 0.5% or more from baseline ($P = 0.009$). Mean HbA_{1c} changes were −0.36% ($P = 0.02$) at 3.0 g/d, −0.34% ($P = 0.02$) at 3.5 g/d, and −0.49% ($P = 0.001$) at 4.0 g/d compared with placebo. Other markers of glycemic control also improved in the 3 salsalate groups, as did circulating triglyceride and adiponectin concentrations. Mild hypoglycemia was more common with salsalate; documented events occurred only in patients taking sulfonylureas. Urine albumin concentrations increased in all salsalate groups compared with placebo. The drug was otherwise well tolerated.

Limitation—The number of patients studied and the trial duration were insufficient to warrant recommending the use of salsalate for type 2 diabetes at this time.

Conclusion—Salsalate lowers HbA_{1c} levels and improves other markers of glycemic control in patients with type 2 diabetes and may therefore provide a new avenue for treatment. Renal and cardiac safety of the drug require further evaluation.

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Case reports published more than a century ago (1, 2) suggested that high-dose sodium salicylate could diminish glycosuria in older diabetic patients. More recently, inflammation and innate immunity have been implicated in the pathogenesis of insulin resistance and type 2 diabetes (3, 4). Obesity activates the transcription factor nuclear factor–κB (NF-κB), which promotes insulin resistance and risk for both type 2 diabetes and cardiovascular disease (5–7). High-dose sodium salicylate inhibits NF-κB (8–10). These findings may explain the original observations and provide potential new avenues for intervention in type 2 diabetes (5).

A pilot trial that used aspirin, approximately 7 g/d (11), also demonstrated decreases in glucose concentrations (12, 13). However, aspirin at high doses is associated with risk for bleeding, which limits clinical utility. Sodium salicylate does not irreversibly inhibit cyclooxygenase-1 and -2 (COX-1 and COX-2) (14, 15) and is thus not antithrombotic, but it also irritates the gastrointestinal tract. We therefore initiated pilot studies of salsalate, a prodrug of salicylate that is well tolerated and considered safe after years of use for arthritis. Salsalate reduced blood glucose, triglyceride, free fatty acid and C-reactive protein concentrations; improved glucose utilization; and increased circulating insulin and adiponectin concentrations in small proof-of-concept studies (16, 17). The TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) trial evaluates whether this generic and inexpensive drug is safe, tolerated, and efficacious in patients with type 2 diabetes.

Methods

Trial Design

The TINSAL-T2D trial was a single-mask lead-in, randomized, double-masked placebo-controlled, dose-ranging multicenter clinical trial conducted at 17 sites in the United States (3 private practices and 14 university or academic centers). The protocol, approved by human subject institutional review boards at each institution, included 1 week of screening, a 4-week single-masked placebo run-in, pretreatment baseline evaluation, and a 14-week treatment period with visits at 2, 4, 8 and 14 weeks after random assignment. Study patients, site investigators and staff, steering committee members, and members of the data coordinating center responsible for clinical activities were masked to treatment assignment. We recruited patients through physician referral and advertisement. The single-masked placebo run-in period provided an interval for metabolic stabilization, which may accompany participation in a clinical trial because of potential changes in lifestyle or adherence to therapies. Patients with 80% or more adherence to masked placebo, assessed by pill count, were eligible for random assignment, which we conducted in clinic blocks by using central computer assignments. We assigned equal numbers to receive either salsalate, in dosages of 3.0, 3.5, or 4.0 g/d, or an identical-appearing placebo, divided into 3 daily doses. Randomization codes were secured at the data coordinating center. We escalated the dosages by 0.5 g/d over 2-week intervals for patients randomly assigned to receive higher dosages. We assessed adherence by pill count.

We systematically assessed adverse events with a questionnaire given at each follow-up visit. Patients were instructed to monitor daily fasting glucose and symptomatic events by using glucometers. The postdosing safety evaluation, conducted 2 weeks after therapy, included a systematic medical history. Staff evaluated vital signs and laboratory chemistries for patients with systolic or diastolic blood pressure greater than 160 or 95 mm Hg, respectively; change from baseline in systolic or diastolic blood pressure greater than 10 mm Hg; decrease from baseline in estimated glomerular filtration rate (GFR) by 20 mL/min per 1.73 m^2; or serum creatinine levels above normal. We reduced dosages for patients with tinnitus, who continued receiving the maximum tolerable dose nearest the original assignment. We also reduced concurrent diabetes therapies for patients with hypoglycemia, either documented by home glucose monitoring or with recurrent consistent symptoms; concurrent oral therapies were increased for documented hyperglycemia at the discretion of the primary care provider. We assessed quality of life by using the total scale and 9 subscales of the Short Form-36 (SF-36) survey, which reflects aspects of physical and mental health and well-being.

Criteria for terminating treatment included patient decision to withdraw consent; pregnancy or lactation; a new diagnosis of an exclusionary medical condition; an intolerable adverse event, as judged by the investigator and the patient; and hospitalization or surgical procedures deemed probably related to the use of the study drug.

Study Population

Eligible adult patients were younger than 75 years; received their diagnosis of type 2 diabetes 8 or more weeks previously; had fasting plasma glucose concentrations of 12.5 mmol/L or less (≤225 mg/dL) and hemoglobin A_{1c} (HbA_{1c}) levels of 7.0% to 9.5% at screening; and were treated by diet and exercise alone or with metformin, an insulin secretagogue, or a dipeptidyl peptidase-4 inhibitor, either as monotherapy or in combination. Concomitant diabetes medication had to have been at stable dosages for at least the past 8 weeks. Patients who received low-dose aspirin (81 to 325 mg/d) were eligible for the trial.

Exclusion criteria included treatment with insulin, thiazolidinedione (because of the potential overlap in mechanism), or exenatide (because of association with weight loss); intentional weight loss of 4.5 kg or more in the previous 6 months; receipt of weight-loss drugs or corticosteroids in the previous 3 months; or recent long-term nonsteroidal anti-inflammatory drug therapy. We also excluded patients who were receiving uricosuric agents or anticoagulants other than low-dose aspirin or had aspirin allergy, severe diabetic neuropathy, peptic ulcer disease or gastritis, unstable cardiovascular disease, uncontrolled hypertension, anemia or thrombocytopenia, hypertriglyceridemia, stage 3 or greater chronic kidney disease or proteinuria, hepatic dysfunction, or other conditions likely to interfere with the conduct of the trial. We added preexisting chronic tinnitus as an exclusion criterion early in the course of the trial.

Study End Points

The primary outcome was change in HbA_{1c} level. Important secondary outcomes included changes in various other metabolic parameters, to determine the effect of salsalate on glucose and lipid homeostasis and coronary risk. We classified hypoglycemia as mild if symptoms were relieved by food or if documented blood glucose concentration was less than 3.3 mmol/L (<60 mg/dL) and as severe if patients required assistance.

Laboratory Measures

Unless otherwise noted, laboratory measurements were performed at Quest Diagnostics (Chantilly, Virginia). Commercial immunoassays for insulin, C-peptide, adiponectin, high-sensitivity C-reactive protein, free fatty acid, and glycated albumin were performed according to assay instructions. Serum cystatin C concentration and cystatin C GFR were measured as described elsewhere (17–19).

Statistical Analysis

The trial was designed to detect a 15% difference in the proportion of patients with an absolute difference in HbA_{1c} level of at least 0.5% from baseline to 14 weeks between placebo and at least 1 treatment group, with statistical power of 90% and an α level of 0.05. We closed the data set before initiating analyses, which followed the intention-to-treat principle. We compared baseline characteristics among groups by using the chi-square test, Fisher exact test, and parametric and nonparametric analysis of variance. We evaluated the primary outcome by using chi-square analyses to compare the proportion of patients in each treatment group whose HbA_{1c} level decreased by 0.5%. We evaluated differences between active treatment groups and placebo after adjusting the α level for multiple comparisons by using the Holm–Bonferroni method (20).

For continuous, normally distributed secondary outcomes, we estimated between-group differences by using linear mixed models adjusted for baseline levels, clinical center, and follow-up. For secondary outcomes that were continuous but not normally distributed, we examined changes from baseline to week 14 by using the Kruskal–Wallis test for an overall treatment effect and, when significant, used the Wilcoxon test to compare active treatment groups with placebo. We compared each active group with placebo; we used the Holm procedure to adjust *P* values for multiple comparisons and report the adjusted α levels. We also report nominal *P* values for the overall test of difference among treatment groups, unadjusted for multiple statistical testing of the secondary hypotheses. All *P* values were 2-sided; we considered values less than 0.05 to be statistically significant. We conducted post hoc analyses to determine whether changes in albumin and creatinine levels at week 14 were associated with changes in baseline variables by using analysis of variance for estimated GFR, blood pressure, and weight and the Fisher exact tests for aspirin and angiotensin modulators.

Role of the Funding Source

The TINSAL-T2D trial is supported by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (Bethesda, Maryland). The funding agency was involved in study design and interpretation of the data. Caraco Pharmaceuticals (Detroit, Michigan) provided study drug and placebo, LifeScan (Miltipas, California) provided glucometers and test strips, and Mercodia (Uppsala, Sweden) provided insulin assay materials. No private company had a role in the design or conduct of the trial, data analysis, or manuscript preparation.

Results

Baseline Characteristics

Of the 277 patients screened, 128 entered the 4-week placebo run-in phase (Figure 1). Most (72%) of the patients excluded at screening had HbA_{1c} levels outside of inclusion criteria. Differences in baseline characteristics among treatment groups were not clinically significant (Table 1).

Study Adherence

Median drug adherence rates, as assessed by pill count, were 94% to 98%. No patients were unmasked during the trial. Of the 27 patients randomly assigned to each treatment group, 25 to 27 per group completed the study.

HbA_{1c} Level and Glycemic Control

Higher proportions of patients in the 3 salsalate treatment groups experienced decreases in HbA_{1c} level of 0.5% or more from baseline; the difference was statistically significant overall ($P = 0.009$) and in pairwise comparisons with placebo for each salsalate dose (Table 2 and Figure 2, *A*). Mean changes in HbA_{1c} level for the salsalate groups were −0.36% at 3.0 g/d ($P = 0.02$), −0.34% at 3.5 g/d ($P = 0.02$), and −0.49% at 4.0 g/d ($P = 0.001$) compared with placebo.

Glycemic control also improved in the 3 salsalate groups compared with placebo, as measured by decreased fasting blood glucose concentration and glycated albumin level (Table 3 and Figure 2, *B* and *C*). A total of 119 mild hypoglycemic events were reported in 22 patients, 2 (7%) in the placebo group and 6 (22%) in the 3.0-g/d, 8 (30%) in the 3.5-g/d, and 6 (22%) in the 4.0-g/d salsalate groups (Table 4). Documented hypoglycemia (glucose concentration ≤3.3 mmol/L [≤60 mg/dL]) occurred only in patients who were also receiving a sulfonylurea. One patient in the 3.5-g/d salsalate group had an episode of severe hypoglycemia that required assistance after missing a meal; the patient was also receiving a sulfonylurea and metformin.

One patient (4%) in the 3.0-g/d, 4 (15%) in the 3.5-g/d, and 3 (11%) in the 4.0-g/d salsalate groups needed to have their concomitant diabetes medication dosages reduced because of hypoglycemia. Two patients (7%) in the placebo group needed to have concomitant drug dosages increased to treat out-of-range hyperglycemia. Improvements in glycemia occurred despite these adjustments, which would blunt differences between the placebo and treatment groups.

Other Measures of Efficacy and Safety

Changes in body weight, blood pressure, and C-peptide and C-reactive protein concentrations from baseline did not significantly differ among groups after adjustments, despite the decreases in C-reactive protein concentration reported in previous pilot studies

(16, 17). Median insulin and adiponectin concentrations increased in the salsalate groups (Figure 2, *D*).

Salsalate decreased mean triglyceride concentrations more than placebo (Table 3 and Figure 2, *E*); mean low-density lipoprotein cholesterol levels increased by 0.39 mmol/L (15 mg/dL) ($P = 0.002$) in the 3.0-g/d group compared with placebo, but did not differ from placebo in the other salsalate groups. Changes from baseline in total cholesterol and high-density lipoprotein cholesterol levels, total cholesterol– high-density lipoprotein cholesterol ratio (Figure 2, *F*), and free fatty acid concentration did not otherwise differ after adjustments; the latter finding contrasts with our earlier, shorter studies (5, 16).

Concentrations of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase did not differ among groups.

The SF-36 survey suggested improvement in the physical and social functioning subscales compared with placebo ($P = 0.02$), although total score did not change.

Renal Function

Median urinary albumin concentration, measured only at baseline and end of treatment and expressed as the albumin– creatinine ratio, increased in all salsalate groups compared with placebo. In the 3.5-g/d group, mean serum creatinine level increased by 8.0 μmol/L (0.09 mg/dL) ($P = 0.009$) but remained within the normal range, and estimated GFR (21) decreased by 8.8 mL/min per 1.73 m^2 ($P = 0.02$). The changes in urine albumin concentration were unrelated to changes in weight, blood pressure, and estimated GFR or to use of aspirin, angiotensin modulators, or antihypertensive medications (data not shown).

In contrast, neither cystatin C concentration nor the GFR calculated by using cystatin C changed in any salsalate treatment group compared with placebo. Salsalate decreased serum uric acid levels by −65 to −67 μmol/L (approximately 20%; $P = 0.003$), consistent with the established uricosuria seen with high-dose salicylate. Anion gap did not change. Thirty-five patients had in-clinic post-dosing visits, 6 in the placebo group and 11, 10, and 8 in the 3.0-g/d, 3.5-g/d, and 4.0-g/d salsalate groups, respectively. For those evaluated, blood pressure returned to baseline levels in all patients except 1 in the placebo group and 2 in each salsalate group, and estimated GFR returned to normal in all patients.

Adverse Events

No serious adverse events were attributable to salsalate. Mild gastrointestinal symptoms (heartburn, nausea, vomiting, or diarrhea) were more frequent among patients receiving salsalate (Table 4), although these did not lead to dosage changes. Hematocrit did not change, and we found no evidence of gastrointestinal bleeding.

Tinnitus, an expected side effect of high-dose salicylates, occurred less frequently than anticipated. Three patients (11%) in the placebo group and 5 to 6 patients (19% to 22%) in each salsalate group reported tinnitus. One patient with long-term tinnitus at baseline withdrew from the study; we reduced the dosage of salsalate for 3 other patients, 2 in the 3.5-g/d group and 1 in the 4.0-g/d group. Exposure rates (proportion of randomly assigned patients whose study medication was within 0.5 g/d of the dosage assigned) were therefore lowest (84%) for the 3.5-g/d group and ranged from 92% to 100% for the other groups. Tinnitus resolved in all patients.

Discussion

In our trial, designed to evaluate the safety and efficacy of salsalate to lower blood glucose concentrations in patients with type 2 diabetes, salsalate lowered HbA_{1c} and other measures of glycemic control (fasting blood glucose and glycated albumin). It lowered circulating triglyceride concentration and raised adiponectin concentration, which may predict decreased cardiovascular risk. Although we observed no major signs of increased cardiovascular risk, the changes in albuminuria and potential trends in low-density lipoprotein cholesterol and blood pressure warrant further careful assessment.

Our study adds to previous, short-term proof-of-concept findings by providing evidence of HbA_{1c} level reduction, the gold standard of clinical diabetes response. It also provides randomized dose comparison data and data on the durability of glycemic response over 3 months.

Several studies (5, 8, 9, 22) have shown that high-dose salicylate inhibits activity of the transcription factor NF-κB, which regulates the production of multiple inflammatory mediators. We have found that NF-κB activity is inhibited by salicylate in diabetic models (5) and circulating patient monocytes (16). Additional mechanisms that may contribute to the glucose-lowering effects of salicylates include inhibition of cellular kinases (23), upregulation of the heat shock response (24), and increases in circulating insulin concentrations (11, 16, 25). Thus, salsalate may decrease glucose concentration in multiple ways. However, the suggestion that salsalate decreases the glucose concentration only by increasing the insulin concentration is incorrect (26). Peroxisome proliferator–activated receptor-γ agonists are also associated with increased adiponectin concentration, but neither insulin nor a medication that increases insulin concentration, such as sulfonylureas, has shown the same ability to elevate adiponectin concentration (27) that we observed here and in our previous salicylate trials (16, 17).

Salsalate has been prescribed for decades to treat joint pain, without serious safety concerns specific to patients with diabetes. The advantage of salsalate is that it is a prodrug that comprises 2 esterified salicylate moieties, which renders it insoluble at acidic pH—allowing it to transit the stomach in suspension and cause less gastric irritation. Salsalate is subsequently hydrolyzed and is present in the blood as free salicylate. Salsalate and other nonacetylated salicylates are atypical nonsteroidal anti-inflammatory drugs whose primary targets are not the cyclooxygenases. This is demonstrated by the minimal effects of salsalate on circulating prostaglandin or renin concentrations (28). In contrast, the acetyl group of aspirin (acetylsalicylate) covalently modifies serine residues of COX-1 and COX-2, which inhibits the rate-limited step in prostaglandin synthesis. Aspirin's acetylation of COX-1 in platelets also accounts for its antithrombotic effects, which explains why salsalate does not alter bleeding times (29). Risk for gastrointestinal bleeding, as assessed by endoscopic and radiographic study, is lower for salsalate than for other nonsteroidal anti-inflammatory drugs and similar to placebo (30–32). Gastrointestinal side effects have been reported with salsalate, but they tend to occur early in therapy in patients with preexisting gastrointestinal disease (33, 34). Thus, we did not enroll patients with gastric ulcer disease in our study, and we neither expected nor observed any bleeding complications. Although some anti-inflammatory drugs are associated with an increased risk for infection, this is not a known side effect of salsalate, and we saw no indications of it in our study.

Hypoglycemia was the most common side effect we observed. Most cases were mild and did not require the assistance of others; documented hypoglycemia occurred only in patients who received sulfonylureas. Although hypoglycemia can be a safety issue, it is also an important indicator of drug efficacy.

Signals for renal safety were mixed. Urine albumin concentrations increased with drug dosage, although this was assessed only once and varies considerably with many conditions, including exercise, time of day, and dietary salt or protein intake. The small changes in creatinine level and estimated GFR, seen only in the 3.5-g/d salsalate group, are of unclear significance because cystatin C concentration, potentially a better marker of renal function (35), was unchanged. Uric acid levels decreased (36).

Although our trial was not designed to evaluate infrequent side effects or long-term risk, our findings are consistent with the safety profile of salsalate obtained from clinical experience in patients with rheumatologic conditions, with and without diabetes. Short-term administration to overweight persons improves endothelial function (37), a surrogate marker of vascular health, but it is important to establish cardiovascular safety. Further studies are needed before widespread clinical use of salsalate as a diabetes treatment can be recommended.

The salsalate dose range we selected for evaluation in the TINSAL-T2D trial was based on efficacy and tolerability established in pilot studies in patients with type 2 diabetes, as well as the therapeutic experience and tolerability of patients with rheumatic pain (16, 33). Although tinnitus occurred at all dosages at nearly twice the rate as with placebo, we permitted dosage adjustments, and only 1 patient stopped receiving the drug because of this established side effect. Gastrointestinal symptoms were more common among patients receiving salsalate, but this did not limit doses or increase dropouts. Our findings suggest that tolerability of salsalate in diabetes would be similar to that established in patients with joint pain.

In conclusion, salsalate was well tolerated in patients with type 2 diabetes and it improved measures of glycemic control over the 3-month trial. The drug's long-term safety in this population, and particularly its effects on renal function, require further investigation. Because of salsalate's anti-inflammatory effects, our results suggest that inflammation plays a role in the pathogenesis of type 2 diabetes and that anti-inflammatory therapy may therefore be useful for treating diabetes. We are conducting a longer trial involving more patients with type 2 diabetes to further establish whether a salsalate dosage of 3.5 g/d provides durable and safe control of blood glucose in this population (ClinicalTrials.gov registration number: NCT00799643).

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Appendix: Contributors

The trial protocol was designed and written by the steering committee: Steven E. Shoelson, MD, PhD (*Chair*); Allison B. Goldfine, MD; Vivian Fonseca, MD; Kathleen Jablonski, PhD; and Myrlene Staten, MD. The local institutional review boards of each participating center approved the protocol. The study statisticians, Kathleen Jablonski, PhD, and Laura Pyle, MS, analyzed the trial data. The manuscript was written by Drs. Goldfine and Shoelson, with contributions by Drs. Fonseca, Jablonski, and Staten and Ms. Pyle. The final submission was approved by Drs. Goldfine, Fonseca, Jablonski, Staten, and Shoelson and Ms. Pyle.

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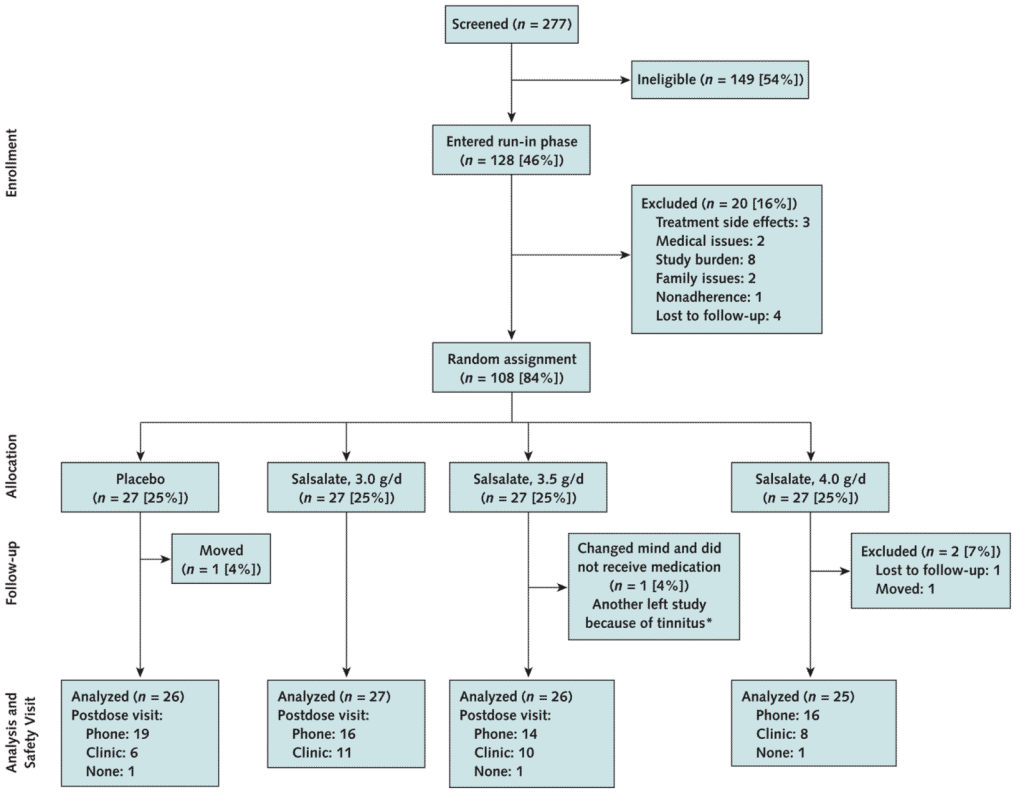

Figure 1. Study flow diagram

* Participant who did not receive medication was excluded; participant who withdrew because of tinnitus was included in analysis.

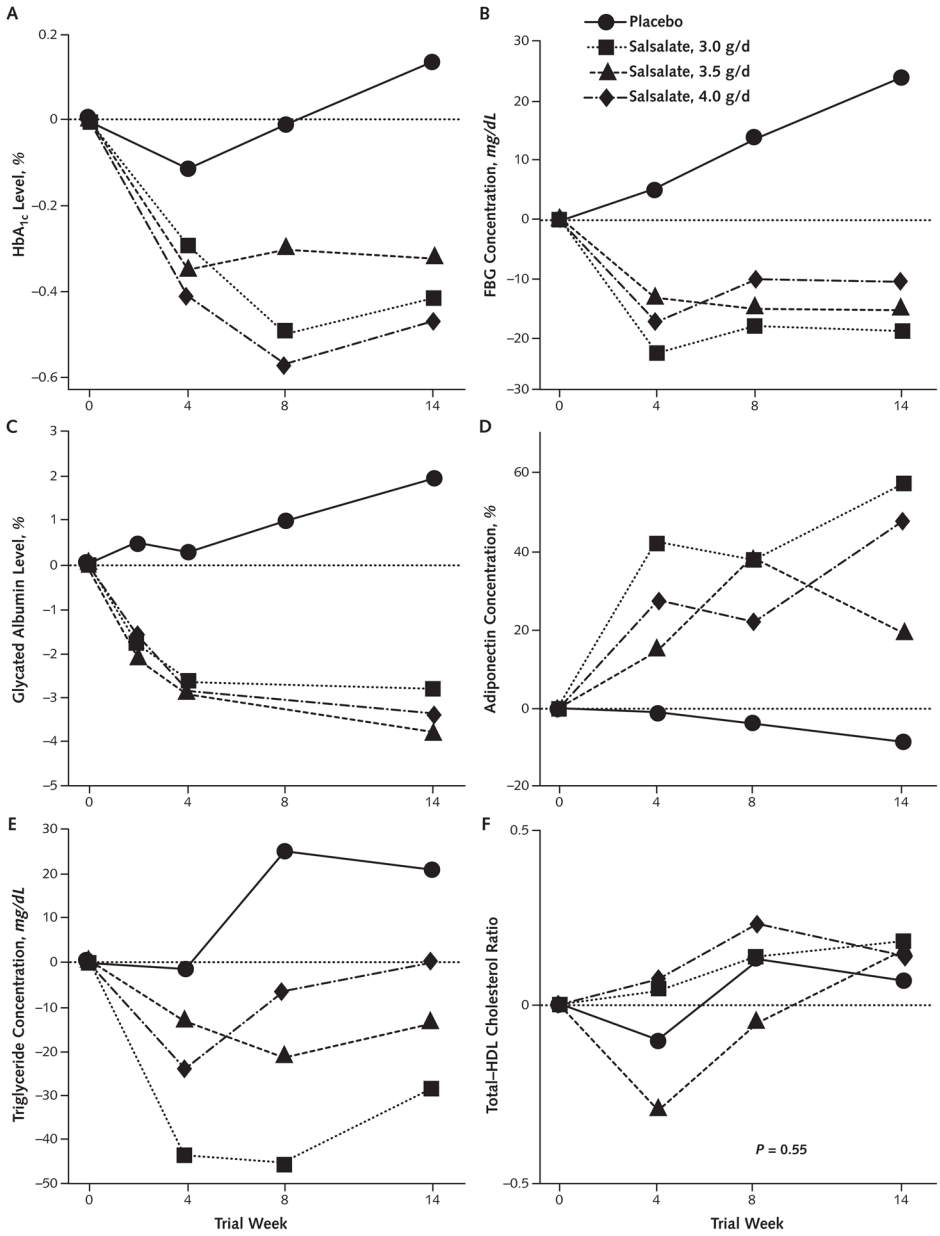

Figure 2. Changes in circulating metabolic measures, by study group

All data are provided as unadjusted mean changes. Each data point represents the mean value for all patients examined. We analyzed 27 patients at baseline in each group. This decreased to 26 patients in the 4.0-g/d group at 4 weeks; 26 and 25 patients in the 3.5- and 4.0-g/d groups, respectively, at 8 weeks; and 26 patients in the placebo and 3.5-g/d groups and 25 in the 4.0-g/d group at 14 weeks (Figure 1). We used the Holm procedure to adjust for multiple comparisons in all cases. FBG = fasting blood glucose; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein. **A.** Trends in HbA_{1c} level over time. The *F* test for the overall effect of treatment group was significant ($P = 0.003$) as was each pairwise test between placebo and salsalate ($P = 0.02$, 0.02, and 0.001 for the 3.0-g/d, 3.5-g/d, and 4.0-g/d groups, respectively). **B.** Trends in FBG concentration over time. To convert results from mg/dL to mmol/L, multiply by 0.0555. **C.** Trends in glycated albumin level over time. **D.** Trends in adiponectin concentration over time. The *F* test for each overall effect in panels *B*,

C, and *D* was significant ($P < 0.001$), as was each pairwise test between placebo and salsalate ($P < 0.001$ for all doses). **E.** Trends in triglyceride concentration over time. The *F* test for the overall effect of treatment group was significant ($P = 0.005$). Each pairwise test between placebo and salsalate was significant ($P = 0.002$, 0.02, and 0.03 for the 3.0-g/d, 3.5-g/d, and 4.0-g/d groups, respectively). To convert results from mg/dL to mmol/L, multiply by 0.0113. **F.** Trends in total–HDL cholesterol ratio over time. This ratio did not change ($P = 0.55$).

Table 1

Baseline Characteristics of Study Patients

Characteristic	Placebo (*n* = 27)	Salsalate, 3.0 g/d (*n* = 27)	Salsalate, 3.5 g/d (*n* = 27)	Salsalate, 4.0 g/d (*n* = 27)
Mean age (SD), *y*	55.9 (8.2)	55.4 (9.4)	56.7 (9.8)	55.0 (10.2)
Women, *n (%)*	12 (44.4)	13 (48.1)	9 (33.3)	11 (40.7)
Mean weight (SD), *kg*	99.1 (22.1)	92.9 (22.2)	97.7 (18.8)	102.2 (20.7)
Mean body mass index (SD), *kg/m²*	34.0 (6.1)	32.3 (6.8)	32.9 (6.5)	35.0 (6.5)
Mean waist circumference (SD), *cm*	104 (22.7)	103 (15.6)	106 (18.7)	109 (23.0)
Mean time since diabetes diagnosis (SD), *y*	5.1 (3.7)	6.4 (5.2)	6.9 (6.0)	6.4 (4.4)
Race or ethnicity, *n (%)*				
White	15 (55.6)	12 (44.4)	14 (51.9)	14 (51.9)
Black	9 (33.3)	12 (46.2)	10 (37.0)	10 (37.0)
Other	3 (11.1)	2 (7.4)	3 (11.1)	1 (3.7)
Medical history, *n (%)*				
Cardiovascular disease*	1 (3.7)	1 (3.7)	1 (3.7)	4 (14.8)
Hypertension†	20 (74.1)	19 (70.4)	19 (70.4)	18 (66.7)
Physical findings				
Mean systolic blood pressure (SD), *mm Hg*	125 (14)	125 (13)	124 (13)	128 (12)
Mean diastolic blood pressure (SD), *mm Hg*	76 (8)	79 (7)	77 (10)	76 (9)
Mean heart rate (SD), *beats/min*	74 (11)	72 (9)	74 (13)	72 (7.1)
Laboratory values				
Mean hemoglobin A_{1c} level (SD), *%*	7.8 (0.8)	7.9 (1.1)	7.4 (0.7)	7.6 (0.9)
Mean fasting glucose concentration (SD)				
mmol/L	8.49 (2.22)	8.55 (2.33)	8.27 (2.16)	7.99 (2.00)
mg/dL	153 (40)	154 (42)	149 (39)	144 (36)
Mean glycated albumin level (SD), *%*	4.4 (0.3)	4.5 (0.2)	4.4 (0.3)	4.4 (0.2)
Median insulin concentration (IQR)				
pmol/L	87.5 (121.5)	95.8 (73.6)	75.0 (40.3)	102.1 (110.4)
μU/mL	12.6 (17.5)	13.8 (10.6)	10.8 (5.8)	14.7 (15.9)
Mean C-peptide concentration (SD)				
nmol/L	1.2 (0.79)	1.0 (0.36)	1.0 (0.5)	1.0 (0.6)
ng/mL	3.6 (2.4)	2.9 (1.1)	3.0 (1.5)	3.0 (1.8)

Characteristic	Placebo (*n* = 27)	Salsalate, 3.0 g/d (*n* = 27)	Salsalate, 3.5 g/d (*n* = 27)	Salsalate, 4.0 g/d (*n* = 27)
Median TSH level (IQR), *mU/L*	1.6 (0.6)	1.5 (1.5)	1.7 (0.9)	1.5 (0.9)
Mean total cholesterol level (SD)				
mmol/L	4.7 (1.3)	4.3 (1.3)	4.8 (1.4)	4.4 (0.7)
mg/dL	180 (49)	164 (50)	186 (54)	170 (27)
Mean HDL cholesterol level (SD)				
mmol/L	1.2 (0.4)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
mg/dL	48 (14)	46 (12)	46 (11)	45 (12)
Mean LDL cholesterol level (SD)				
mmol/L	2.8 (1.1)	2.4 (0.8)	3.0 (1.2)	2.6 (0.7)
mg/dL	109 (44)	92 (32)	117 (46)	101 (25)
Mean triglyceride concentration (SD)				
mmol/L	2.1 (1.1)	2.1 (2.0)	1.7 (0.9)	1.8 (0.9)
mg/dL	183 (93)	184 (178)	151 (76)	160 (81)
Mean total–HDL cholesterol ratio (SD)	3.9 (1.3)	3.7 (1.1)	4.2 (1.5)	4.0 (1.3)
Median FFA concentration (IQR), *mmol/L*	0.60 (0.30)	0.60 (0.32)	0.61 (0.29)	0.60 (0.21)
Mean creatinine level (SD)				
μmol/L	74.26 (17.68)	76.91 (23.87)	80.44 (17.68)	69.84 (14.14)
mg/dL	0.84 (0.20)	0.87 (0.27)	0.91 (0.20)	0.79 (0.16)
Mean MDRD eGFR (SD), *mL/min per 1.73 m^2*	98.2 (19.9)	97.5 (24.4)	93.9 (23.8)	108.4 (26.2)
Mean cystatin C concentration (SD), *mg/L*	0.79 (0.15)	0.76 (0.12)	0.79 (0.18)	0.78 (0.12)
Mean CC eGFR (SD), *mL/min*	27.1 (4.2)	28.2 (4.2)	27.7 (6.3)	26.9 (3.5)
Mean uric acid level (SD), *μmol/L*	345 (72)	333 (95)	321 (77)	345 (83)
Median albumin–creatinine ratio (IQR), *μg/mg Cr*	8 (23)	8 (28)	9.5 (9)	10 (25)
Median ALT concentration (IQR), *U/L*	22 (13)	23 (21)	22 (11)	23 (18)
Median AST concentration (IQR), *U/L*	18 (10)	19 (8)	20 (7)	17 (9)
Median GGT concentration (IQR), *U/L*	32 (25)	32 (18)	29 (18)	21 (22)
Median CRP level (IQR), *nmol/L*	30.5 (51.4)	27.6 (31.4)	21.9 (20.0)	32.4 (81.9)
Mean hematocrit (SD), *%*	40.8 (4.2)	41.8 (3.0)	43.1 (3.9)	41.6 (4.2)
Mean leukocyte count (SD), *$\times 10^9$ cells/L*	6.6 (1.7)	7.3 (2.2)	6.4 (1.7)	6.7 (1.9)
Mean adiponectin concentration (SD), *μg/mL*	5.2 (4.2)	5.0 (4.1)	5.1 (4.9)	6.0 (6.2)

Characteristic	Placebo (*n* = 27)	Salsalate, 3.0 g/d (*n* = 27)	Salsalate, 3.5 g/d (*n* = 27)	Salsalate, 4.0 g/d (*n* = 27)
Ongoing diabetes therapies, *n (%)*				
Metformin	22 (81.5)	22 (81.5)	18 (66.7)	23 (85.2)
Insulin secretagogue	13 (48.1)	10 (37.0)	12 (44.4)	12 (44.4)
α-Glucosidase inhibitor	0 (0)	0 (0)	0 (0)	0 (0)
Dipeptidyl peptidase-4 inhibitor	1 (3.7)	1 (3.7)	0 (0)	0 (0)
≥2 diabetes drugs	12 (44.4)	10 (37.0)	8 (29.6)	11 (40.7)
Lifestyle modification only	4 (14.8)	4 (14.8)	5 (18.5)	3 (11.1)
Other relevant drugs, *n (%)*				
Low-dose aspirin	6 (22)	10 (37)	7 (26)	11 (41)
ACE inhibitor or ARB	21 (77)	18 (67)	13 (48)	15 (56)
Other antihypertensive medication[‡]	18 (67)	15 (56)	17 (63)	12 (44)
HMG-CoA reductase inhibitor (statin)	17 (63)	20 (74)	14 (52)	14 (52)
Other lipid-lowering medication[§]	2 (7)	4 (15)	3 (11)	0 (0)

ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; ARB = angiotensin-receptor blocker; AST = aspartate aminotransferase; CC eGFR = glomerular filtration rate estimated by using cystatin C level; CRP = C-reactive protein; FFA = free fatty acid; GGT = γ-glutamyltransferase; HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IQR = interquartile range; LDL = low-density lipoprotein; MDRD eGFR = glomerular filtration rate estimated by using the Modification of Diet in Renal Disease equation; TSH = thyroid-stimulating hormone.

[*] Defined as coronary heart disease, heart attack, percutaneous transluminal angioplasty, coronary artery bypass surgery, or stroke.

[†] Defined as systolic blood pressure >140 mm Hg; diastolic blood pressure >90 mm Hg; or receiving medication, such as diuretics, calcium-channel blockers, peripheral α-blockers, central α-adrenergic agonists, β-blockers, vasodilators, or reserpine.

[‡] Diuretics, calcium-channel blockers, peripheral α-blockers, central α-adrenergic agonists, β-blockers, vasodilators, or reserpine.

[§] Bile-acid sequestrants, fibrates, cholesterol absorption inhibitors, niacin, or nicotine acid.

Table 2

Response Rates for Decreasing HbA_{1c} Level by More Than 0.5%

Treatment Group	All Patients, *n*	Patients With >0.5% Decrease in HbA_{1c} Level, *n*	Proportion (95% CI)*
Placebo	26	4	0.15 (0.02–0.30)
Salsalate, 3.0 g/d	27	12	0.44 (0.26–0.63)
Salsalate, 3.5 g/d	26	14	0.54 (0.35–0.73)
Salsalate, 4.0 g/d	25	15	0.60 (0.42–0.78)

HbA_{1c} = hemoglobin A_{1c}.

* Calculated by using the chi-square test ($P = 0.009$).

Table 3

Outcomes Related to Safety and Efficacy*

Measurement	Placebo	Salsalate, 3.0 g/d			Salsalate, 3.5 g/d			Salsalate, 4.0 g/d			*F* Test *P* Value†
	Mean Change From Baseline (95% CI)	Mean Change From Baseline (95% CI)	Difference in Change‡	*P* Value§	Mean Change From Baseline (95% CI)	Difference in Change‡	*P* Value§	Mean Change From Baseline (95% CI)	Difference in Change‡	*P* Value§	
Vital signs											
Weight, *kg*	0.3 (−0.4 to 0.9)	0.8 (0.1 to 1.5)	0.6 (−0.3 to 1.4)	0.54	0.6 (−0.1 to 1.3)	0.3 (−0.5 to 1.1)	0.78	0.6 (−0.1 to 1.3)	0.4 (−0.5 to 1.2)	0.78	0.60
Systolic BP, *mm Hg*	0.3 (−3.2 to 3.8)	1.9 (−1.7 to 5.4)	1.6 (−2.8 to 5.9)	0.97	4.5 (1.0 to 8.0)	4.2 (−0.2 to 8.6)	0.190	1.8 (−1.8 to 5.4)	1.5 (−3.0 to 6.0)	0.97	0.31
Diastolic BP, *mm Hg*	−0.5 (−2.9 to 2.0)	0.8 (−1.7 to 3.2)	1.3 (−2.1 to 4.6)	0.93	2.1 (−0.4 to 4.5)	2.5 (−0.9 to 5.9)	0.43	0.2 (−2.3 to 2.7)	0.7 (−2.7 to 4.0)	0.93	0.51
Endocrine											
HbA_{1c} level, *%*	0.0 (−0.2 to 0.2)	−0.4 (−0.6 to −0.2)	−0.4 (−0.6 to −0.1)	0.017	−0.3 (−0.5 to −0.2)	−0.3 (−0.6 to −0.1)	0.017	−0.5 (−0.7 to −0.3)	−0.5 (−0.8 to −0.2)	0.001	0.003
Fasting glucose concentration				<0.001			<0.001			<0.001	<0.001
mmol/L	0.72 (0.11 to 1.33)	−1.05 (−1.67 to −0.44)	−1.8 (−2.9 to −1.2)		−0.78 (−1.4 to −0.17)	−1.5 (−2.1 to −0.8)		−0.83 (−1.4 to −0.22)	−1.565 (−2.2 to −0.94)		
mg/dL	13 (2 to 24)	−19 (−30 to −8)	−32 (−43 to −21)		−14 (−25 to −3)	−27 (−38 to −15)		−15 (−26 to −4)	−28 (−40 to −17)		
Glycated albumin level, *%*	0.2 (−0.4 to 0.7)	−2.4 (−2.9 to −1.9)	−2.5 (−3.1 to −2.0)	<0.001	−2.7 (−3.2 to −2.2)	−2.9 (−3.5 to −2.3)	<0.001	−2.3 (−2.8 to −1.8)	−2.5 (−3.1 to −1.9)	<0.001	<0.001
Insulin concentration			–¶	0.031**		–¶	0.28**		–¶	0.023**	0.010††
pmol/L	−3.0 (36)//	15 (27)||			7.6 (29)||			27 (58)||		
μU/mL	−0.4 (5.2)//	2.2 (4.0)||			1.1 (4.2)||			3.9 (8.4)||		
C-peptide concentration				0.129			0.25			0.37	0.20
nmol/L	0.10 (0.00 to 0.20)	−0.07 (−0.17 to 0.01)	−0.07 (−0.10 to 0.00)		−0.03 (−0.13 to 0.10)	−0.03 (−0.07 to 0.0)		0.03 (−0.07 to 0.13)	−0.00 (−0.07 to 0.03)		
ng/mL	0.3 (0.0 to 0.6)	−0.2 (−0.5 to 0.2)	−0.2 (−0.3 to 0.0)		−0.1 (−0.4 to 0.3)	−0.1 (−0.2 to 0.0)		0.1 (−0.2 to 0.4)	−0.0 (−0.2 to 0.1)		
TSH level, *mU/L*	0.1 (−0.3 to 0.4)	−0.1 (−0.4 to 0.3)	−0.1 (−0.6 to 0.3)	1.00	0.0 (−0.4 to 0.3)	−0.1 (−0.6 to 0.4)	1.00	0.1 (−0.3 to 0.4)	0.0 (−0.5 to 0.5)	1.00	0.93
Lipid											
Total cholesterol level				0.43			0.86			0.55	0.29

Measurement	Placebo	Salsalate, 3.0 g/d			Salsalate, 3.5 g/d			Salsalate, 4.0 g/d			*F* Test *P* Value[†]
	Mean Change From Baseline (95% CI)	Mean Change From Baseline (95% CI)	Difference in Change[‡]	*P* Value[§]	Mean Change From Baseline (95% CI)	Difference in Change[‡]	*P* Value[§]	Mean Change From Baseline (95% CI)	Difference in Change[‡]	*P* Value[§]	
mmol/L	0 (−0.2 to 0.2)	0.2 (0.03 to 0.41)	0.2 (−0.08 to 0.49)		−0.03 (−0.2 to 0.2)	−0.03 (−0.3 to 0.3)		0.2 (0.0 to 0.4)	0.2 (−0.1 to 0.4)		
mg/dL	0 (−7 to 8)	8 (1 to 16)	8 (−3 to 19)		−1 (−9 to 7)	−1 (−12 to 10)		6 (−1 to 14)	6 (−5 to 17)		
HDL cholesterol level				0.080			0.47			0.27	0.132
mmol/L	0 (−0.05 to 0.03)	0.1 (0.03 to 0.1)	0.1 (0 to 0.2)		0.03 (−0.03 to 0.08)	0.03 (−0.05 to 0.1)		0.05 (0 to 0.1)	0.05 (0.03 to 0.1)		
mg/dL	0 (−2 to 1)	3 (1 to 4)	3 (0 to 6)		1 (−1 to 3)	1 (−2 to 4)		2 (0 to 4)	2 (1 to 5)		
LDL cholesterol level				0.002			0.43			0.119	0.007
mmol/L	0 (−0.2 to 0.2)	0.4 (0.2 to 0.6)	0.39 (0.16 to 0.62)		0.08 (−0.08 to 0.26)	0.10 (−0.13 to 0.34)		0.21 (0.05 to 0.39)	0.23 (0 to 0.44)		
mg/dL	0 (−7 to 6)	15 (9 to 22)	15 (6 to 24)		3 (−3 to 10)	4 (−5 to 13)		8 (2 to 15)	9 (0 to 17)		
Triglyceride concentration				0.002			0.020			0.030	0.005
mmol/L	0.17 (−0.07 to 0.41)	−0.38 (−0.62 to −0.15)	−0.55 (−0.86 to −0.24)		−0.25 (−0.49 to 0.00)	−0.42 (−0.73 to −0.09)		−0.18 (−0.43 to 0.06)	−0.35 (−0.67 to −0.03)		
mg/dL	15 (−6 to 36)	−34 (−55 to −13)	−49 (−76 to −21)		−22 (−43 to 0)	−37 (−65 to −8)		−16 (−38 to 5)	−31 (−59 to −3)		
Total–HDL cholesterol ratio	0.0 (−0.2 to 0.3)	0.1 (−0.1 to 0.4)	0.1 (−0.3 to 0.4)	0.69	−0.1 (−0.3 to 0.2)	−0.1 (−0.4 to 0.2)	0.56	0.2 (−0.1 to 0.4)	0.1 (−0.2 to 0.5)	0.41	0.55
FFA concentration, *mmol/L*	−0.01 (0.32)[//]	−0.09 (0.30)[//]	–[¶]	0.36[**]	−0.07 (0.23)[//]	–[¶]	0.57[**]	−0.05 (0.17)[//]	–[¶]	0.42[**]	0.43[††]
Renal											
Creatinine level				0.83			0.009			0.56	0.012
μmol/L	−1.8 (−5.3 to 2.7)	−0.9 (−4.4 to 2.7)	0.9 (−4.4 to 5.3)		6.2 (2.7 to 9.7)	8.0 (2.7 to 13)		0.9 (−2.7 to 5.3)	2.7 (−2.7 to 8.0)		
mg/dL	−0.02 (−0.06 to 0.03)	−0.01 (−0.05 to 0.03)	0.01 (−0.05 to 0.06)		0.07 (0.03 to 0.11)	0.09 (0.03 to 0.15)		0.01 (−0.03 to 0.06)	0.03 (−0.03 to 0.09)		
MDRD eGFR, *mL/min per 1.73 m*[2]**	2.1 (−2.3 to 6.5)	−0.3 (−4.6 to 4.1)	−2.3 (−8.4 to 3.7)	0.45	−6.7 (−11.1 to −2.2)	−8.8 (−14.9 to −2.6)	0.016	−1.8 (−6.4 to 2.7)	−3.9 (−10.2 to 2.3)	0.43	0.040
Cystatin C concentration, *mg/L*	−0.02 (−0.04 to 0.00)	−0.03 (−0.05 to −0.01)	−0.02 (−0.04 to 0.01	0.81	−0.02 (−0.04 to −0.00)	−0.01 (−0.03 to 0.02)	0.81	−0.03 (−0.05 to −0.01)	−0.01 (−0.04 to 0.01)	0.81	0.68
CC eGFR, *mL/min***	0.7 (−0.1 to 1.5)	1.1 (0.3 to 1.8)	0.4 (−0.7 to 1.4)	1.00	1.1 (0.3 to 1.9)	0.4 (−0.7 to 1.4)	1.00	1.2 (0.4 to 2.0)	0.5 (−0.5 to 1.5)	1.00	0.80

Measurement	Placebo	Salsalate, 3.0 g/d			Salsalate, 3.5 g/d			Salsalate, 4.0 g/d			*F* Test *P* Value†
	Mean Change From Baseline (95% CI)	Mean Change From Baseline (95% CI)	Difference in Change‡	*P* Value§	Mean Change From Baseline (95% CI)	Difference in Change‡	*P* Value§	Mean Change From Baseline (95% CI)	Difference in Change‡	*P* Value§	
Uric acid level, *μmol/L*	11.90 (−23.79 to 41.64)	−53.54 (−83.28 to −23.79)	−65.43 (−107.07 to −23.79)	0.009	−71.38 (−101.12 to −35.69)	−77.33 (−124.92 to −35.69)	0.002	−53.54 (−89.23 to −23.79)	−65.43 (−113.02 to −23.79)	0.009	0.003
Albumin–creatinine ratio, *μg/mg Cr*	3 (8)‖	4 (20)‖	–¶	0.085**	10 (21)‖	–¶	0.032**	19 (40)‖	–¶	<0.001**	<0.001††
Hepatic											
ALT concentration, *U/L*	0 (10)‖	−2 (11)‖	–¶	0.57**	−1.5 (9.0)‖	–¶	0.86**	1 (13)‖	–¶	0.98**	0.51††
AST concentration, *U/L*	1 (5)‖	0 (6)‖	–¶	0.45**	1 (9)‖	–¶	1.00**	1 (9)‖	–¶	1.00**	0.51††
GGT concentration, *U/L*	0 (11)‖	−3 (10)‖	–¶	0.150**	−1 (12)‖	–¶	0.45**	0 (4.5)‖	–¶	0.48**	0.25††
Other											
CRP level, *nmol/L*	0.2 (19)‖	−0.6 (23)‖	–¶	0.68**	−1.9 (15)‖	–¶	0.45**	−4.8 (19)‖	–¶	0.35**	0.41††
Hematocrit, *%*	−0.5 (−1.4 to 0.4)	−0.5 (−1.3 to 0.4)	0.0 (−1.2 to 1.3)	0.97	0.8 (−0.0 to 1.7)	1.3 (0.1 to 2.6)	0.114	0.3 (−0.6 to 1.3)	0.8 (−0.4 to 2.1)	0.38	0.095
Leukocyte count, × 10^9 *cells/L*	−0.1 (−0.6 to 0.4)	−0.3 (−0.8 to 0.2)	−0.2 (−1.0 to 0.5)	0.63	−0.8 (−1.3 to −0.3)	−0.7 (−1.4 to 0.0)	0.175	−0.5 (−1.0 to 0.1)	−0.4 (−1.1 to 0.4)	0.63	0.28
Adiponectin concentration, *μg/mL*	−0.1 (−1.0 to 0.8)	2.6 (1.7 to 3.6)	2.7 (1.6 to 3.8)	<0.001	2.7 (1.8 to 3.7)	2.8 (1.7 to 3.9)	<0.001	1.6 (0.7 to 2.5)	1.7 (0.6 to 2.8)	0.003	<0.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CC eGFR = glomerular filtration rate estimated by using cystatin C level; CRP = C-reactive protein; FFA = free fatty acid; GGT = γ-glutamyltransferase; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MDRD eGFR = glomerular filtration rate estimated by using the Modification of Diet in Renal Disease equation; TSH = thyroid-stimulating hormone.

* All measures after overnight fast.

† Unless otherwise noted, *F* tests are mixed-model tests of the overall treatment effect after adjustment for clinic and follow-up time over the 14-week study.

‡ Provided for normally distributed variables only because we cannot provide statistically valid estimates (95% CIs) for nonnormally distributed (skewed) data.

§ From mixed models unless otherwise indicated, active treatment compared with placebo, and adjusted for multiple comparisons by using the Holm procedure; models are adjusted for clinic and follow-up time.

‖ Median (interquartile range).

¶ Nonnormally distributed variable.

** Wilcoxon 2-sample test with adjusted *P* values for multiple comparisons.

†† Kruskal–Wallis test testing the null hypothesis of no difference between treatment groups in change in measurements from baseline to 14 weeks.

Table 4

Adverse Events*

Adverse Events	Placebo (*n* = 27)		Salsalate, 3.0 g/d (*n* = 27)		Salsalate, 3.5 g/d (*n* = 27)		Salsalate, 4.0 g/d (*n* = 27)	
	Patients, *n*	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*	Events, *n*
Hyperglycemia	2	7	0	0	0	0	0	0
Hypoglycemia†								
All events	2	2	5	63	6	46	6	7
Not documented	1	1	2	13	2	11	3	3
Documented								
Mild	1	1	4	50	8	34	4	4
Severe	0	0	0	0	1	1	0	0
Neurologic								
Blurry vision	1	1	1	1	0	0	2	2
Dots or flashes	1	1	2	3	1	1	0	0
Ringing in the ears	3	5	5	6	6	6	5	5
Numbness or tingling	2	2	2	3	1	1	0	0
Cardiorespiratory								
Palpitations	0	0	1	1	0	0	2	4
Chest pain or discomfort	2	6	1	2	0	0	0	0
Swelling of legs or feet	1	1	2	2	1	1	1	1
Gastrointestinal								
Heartburn	0	0	3	4	1	1	4	5
Nausea	1	1	4	5	6	6	1	1
Vomiting	1	2	0	0	0	0	2	3

Adverse Events	Placebo (*n* = 27)		Salsalate, 3.0 g/d (*n* = 27)		Salsalate, 3.5 g/d (*n* = 27)		Salsalate, 4.0 g/d (*n* = 27)	
	Patients, *n*	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*	Events, *n*
Diarrhea	0	0	4	4	1	1	1	2
Musculoskeletal								
Stiffness	2	2	1	1	0	0	0	0
Muscle or joint pains	3	5	5	7	4	4	1	1
Arthritis	0	0	1	1	0	0	0	0
Backache	2	2	2	2	1	1	2	2
Infection	0	0	0	0	0	0	0	0
General								
Fainting	0	0	0	0	0	0	1	1
Dizziness	3	3	4	4	2	2	1	1
Weakness or fatigue	1	1	3	4	2	2	0	0

*A patient could have ≥1 symptoms.

†We considered patients to have undocumented hypoglycemia if they had symptoms consistent with hypoglycemia that were relieved by food but no laboratory confirmation; documented mild hypoglycemia if their glucose level was ≤3.33 mmol/L (≤60 mg/dL) by home glucose monitoring, but they did not require assistance; and documented severe hypoglycemia if their glucose level was ≤3.33 mmol/L (≤60 mg/dL) by home glucose monitoring and they did require assistance.