Salicylate (Salsalate) in Patients With Type 2 Diabetes
A Randomized Trial

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Background: Short-duration studies show that salsalate improves glycemia in type 2 diabetes mellitus (T2DM).

Objective: To assess 1-year efficacy and safety of salsalate in T2DM.

Design: Placebo-controlled, parallel trial; computerized randomization and centralized allocation, with patients, providers, and researchers blinded to assignment. (ClinicalTrials.gov: NCT00799643)

Setting: 3 private practices and 18 academic centers in the United States.

Patients: Persons aged 18 to 75 years with fasting glucose levels of 12.5 mmol/L or less ($\leq$225 mg/dL) and hemoglobin A_{1c} (HbA_{1c}) levels of 7.0% to 9.5% who were treated for diabetes.

Intervention: 286 participants were randomly assigned (between January 2009 and July 2011) to 48 weeks of placebo ($n = 140$) or salsalate, 3.5 g/d ($n = 146$), in addition to current therapies, and 283 participants were analyzed (placebo, $n = 137$; salsalate, $n = 146$).

Measurements: Change in hemoglobin A_{1c} level (primary outcome) and safety and efficacy measures.

Results: The mean HbA_{1c} level over 48 weeks was 0.37% lower in the salsalate group than in the placebo group (95% CI, −0.53% to −0.21%; $P < 0.001$). Glycemia improved despite more reductions in concomitant diabetes medications in salsalate recipients than in placebo recipients. Lower circulating leukocyte, neutrophil, and lymphocyte counts show the anti-inflammatory effects of salsalate. Adiponectin and hematocrit levels increased more and fasting glucose, uric acid, and triglyceride levels decreased with salsalate, but weight and low-density lipoprotein cholesterol levels also increased. Urinary albumin levels increased but reversed on discontinuation; estimated glomerular filtration rates were unchanged.

Limitation: Trial duration and number of patients studied were insufficient to determine long-term risk–benefit of salsalate in T2DM.

Conclusion: Salsalate improves glycemia in patients with T2DM and decreases inflammatory mediators. Continued evaluation of mixed cardiorenal signals is warranted.

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Salicylate is one of the oldest drugs in clinical practice, with documented use of relevant plant extracts for treating pain and inflammation dating back at least 3500 years (1). Nevertheless, its medicinal properties and mechanisms of action remain incompletely understood. Chemically pure forms were introduced during the 19th century (2, 3), but by the century's end, salicylate had been acetylated by chemists to yield aspirin, which became the most used—and most marketed—drug in history (1, 4). The mechanism of aspirin is well-established; the acetyl group covalently modifies a serine at the active site of the cyclooxygenase (COX) enzymes (5), making it the prototypic nonsteroidal anti-inflammatory drug (NSAID). Salicylate lacks an acetyl group and, thus, must have a different mechanism of action. Neither salicylate nor prodrugs, including salsalate or trilisate, which are marketed for pain, have been tested for efficacy and safety under what regulatory agencies now consider to be current standard practice in clinical trials.

Interest in salicylate was renewed after suggestions that it lowers blood glucose in type 2 diabetes mellitus (T2DM) (6). Results from proof-of-principle studies using salsalate in patients with T2DM demonstrated reduced blood glucose, triglyceride, free fatty acid, and C-reactive protein concentrations; improved glucose utilization during euglycemic hyperinsulinemic clamp (defined as the glucose infusion rate required to maintain euglycemia at steady state during insulin infusion); and increased circulating insulin and adiponectin levels (7). The National Institutes of Health–sponsored TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) trials determine whether this generic and inexpensive drug is safe, tolerated, and efficacious in diabetes. Stage 1, a dose-ranging study, was reported (8); stage 2 of TINSAL-T2D is a larger study to assess the magnitude and durability of glycemic efficacy over 1 year, tolerability, and an array of safety variables relevant to patients with diabetes.

METHODS
Design Overview
Stage 2 of TINSAL-T2D was a single-blind, placebo lead-in, randomized (1:1), placebo-controlled, parallel clinical trial to assess whether salsalate is superior to placebo in

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Context

Salicylate is one of the oldest drugs in clinical practice. Neither salicylate nor its prodrug forms, including salsalate, have been tested for efficacy and safety according to currently accepted regulatory practices. Preliminary data suggest that salsalate may improve glycemic control in type 2 diabetes.

Contribution

In this randomized trial of patients with type 2 diabetes and inadequate glycemic control, salsalate improved hemoglobin A_{1c} levels and decreased inflammatory markers over 1 year compared with placebo. Increases in weight and total and low-density lipoprotein cholesterol levels were seen, as was a reversible increase in albuminuria.

Implication

Salsalate may be an effective treatment for glucose control in type 2 diabetes, but further study on the effects on cardiac and renal disease is warranted.

—*The Editors*

patients with T2DM and inadequate glycemic control. Participants were randomly assigned between January 2009 and July 2011, and the last participant visit occurred in September 2011.

Setting and Participants

The study was conducted at 21 U.S. sites (3 private practice and 18 academic centers). Participants were recruited from practices or through advertising. Eligible adult patients were 75 years or younger; had hemoglobin A_{1c} (HbA_{1c}) levels of 7.0% to 9.5% at screening; and were treated by lifestyle modification or with metformin, insulin secretagogue, or dipeptidyl peptidase-4 inhibitor, alone or in combination. Participants using insulin, thiazolidinediones, glucagon-like peptide-1 agonists, NSAIDs, warfarin, or uricosuric agents were not eligible (**Appendix 2**, available at www.annals.org).

Randomization and Intervention

The protocol, approved by human subject institutional review boards, included 1-week screening; a 4-week, single-blind placebo run-in phase; pretreatment baseline evaluation; and 48 weeks of treatment. Salsalate was administered at 3.0 g daily for 2 weeks then escalated to 3.5 g daily, as tolerated, divided into 3 daily doses. Randomization was computer-generated in blocks of 4 with centralized allocation and codes secured at the data coordinating center. Participants were blinded during the run-in phase. Study participants, site investigators and staff, steering committee members, and data coordinating center staff responsible for clinical activities were blinded to treatment assignment. To assess study drug effect, we recommended that patients maintain stable dosages of diabetes, lipid-lowering, and hypertension medications for 24 weeks

whenever possible. Dose reductions in diabetes medications were immediate for hypoglycemia. After 24 weeks of randomization, good clinical practice was recommended with planned "rescue therapy" for very poorly controlled diabetes (**Appendix 2**).

Follow-up and Outcomes

Clinic visits followed an overnight fast at screening; run-in; randomization; and 4, 8, 12, 16, 24, 36, and 48 weeks to assess safety, adherence, and treatment response. A visit after dosing occurred at 50 weeks. An additional visit at week 56 was added for patients with persistent tinnitus, elevated urinary albumin levels, or increased blood pressure. Adverse events were assessed by questionnaire at follow-up visits. Quality of life was assessed using the Short Form-36 Health Survey at baseline and weeks 24 and 48. Clinical laboratory evaluations were done at Quest Diagnostics (Chantilly, Virginia).

The primary outcome was change in HbA_{1c} level. Key secondary outcomes included change in other variables to determine effects on glucose homeostasis and cardiometabolic risk (**Appendix 2**). Outcomes were assessed after the last patient visit. Hypoglycemia was classified 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 severe if patients required assistance.

Statistical Analyses

We calculated a sample size of 286 to detect a 0.5% difference in HbA_{1c} level between groups at week 48, based on 80% power, an α level of 0.05, an SD of 1.33, and a 20% withdrawal rate. We analyzed data following intention-to-treat principles, with persons in groups as assigned regardless of study drug adherence. Analyses included data from patients with baseline HbA_{1c} measurements through the end of the trial or withdrawal.

Differences in baseline characteristics between groups used analysis of variance for normally distributed continuous traits and chi-square or Fisher exact test for categorical traits. For normally distributed continuous outcomes, we estimated mean group differences using linear-regression mixed models, including HbA_{1c} measurements adjusted for baseline over the 48-week study. Natural log-transformations were used for variables with log-normal distributions. We assumed an autoregressive, moving-average covariance structure. Group was tested as a fixed effect and clinical center and study time were tested as random effects. For continuous outcomes with nonparametric distributions that could not be transformed to the normal distribution (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase), we used the Wilcoxon test to compare change from baseline between groups at week 48. Differences between categorized outcomes were tested using chi-square analysis. For testing recurring events, such as hypoglycemia, a patient was categorized as ever or never having the event. All statistical tests report 2-sided P values; a P value less than 0.050 was

considered significant. We used SAS, version 9.2 (SAS Institute, Cary, North Carolina) for analysis.

Role of the Funding Source

The study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases, which participated in study design and data interpretation. Caraco Pharmaceutical Laboratories (Detroit, Michigan) provided salsalate and placebo, LifeScan (Milpitas, California) provided glucometers and test strips, and Mercodia (Uppsala, Sweden) provided insulin assay materials. No private company had roles in trial design, conduct, data analysis, or manuscript preparation.

RESULTS

Baseline Characteristics

Of the 638 patients screened, 326 entered the 4-week placebo run-in phase and 286 were randomly assigned (140 to placebo and 146 to salsalate) (**Figure 1**). Groups were similar for multiple baseline characteristics (**Table 1**). Most participants (88.1%) used metformin, 40.9% took a single diabetes drug, 49% used dual therapy, and 5.6% were already using triple therapy. Only 4.5% of participants were treated with lifestyle modifications alone. Although HbA_{1c} levels were 7.0% to 9.5% at screening (mean, 7.85% [95% CI, 7.77% to 7.93%]), 5 weeks later at randomization after the single-blind placebo run-in phase, the mean HbA_{1c} level decreased by 0.15% (CI, −0.21% to −0.09%; $P < 0.001$, 1-sample t-test). Results were reported for the 137 placebo recipients and 146 salsalate recipients with a baseline HbA_{1c} measurement. For the primary outcome of change in HbA_{1c} level, the placebo group was missing 16% of measurements and the salsalate group was missing 17% due to participant withdrawal and laboratory specimen problems (**Figure 2**, *A*). When possible, missing laboratory results were redrawn at interim visits or at the next scheduled visit.

Study Adherence

Mean medication adherence rates were 91% for placebo and 92% for salsalate; 7.7% of participants had mean adherence less than 80%. Expected visits were 98% completed. Total and time to withdrawal did not differ between salsalate and placebo groups. No participants were unblinded during the trial.

Hemoglobin A_{1c} Level and Glycemic Control

The mean difference in HbA_{1c} levels over 48 weeks between the salsalate and placebo groups was −0.37% (CI, −0.53% to −0.21%; $P < 0.001$). The mean HbA_{1c} level in the salsalate group was 0.33% lower than at baseline after 48 weeks of treatment (CI, −0.44% to −0.22%; $P < 0.001$) and essentially unchanged (increase of 0.04%) over 48 weeks in the placebo group (CI, −0.08% to 0.15%; $P = 0.51$). Significant differences between groups were seen at every time point (**Figure 2**, *A*).

There was an interaction between baseline HbA_{1c} levels and group ($P < 0.001$). Baseline HbA_{1c} levels were not associated with change in HbA_{1c} levels in the placebo group ($P = 0.93$). For salsalate, baseline glycemia affected the magnitude of glycemic decreases, because participants with greater baseline HbA_{1c} levels had the greatest magnitudes of change. For every 1% increase in baseline HbA_{1c} level, the mean ($\pm$SE) decrease in HbA_{1c} levels over 48 weeks was 0.43% $\pm$ 0.081% greater ($P < 0.001$). At 48 weeks, more patients receiving salsalate (41% salsalate v. 23% placebo) achieved reductions of 0.5% or greater in HbA_{1c} levels ($P = 0.005$).

Consistent with HbA_{1c} levels decreasing, the mean change in fasting glucose level was −0.83 mmol/L (−15 mg/dL) greater for salsalate than placebo over 48 weeks (CI, −1.14 to −0.53 mmol/L [−20.5 to −9.6 mg/dL]; $P < 0.001$) (**Figure 2**, *C*).

Also related to glycemic control, mild hypoglycemic events occurred more frequently with salsalate than placebo. Forty-one participants receiving salsalate and 23 receiving placebo had mild hypoglycemic events ($P = 0.036$) (**Figure 2**, *B*), with a 6-fold increased relative risk for mild hypoglycemia when salsalate was added to sulfonylurea ($P < 0.001$). Fewer safety alerts for crossing hyperglycemic thresholds occurred for salsalate than placebo (**Figure 2**, *D*). Glycemia improved despite adjustments in concomitant diabetes medications in 76 participants (27%). Whereas numbers of adjustments were similar for salsalate ($n = 39$) and placebo ($n = 37$), dose reductions and discontinuations were more frequent for salsalate (62%) than placebo (13%). Conversely, concomitant diabetes medications were increased and new therapies instituted more frequently for patients receiving placebo (87%) than those receiving salsalate (38%) ($P < 0.001$) (**Appendix Tables 1 and 2**, available at www.annals.org).

The paradoxical increase in fasting insulin and decrease in C-peptide concentrations for salsalate compared with placebo were seen, as in previous reports (**Table 2**) (7, 8).

Other Measures of Efficacy and Safety

Anti-inflammatory effects of salsalate were evidenced by changes in circulating leukocyte and differential counts. Mean differences in change over 48 weeks demonstrated decreases in leukocyte, neutrophil, and lymphocyte counts with salsalate compared with placebo (**Table 2** and **Figure 3**, *A*, *C*, and *E*). All counts remained within normal ranges.

Adiponectin, a potentially cardioprotective protein from adipocytes, increased by 27% over 48 weeks ($P < 0.001$) compared with placebo. Uric acid levels, which are associated with cardiometabolic conditions and progression of renal insufficiency, decreased by 18% in salsalate versus placebo groups ($P = 0.003$) (**Table 2**; **Figure 3**, *D*; and **Figure 4**, *B*).

Figure 1. Study flow diagram.
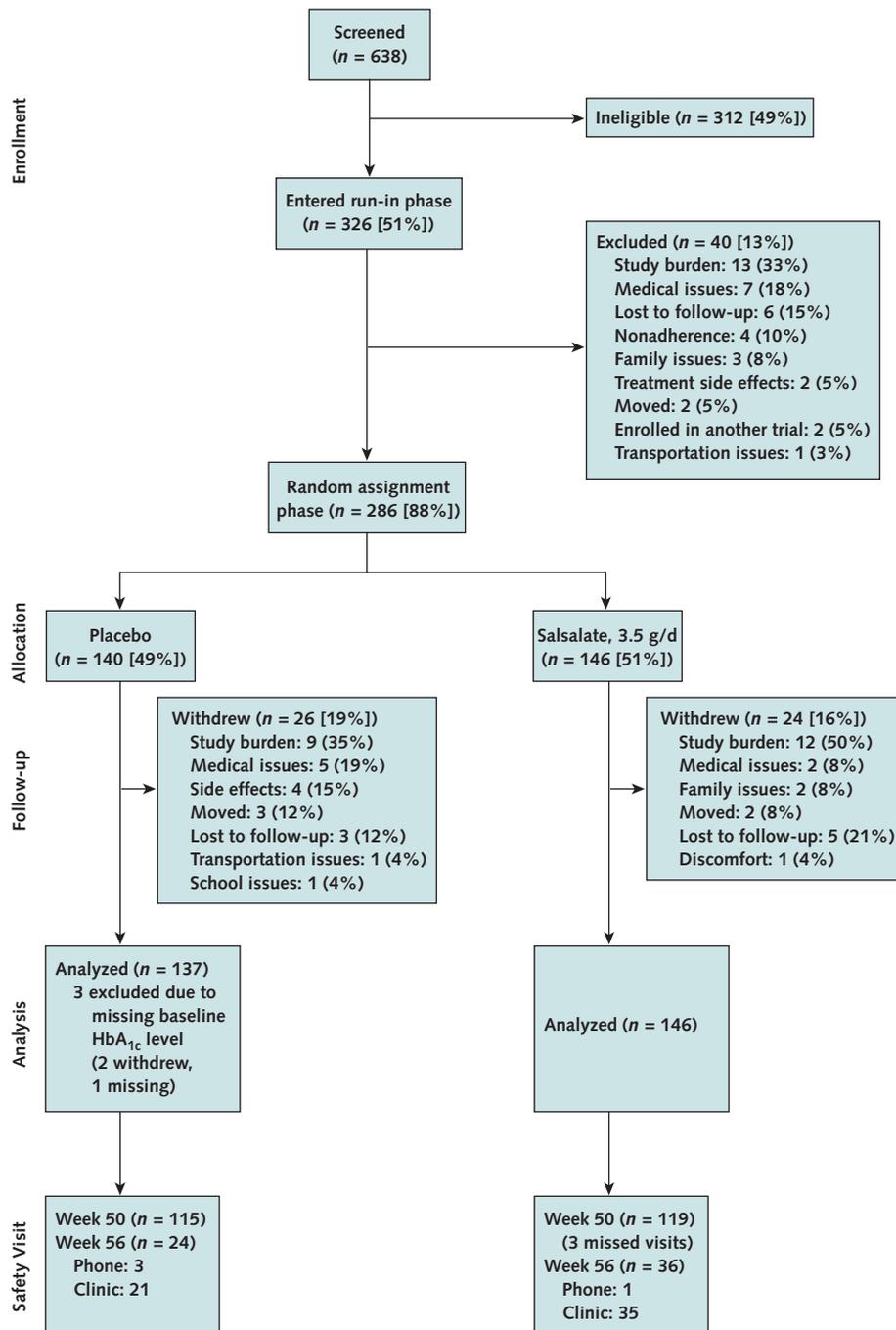
All data were used through trial completion or point of withdrawal for patients with a baseline HbA_{1c} measurement. Two participants withdrew after randomization but before the blood draw; 1 additional participant did not have baseline HbA_{1c} measurement from the laboratory. Percentages may not sum to 100 due to rounding. HbA_{1c} = hemoglobin A_{1c}.

For salsalate recipients, there was a 1.3-kg placebo-corrected increase in weight ($P < 0.001$), a trend toward increased systolic blood pressure, and lower heart rate ($P = 0.010$) (**Table 2**).

Salsalate decreased median triglyceride concentrations by 9% compared with placebo ($P = 0.002$). In contrast,

mean total and directly measured low-density lipoprotein (LDL) cholesterol levels (**Figure 3**, *F*) both increased ($P < 0.001$) with salsalate versus placebo, without changes in high-density lipoprotein (HDL) cholesterol levels. Increased LDL cholesterol levels in the salsalate group were independent of baseline statin use.

Alanine aminotransferase trended lower and γ-glutamyltransferase levels decreased (**Table 2**) with salsalate compared with placebo.

Renal Function

The urinary albumin–creatinine ratio (ACR) increased by 2.3 μg/mg (CI, 2.0 to 2.7 μg/mg; $P < 0.001$) in patients treated with salsalate compared with placebo (**Figure 4**, *A*). Of 248 participants with urinary ACRs less than 30 μg/mg at screening and baseline, 7 of the 120 receiving placebo compared with 24 of 128 participants receiving salsalate had greater values at week 48. However, if the urinary ACR increased to greater than 30 μg/mg at any time during randomized treatment, it tended to remain increased in the placebo group (**Figure 4**, *C*) but reversed during the 8-week washout period in the salsalate group (**Figure 4**, *D*). One participant in each group had frank albuminuria (ACR >300 μg/mg) at the end of the study. Change in weight, blood pressure, and salicylate concentrations were modestly correlated with changes in albuminuria, but estimated glomerular filtration rate (GFR), aspirin use, and antihypertensive medications—including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers—were not correlated (data not shown).

Estimated GFR did not change within or between groups ($P = 0.176$) (**Figure 4**, *E*). However, serum creatinine levels were greater with salsalate than with placebo ($P = 0.008$). In contrast, serum cystatin C levels did not differ between groups ($P = 0.50$) and, similarly, estimated GFR calculated using cystatin C levels did not change between salsalate and placebo groups ($P = 0.28$) (**Figure 4**, *F*).

Table 1. **Baseline Characteristics, by Treatment Group***

Characteristic	Total (n = 286)	Placebo (n = 140)	Salsalate (n = 146)
Mean age (SD), y	55.8 (9.6)	55.8 (10.0)	55.8 (9.2)
Male sex	156 (54.5)	74 (52.9)	82 (56.2)
Race/ethnity†			
White	151 (52.8)	75 (53.6)	76 (52.1)
Black	95 (33.2)	47 (33.6)	48 (32.9)
Other	40 (14.0)	18 (12.9)	22 (15.1)
BMI (SD), kg/m²	33.3 (6.7)	33.2 (6.8)	33.3 (6.7)
Median time since diabetes diagnosis (min, max), y	4.9 (0.1, 38.3)	4.9 (0.2, 35.0)	5.3 (0.1, 38.3)
Medical history			
Established CVD‡	32 (11.2)	14 (10.0)	18 (12.3)
Hypertension§	208 (72.7)	101 (72.1)	107 (73.3)
Dyslipidemia‖	199 (69.6)	97 (69.3)	102 (69.9)
Family history¶ of T1DM	13 (4.5)	6 (4.3)	7 (4.8)
Family history¶ of T2DM	190 (66.4)	93 (66.4)	97 (66.4)
Family history¶ of CVD	163 (57.0)	82 (58.6)	81 (55.5)
Taking diabetes medications			
Metformin	252 (88.1)	124 (88.6)	128 (87.7)
Insulin secretagogue	149 (52.1)	65 (46.4)	84 (57.5)
α-Glucosidase inhibitor	1 (0.3)	0 (0.0)	1 (0.7)
DPP-4 inhibitor	43 (15.0)	20 (14.3)	23 (15.8)
Lifestyle only (no diabetes drugs)	13 (4.5)	7 (5.0)	6 (4.1)
Taking 1 diabetes medication	117 (40.9)	62 (44.3)	55 (37.7)
Taking 2 diabetes medications	140 (49.0)	66 (47.1)	74 (50.7)
Taking 3 diabetes medications	16 (5.6)	5 (3.6)	11 (7.5)
Taking lipid medications**	180 (62.9)	85 (60.7)	95 (65.1)
Statin	171 (59.8)	80 (57.1)	91 (62.3)
Other lipid medications	28 (9.8)	13 (9.3)	15 (10.3)
Taking antihypertensive medications††	185 (64.7)	91 (65.0)	94 (64.4)
ACE inhibitor or ARB	159 (55.6)	75 (53.6)	84 (57.5)
Other antihypertensive medications	111 (38.8)	62 (44.3)	49 (33.6)
Taking low-dose aspirin‡‡	116 (40.6)	57 (40.7)	59 (40.4)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; max = maximum; min = minimum; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
* All values are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100 due to rounding.
† Patients appearing in >1 category are grouped with "other."
‡ A history of stroke, angina, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty.
§ Systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or taking antihypertensive drugs, including loop, thiazide, or potassium-sparing diuretics, potassium supplements, ACE inhibitors, ARBs, calcium-channel blockers, peripheral α-blockers, central α-adrenergic agonists, β-blockers, vasodilators, or reserpine.
‖ Low-density lipoprotein cholesterol level >3.89 mmol/L (>150 mg/dL) or taking cholesterol-lowering drugs, including bile acid sequestrants, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), fibrates, cholesterol absorption inhibitors, niacin, and nicotinic acid.
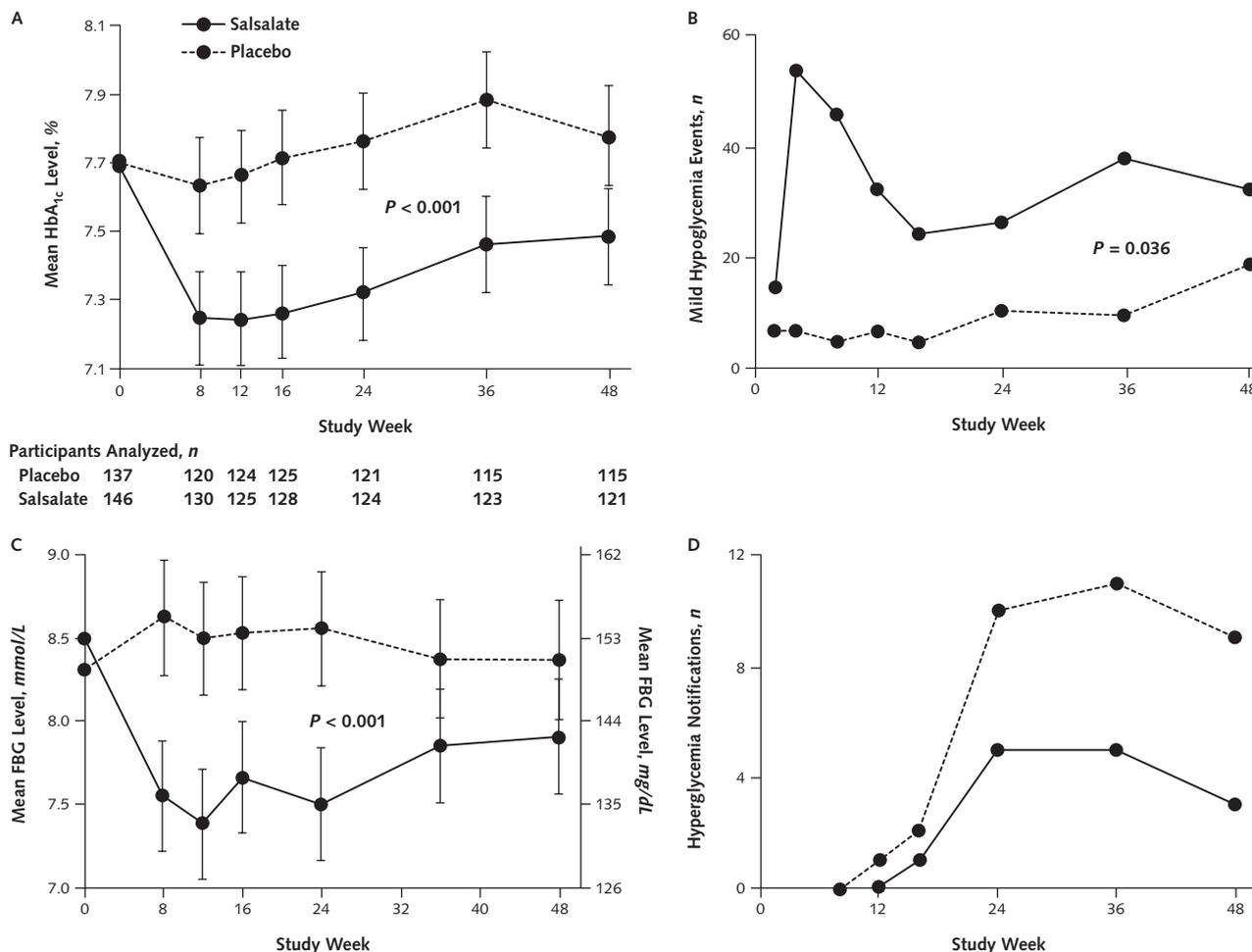¶ First-degree relatives.
** Some participants take statins and "other" lipid medications.
†† Some participants take ACE inhibitors or ARBs and "other" antihypertensive agents.
‡‡ 81–325 mg/d.

Figure 2. Glycemic effects of salsalate.

HbA$_{1c}$ (A) and FBG (C) levels are graphed as unadjusted means and 95% CIs. In panel A, the numbers of participants analyzed for the primary end point of HbA$_{1c}$ levels at each time point are displayed below study week. Mild hypoglycemia events (B) and notifications for hyperglycemia (D) sent to the primary caregivers are based on HbA$_{1c}$ levels >10.5% before week 24 and >9.5% after week 24. Participants could have >1 mild hypoglycemic event or exceed the hyperglycemic threshold >1 time during the trial. FBG = fasting blood glucose; HbA$_{1c}$ = hemoglobin A$_{1c}$.

Adverse Events

No serious adverse events were attributed to salsalate. Tinnitus, an expected adverse effect of high-dose salicylates, was reported by 16 (11%) patients receiving salsalate and 7 (5%) receiving placebo ($P = 0.082$). Two placebo recipients and 7 salsalate recipients had dose adjustments for tinnitus ($P = 0.174$, Fisher exact test). Tinnitus resolved or returned to baseline in all participants by the end of the study. There was no evidence of gastrointestinal bleeding by history, and hematocrit levels actually increased ($P < 0.001$) (**Figure 3**, D). The Short Form-36 questionnaire did not detect differences in quality of life. Adverse events that occurred with frequencies of 5% or greater and numerically more frequently in salsalate recipients than placebo recipients are listed in **Appendix Table 3** (available at www.annals.org). Gastrointestinal side ef-

fects did not differ between groups (**Appendix Table 4**, available at www.annals.org).

DISCUSSION

This trial evaluated glycemic effects of salsalate compared with placebo as add-on therapy for patients with inadequately treated, established T2DM. Salsalate reduced both HbA$_{1c}$ and fasting blood glucose levels at all study time points. The magnitude of glycemic improvement in the first few months was consistent with those seen in our previous trial, which also included patients with established diabetes who were using as many as 3 oral diabetes medications (8), but was lower in magnitude than the between-group 2.3% reduction in HbA$_{1c}$ levels seen over 12 weeks in drug-naive patients with new-onset T2DM (9). The

Table 2. **Baseline Clinical and Biochemical Status and Change From Baseline During Study, by Treatment Group**

Variable	Placebo		Salsalate		Difference in Change (95% CI)*	P Value†
	Mean Baseline Value (SD)	Mean Change From Baseline (95% CI)	Mean Baseline Value (SD)	Mean Change From Baseline (95% CI)		
Vital signs						
Weight, *kg*	95.4 (22.3)	−0.40 (−0.76 to −0.04)	97.0 (22.7)	0.94 (0.59 to 1.30)	1.34 (0.85 to 1.84)	<0.001
Heart rate, *beats/min*	72 (10)	1.1 (0.2 to 2.0)	74 (10)	−0.7 (−1.6 to 0.2)	−1.8 (−3.0 to 0.5)	0.007
Systolic BP, *mm Hg*	126.4 (13.9)	0.6 (−0.6 to 1.8)	125.9 (12.9)	2.1 (1.0 to 3.3)	1.6 (−0.1 to 3.2)	0.063
Diastolic BP, *mm Hg*	76.9 (8.0)	0.5 (−0.3 to 1.2)	76.0 (8.8)	0.8 (0.1 to 1.6)	0.4 (−0.7 to 1.4)	0.49
Endocrine						
HbA$_{1c}$ level, %	7.7 (0.7)	0.04 (−0.07 to 0.15)	7.7 (0.7)	−0.33 (−0.44 to −0.22)	−0.37 (−0.53 to −0.21)	<0.001
Fasting glucose level						
mmol/L	8.30 (2.09)	0.11 (−0.11 to 0.33)	8.49 (2.14)	−0.72 (−0.94 to −0.51)	−0.83 (−1.14 to −0.53)	<0.001
mg/dL	150 (38)	2.0 (−1.9 to 5.9)	153 (39)	−13.1 (−16.9 to −9.2)	−15.0 (−20.5 to −9.6)	<0.001
Insulin level, *pmol/L*	87.4 (56.1 to 141.2)‡	2.9 (−4.0 to 10.4)§	96.1 (69.5 to 152.4)‡	15.2 (6.9 to 24.0)§	10.5 (0.3 to 21.8)	0.042§
C-peptide level						
nmol/L	0.92 (0.42)	0.01 (−0.03 to 0.05)	1.00 (0.43)	−0.07 (−0.11 to −0.03)	−0.08 (−0.14 to −0.02)	0.009
ng/mL	2.76 (1.25)	0.03 (−0.10 to 0.16)	2.94 (1.28)	−0.21 (−0.34 to −0.08)	−0.24 (−0.42 to −0.06)	0.009
Lipids						
Total cholesterol level						
mmol/L	4.29 (1.04)	0.00 (−0.08 to 0.09)	4.27 (1.09)	0.22 (0.14 to 0.31)	0.22 (0.10 to 0.34)	<0.001
mg/dL	166 (40)	0.0 (−3.3 to 3.3)	165 (42)	8.6 (5.4 to 11.9)	8.6 (4.0 to 13.2)	<0.001
HDL cholesterol level						
mmol/L	1.26 (0.33)	0.03 (0.01 to 0.05)	1.20 (0.32)	0.02 (0.00 to 0.04)	−0.01 (−0.04 to 0.02)	0.50
mg/dL	48.65 (12.74)	1.16 (0.39 to 1.93)	46.33 (12.36)	0.77 (0.00 to 1.54)	−0.39 (−1.54 to 0.77)	0.50
LDL cholesterol level						
mmol/L	2.64 (0.82)	−0.02 (−0.10 to 0.05)	2.64 (0.89)	0.27 (0.20 to 0.34)	0.29 (0.19 to 0.40)	<0.001
mg/dL	102 (32)	−0.8 (−3.7 to 2.1)	102 (35)	10.4 (7.6 to 13.3)	11.2 (7.2 to 15.3)	<0.001
Triglyceride level						
mmol/L	1.51 (1.07 to 2.19)‡	−0.05 (−0.11 to 0.02)§	1.56 (1.12 to 2.20)‡	−0.18 (−0.24 to −0.12)§	−0.14 (−0.22 to −0.05)§	0.002§
mg/dL	134 (95 to 194)‡	−4.4 (−9.7 to −1.8)§	138 (99 to 195)‡	−15.9 (−21.2 to −10.6)§	−12.4 (−19.5 to −4.4)§	0.002§
FFA level, *mmol/L*	0.48 (0.23)	−0.02 (−0.04 to 0.01)	0.50 (0.22)	−0.00 (−0.03 to 0.02)	0.02 (−0.02 to 0.05)	0.41
Total–HDL cholesterol ratio	3.58 (1.07)	−0.10 (−0.19 to −0.01)	3.75 (1.16)	0.21 (0.12 to 0.30)	0.31 (0.19 to 0.44)	<0.001
Renal						
Creatinine level						
μmol/L	73.5 (14.9)	−0.5 (−1.7 to 0.7)	72.4 (15.0)	1.8 (0.6 to 3.0)	2.3 (0.6 to 4.0)	0.007
mg/dL	0.83 (0.17)	−0.01 (−0.02 to 0.01)	0.82 (0.17)	0.02 (0.01 to 0.03)	0.03 (0.01 to 0.05)	0.007
MDRD eGFR, *mL/min per 1.73 m²*	99.0 (19.9)	1.2 (−0.9 to 3.3)	101.6 (21.7)	−0.8 (−2.8 to 1.3)	−2.0 (−4.9 to 0.9)	0.178
Cystatin C level, *mg/L*	71.7 (15.1)	−1.2 (−2.6 to 0.2)	72.2 (14.6)	−1.9 (−3.2 to −0.5)	−0.7 (−2.6 to 1.3)	0.50
Cystatin C–based eGFR, *mL/min per 1.73 m²*	22.7 (4.4)	0.4 (−0.05 to 0.8)	22.4 (4.2)	0.71 (0.3 to 1.1)	0.3 (−0.3 to 0.9)	0.28
Uric acid level, *μmol/L*	349 (90)	−10.7 (−21.6 to 0.28)	371 (87)	−71.3 (−82.1 to −60.5)	−60.7 (−76.0 to −45.3)	<0.001
ACR, *μg/mg*	8.0 (5.0 to 13.0)‡	1.1 (1.0 to 1.2)	7.0 (5.0 to 13.0)‡	2.6 (2.3 to 2.8)	2.3 (2.0 to 2.7)	<0.001§
Hepatic						
ALT level, *U/L*	0.35 (0.27 to 0.52)‡	0.00 (−0.10 to 0.05)‡	0.33 (0.25 to 0.52)‡	−0.03 (−0.10 to 0.03)‡		0.068‖
AST level, *U/L*	0.32 (0.25 to 0.42)‡	0.00 (−0.05 to 0.05)‡	0.32 (0.25 to 0.40)‡	0.00 (−0.05 to 0.03)‡		0.81‖
GGT level, *U/L*	0.45 (0.32 to 0.72)‡	0.00 (−0.12 to 0.05)‡	0.43 (0.32 to 0.60)‡	−0.03 (−0.12 to 0.03)‡		<0.001‖
Albumin level, *g/L*	44.0 (2.9)	−0.03 (−0.3 to 0.2)	43.7 (2.7)	−1.9 (−2.2 to −1.7)	−1.9 (−2.3 to −1.5)	<0.001
Other						
Hematocrit, %	41.2 (4.1)	−0.19 (−0.48 to 0.10)	41.3 (4.3)	0.60 (0.31 to 0.88)	0.79 (0.39 to 1.19)	<0.001
Leukocyte count, × 10⁹ *cells/L*	6.60 (1.93)	0.00 (−0.14 to 0.15)	7.00 (2.09)	−0.63 (−0.77 to −0.48)	−0.63 (−0.83 to −0.43)	<0.001
Neutrophil count, × 10⁹ *cells/L*	2.12 (0.72)	−0.02 (−0.07 to 0.04)	2.16 (0.67)	−0.27 (−0.32 to 0.21)	−0.25 (−0.32 to −0.18)	0.001
Lymphocyte count, × 10⁹ *cells/L*	3.89 (1.44)	−0.4 (−0.17 to 0.10)	4.31 (1.70)	−0.36 (−0.50 to −0.23)	−0.32 (−0.52 to −013)	<0.001
Adiponectin level, *μg/mL*	3.98 (3.02 to 6.00)§	0.25 (0.08 to 0.43)§	4.17 (3.06 to 5.86)‡	1.51 (1.29 to 1.74)§	1.16 (0.88 to 1.47)§	<0.001§
hs-CRP level, *nmol/L*	33.1 (16.3 to 58.8)‡	−0.68 (−3.51 to 2.45)§	32.5 (14.7 to 67.7)‡	−2.45 (−5.06 to 0.43)§	−1.80 (−5.51 to 2.46)§	0.39§
TNF-α level, *pg/mL*	1.69 (0.79)	0.00 (−0.07 to 0.07)§	1.83 (2.31)	0.05 (−0.02 to 0.11)§	0.05 (−0.05 to 0.15)§	0.32§
TNF–receptor 1 level, *ng/mL*	3.06 (0.72)	−0.04 (−0.11 to 0.03)§	3.04 (0.83)	−0.06 (−0.13 to 0.01)§	−0.00 (−0.13 to 0.08)§	0.62§
TNF–receptor 2 level, *ng/mL*	8.21 (1.95)	−0.21 (−0.41 to −0.01)§	8.14 (2.20)	−0.05 (−0.25 to 0.15)§	0.16 (−0.13 to 0.46)§	0.28§

ACR = albumin–creatinine ratio; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; eGFR = estimated glomerular filtration rate; FFA = free fatty acid; GGT = γ-glutamyltransferase; HbA$_{1c}$ = hemoglobin A$_{1c}$; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MDRD = Modification of Diet in Renal Disease; TNF = tumor necrosis factor.
* Salsalate minus placebo.
† Unless otherwise noted, *P* values are mixed-model tests of the overall treatment effect after adjustment for clinical and follow-up time over the 48-wk study.
‡ Median (25th–75th percentiles).
§ Test based on natural log-transformation, results are back-transformed, and the change ratio is multiplied by the group mean.
‖ Wilcoxon 2-sample test; 2-sided *P* > |Z|. The probability test statistic was calculated using the *Z*-score from a standard normal table; there are no estimates of a difference in change when rank testing was used.

Figure 3. Mean values and 95% CIs for leukocyte count (A), hematocrit (B), neutrophil count (C), adiponectin level (D), lymphocyte count (E), and LDL cholesterol level (F).
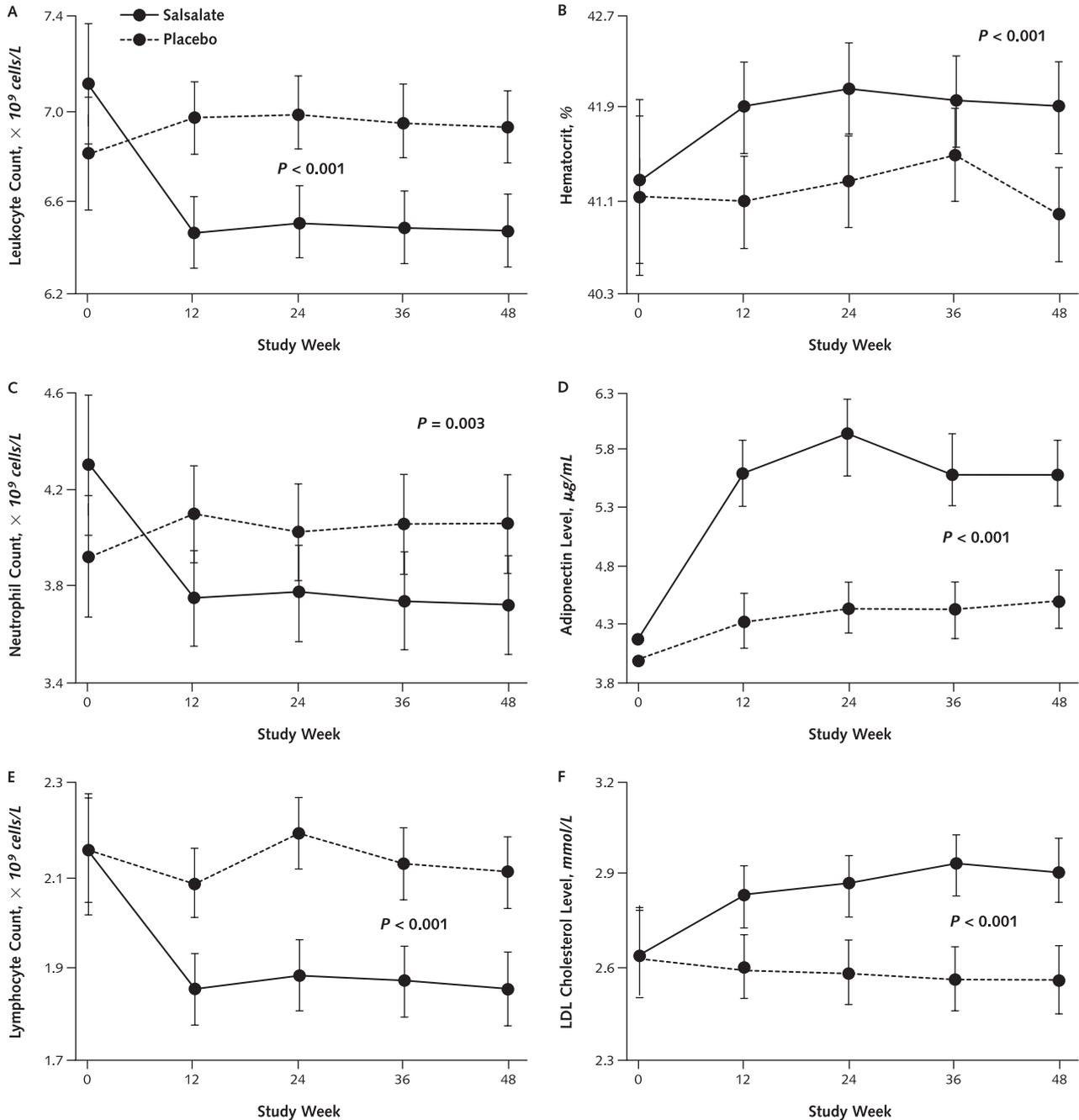
LDL = low-density lipoprotein.

magnitude of change in HbA_{1c} levels with salsalate was similar to that seen in recent studies for other marketed drugs used clinically to treat T2DM in which baseline HbA_{1c} levels were less than 8%. For example, a recent study compared linagliptin with glimepiride in patients receiving metformin. The baseline HbA_{1c} level of 7.7% was similar to participants in our study. The mean changes in

HbA_{1c} level was −0.16% for linagliptin −0.36% for glimepiride (10). The effect of salsalate on HbA_{1c} levels of −0.37% was of similar magnitude.

There was attenuation of HbA_{1c} levels decreasing at 1 year. This was partially attributable to adjustments in concomitant diabetes medications, which had been discouraged during the first 24 weeks of the trial. Disease progres-

sion and attenuation of drug efficacy may contribute. Concomitant diabetes medications were adjusted in more than 25% of participants, with more reductions for participants who received salsalate and more increases for those who received placebo, thus diminishing estimates of salsalate efficacy.

Hypoglycemia is both a measure of efficacy and the most commonly seen side effect in this trial. The relative

Figure 4. Renal effects of salsalate.
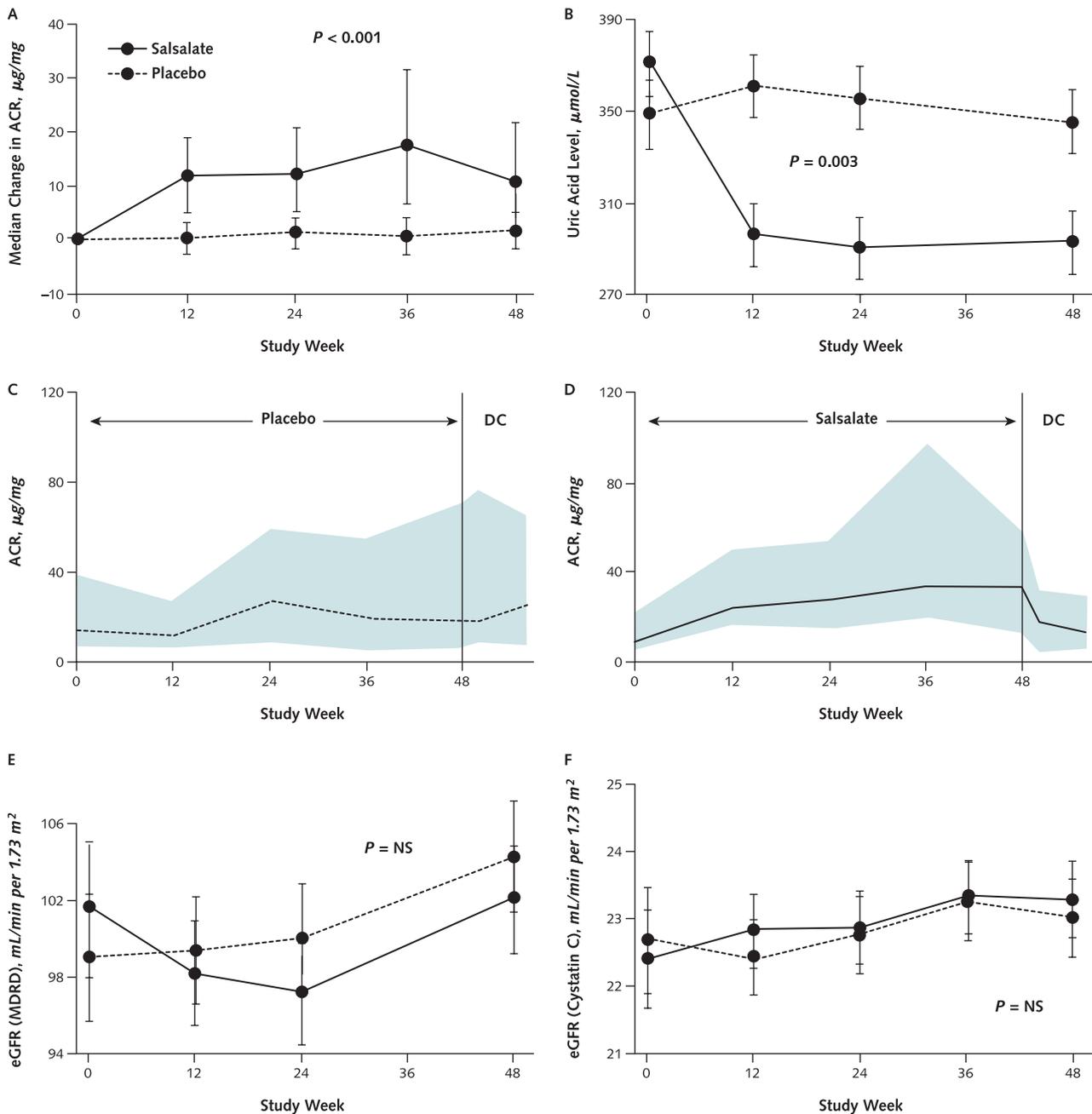
ACR = albumin–creatinine ratio; DC = discontinued; eGFR = estimated glomerular filtration rate; IQR = interquartile range; MDRD = Modification of Diet in Renal Disease; NS = not significant. **A.** Median changes and IQRs for urinary ACR. Error bars represent the IQRs. The 2.3-μg/mg between-group difference in ACR reported in the text and values reported in **Table 2** were obtained by back-transformation of log-transformed data for ACR because ACR was not normally distributed. **B.** Mean changes and 95% CIs in circulating uric acid levels. **C** and **D.** ACRs for the 23 participants receiving placebo (*C*) and 33 receiving salsalate (*D*) who were asked to return at week 56, after 8-week washout period, because ACR or blood pressure was elevated at week 48. Lines are median values; shaded areas are 25th through 75th quartiles. **E** and **F.** Mean changes and 95% CIs for eGFRs, using creatinine concentrations and the MDRD equation (*E*) or cystatin C concentrations (*F*).

risk for mild hypoglycemia was 6-fold greater when salsalate was coadministered with sulfonylureas. These findings are consistent with the absence of hypoglycemia in persons who do not have diabetes but use salsalate for pain management.

Salicylates, including salsalate, have been used extensively for joint pain, without safety concerns specific to T2DM or cardiovascular disease (CVD). There were no major signs of increased cardiovascular risk, yet modest changes in placebo-adjusted weight and LDL cholesterol and urinary albumin levels warrant further assessment. Some diabetes medications cause weight gain through increased adiposity and fluid retention. Salicylates are not known to increase adiposity. Insulin increases weight through improved tissue glucose utilization, and salsalate increases circulating insulin levels. Salicylates may also reverse loss of muscle mass associated with diabetes and aging (11). Biological modifiers, including anti–tumor necrosis factor-α and anti–interleukin-6, also increase LDL cholesterol levels (12). Potential benefits of salicylates in CVD are being tested (ClinicalTrials.gov: NCT00624923).

The anti-inflammatory properties of salsalate were evidenced by reductions in circulating leukocyte, neutrophil, and lymphocyte counts. These are previously unrecognized clinical effects of salicylates, including those used for rheumatologic conditions. Although decreased leukocyte counts could signify a bone marrow effect, hematocrit levels increased, making general bone marrow depression unlikely. Leukocyte and differential counts are elevated in obesity and the metabolic syndrome (13) and predict incident T2DM (14, 15), CVD, and poor outcomes in CVD (16–18). We speculate that reductions from higher to lower normal ranges may benefit patients at cardiometabolic risk and that nuclear factor-κB inhibition is the likely molecular mechanism for these reductions (6, 19–22). Cyclooxygenase inhibitors are not known to decrease leukocyte and differential counts, distinguishing these drug classes and potential mechanisms. In addition, statins do not decrease leukocyte counts and this effect occurred in patients receiving statins, thus demonstrating anti-inflammatory effects of salsalate independent from and in addition to those of statins. By contrast, salsalate had little effect on high-sensitivity C-reactive protein levels, which are decreased by statins, further supporting different mechanisms of action.

Salsalate also increased adiponectin and decreased uric acid levels, as seen previously (8), suggesting improved cardiometabolic risk (23). Reductions in liver aminotransferases, γ-glutamyltransferase and a trend for alanine aminotransferase, are also consistent with metabolic improvements and anti-inflammatory efficacy.

Cyclooxygenase inhibitors have been associated with acute kidney injury, especially in patients with diabetes or those using diuretics. Renal side effects of salsalate, an NSAID with distinct mechanisms of action, are lower than nonselective COX inhibitors (24). Renal safety signals were mixed. Urinary albumin levels increased more frequently with salsalate than with placebo, although this was reversible in the salsalate group. The magnitude of change is of unclear clinical relevance, particularly when estimated GFR was unchanged, calculated using either creatinine or cystatin C levels.

Mechanisms of salsalate action differ considerably from the COX inhibitors. Salsalate does not alter platelet or renal prostaglandins, which are suppressed by aspirin and other NSAIDs (25, 26), or alter prothrombin times, bleeding times, or platelet aggregation (27–29). Salsalate is also less prone than aspirin and other NSAIDs to cause gastric irritation (30–33).

Although decreases in leukocyte counts are probably nuclear factor-κB–mediated effects, mechanisms for decreases in glucose levels are more difficult to pinpoint. Inflammation seems to participate in the pathogenesis of insulin resistance and T2DM, suggesting that there may be tractable anti-inflammatory strategies for decreasing glucose levels (34, 35). Although salsalate decreases both glucose levels and inflammation and these are associated in our trial, we have not proven a mechanistic link. The glucose level–decreasing effects of interleukin-1β blockade support a general strategy to targeting inflammation, albeit using an independent anti-inflammatory approach (36, 37). Salicylate has additional potential mechanisms to consider, including effects on mitochondrial dehydrogenases (38, 39), transcription factors in addition to nuclear factor-κB (40–42), and cellular kinases (43–49). Recently, salicylate has also been shown to inhibit 11-β hydroxysteroid dehydrogenase type 1 in adipose tissue (50) and to stimulate adenosine monophosphate–activated protein kinase (51). Relative contributions for these potential mechanisms have not been distinguished.

Elevated circulating insulin levels may contribute to decreasing glucose levels. However, the reduced insulin clearance seen in humans receiving salicylates is not observed in rodents, making mechanistic evaluations more difficult (7, 8, 52, 53).

Limitations of our study include the relatively small number of patients and short trial duration, which restricts assessments of long-term durability and cardiovascular outcomes. Current results do not distinguish whether decreases in glucose levels are greater for salsalate alone or in certain therapeutic combinations. In addition, changes in concomitant diabetes drugs confound estimates of the efficacy of salsalate.

To our knowledge, this was the first evaluation of either salicylate or salsalate conducted using a multicenter, randomized, double-blinded, placebo-controlled trial format lasting longer than 3 months. The drug was well-tolerated and the primary end point of HbA$_{1c}$ level decreasing was achieved at all points tested. The magnitude of effect was similar to other oral diabetes therapies currently in use when added to metformin. Anti-inflammatory effects of salsalate were readily apparent at all time points

as reductions in leukocyte and differential counts. Glucose level–decreasing and anti-inflammatory effects were associated, although this does not prove a mechanistic connection. Changes in renal function or LDL cholesterol levels and associated long-term cardiorenal safety and outcomes require continued evaluation before salsalate can be recommended for widespread use in T2DM.

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APPENDIX 2: METHODS

Trial Design

The single-blind placebo run-in period provided an interval for metabolic stabilization to assess adherence to study drugs. The study statistician produced computer-generated random-sequence assignments in a 1:1 ratio using the urn method of randomization, producing separate sequences for each clinical center in blocks of 4. All study personnel, except a limited subset at the data coordinating center, were blinded to assignment. Equal numbers were assigned to receive either salsalate or placebo (both provided by Caraco Pharmaceutical Laboratories). Patients with 80% adherence or more (assessed by pill count) to blinded placebo during the run-in phase were eligible for randomization, which was conducted in clinic blocks by using central computer assignments.

Participants and their personal physicians were asked not to change dosages of diabetes, lipid-lowering, and blood pressure medications for the first 24 weeks, if possible, to assess study drug effects. Adjustments afterward were based on good clinical practice. Adverse events were systematically assessed by questionnaires administered at each follow-up visit. Patients were instructed to monitor daily fasting glucose levels and symptomatic events using provided glucometers (LifeScan). Concurrent diabetes therapies were reduced for patients experiencing 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. Dosages of the study drug were reduced to the maximum tolerable dose for new or worsening tinnitus. Quality of life was assessed using the total scale and 9 subscales of the Short Form-36 survey, which reflect 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 investigator and patient; and hospitalization or surgical procedures that were probably related to the use of the study drug.

Protocol Modifications After Trial Initiation

The following 4 modifications were made to the protocol after trial initiation: The inclusion criteria were amended to improve enrollment rates by permitting use of up to 3 rather than 2 oral diabetes medications; rescue therapy for hyperglycemia was modified to permit addition of oral medications (or insulin) as they were approved by the U.S. Food and Drug Administration; the definition and management of hypoglycemia were clarified; the role of the site investigator was revised to manage diabetes concomitant medications for patient safety; and a visit after dosing was added at study week 56 to assess safety specifically for participants having new-onset tinnitus persistent at week 50, ACR greater than 30 μg/mg at week 48, an increase in systolic or diastolic blood pressure greater than 10 mm Hg at weeks 48 and 50 compared with baseline, or blood pressure greater than 150/90 mm Hg despite treatment.

Study Population

Eligible adult patients were 75 years or younger; received their diagnosis of T2DM at least 8 weeks earlier; had fasting plasma glucose concentrations of 12.5 mmol/L or less ($\leq$225 mg/dL) and HbA$_{1c}$ levels of 7% to 9.5% at screening; and were treated with diet and exercise alone or with metformin, insulin secretagogue, or dipeptidyl peptidase-4 inhibitor, either as monotherapy or in combination. Concomitant diabetes medications were at stable dosages for more than 8 weeks. Patients receiving low-dose aspirin (81 to 325 mg/d) were eligible and were encouraged to continue use as prescribed.

Exclusion criteria included treatment with insulin, thiazolidinedione (for potential overlap in mechanism), or exenatide (associated 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 long-term or continuous use (daily for more than 7 days) of NSAIDs within the preceding 2 months other than low-dose aspirin (81 to 325 mg/d). We also excluded patients receiving uricosuric agents or anticoagulants other than low-dose aspirin; those with aspirin allergies; or patients having severe diabetic neuropathy, peptic ulcer disease, gastritis, unstable cardiovascular disease, uncontrolled hypertension, anemia, thrombocytopenia, hypertriglyceridemia, stage 3 or greater chronic kidney disease or proteinuria, hepatic dysfunction, preexisting chronic tinnitus, or other conditions likely to interfere with the conduct of the trial.

Adjunct Care

Medical management of the patient was the responsibility of the participant's primary care physician. However, hyperglycemic safety alerts were sent to the study team for HbA$_{1c}$ levels greater than 10.5% during the first 24 weeks and greater than 9.5% during the latter half of the trial; TINSAL-T2D investigators were to make recommendations to the primary care physician about dosing of diabetes and concomitant medications, particularly if the participant met criteria for initiation of rescue therapy for hyperglycemia or for either severe or recurrent mild hypoglycemia. Due to the number of mild hypoglycemic events, the role of the site investigator was revised to manage diabetes concomitant medications for patient safety (as previously described).

Participants with signs and symptoms of hyperglycemia (excessive thirst, urination, or weight loss) or 3 home glucose levels greater than 13.9 mmol/L (>250 mg/dL) in 1 week were instructed to call their investigator. An interim appointment was scheduled within 1 week for additional history, examination, and fasting laboratory assessment. Confirmation of fasting glucose levels greater than 13.9 mmol/L (>250 mg/dL) warranted medication adjustments. For participants without symptoms of hyperglycemia and fasting home glucose monitoring levels greater than 13.9 mmol/L (>250 mg/dL) but for whom the fasting glucose levels on scheduled visit were greater than 13.9 mmol/L (>250 mg/dL) or HbA$_{1c}$ levels of 10.5% or greater during the first 24 weeks of the trial or 9.5% or greater thereafter, the laboratory profile was to be repeated within 2 weeks. If similar hyperglycemia was detected on repeated evaluation, then medication adjustment was warranted.

If medication adjustments were warranted, the study investigators recommended this to the participant's primary care physician. For participants not receiving maximal metformin and sulfonylurea, treatments were maximized as follows: For persons receiving lifestyle or sulfonylurea therapy, metformin was to be added. For persons receiving submaximal metformin, metformin dosing was titrated. For persons already receiving maximal-dose metformin, glipizide was to be added. If or when metformin and sulfonylurea combination therapy was maximal and hyperglycemia adjustment was warranted, addition of a third agent was recommended (either another oral insulin or neutral protamine Hagedorn insulin [10 IU subcutaneously every evening] at the discretion of the physician). If 3 oral agents were maximized, then insulin was to be added and titrated to current practice medical goals by the investigator or clinician. Investigators and providers were cautioned that salsalate has not been specifically studied in combination with insulin. In view of the Action to Control Cardiovascular Risk in Diabetes trial results and lack of data on interaction of the study drug with insulin, we did not recommend aggressive titration of insulin. Participants were to be followed through the end of the trial, and all medication adjustments were noted.

Patients with long-term NSAID use (daily for >7 days within the preceding 2 months, other than low-dose aspirin at 81 to 325 mg daily) were excluded from the study. We recommended against use during the trial. No participants withdrew from the trial after randomization for new-onset, long-term NSAID use.

Prespecified Outcomes

The primary outcome for the TINSAL-T2D study was change in HbA$_{1c}$ level from baseline to week 48 in the intention-to-treat population. Important secondary prespecified outcomes included change from baseline to either 48 weeks or last HbA$_{1c}$ measurement before rescue therapy; trends in HbA$_{1c}$ levels over time; change from baseline and trends in fasting glucose levels over time; response rates for decrease in fasting glucose levels of 1.11 mmol/L or greater ($\geq$20 mg/dL), a decrease in HbA$_{1c}$ levels of 0.5% or greater, and a decrease in HbA$_{1c}$ levels of 0.8% or greater; change in lipid levels (LDL cholesterol, non–HDL cho-

lesterol, triglycerides, total cholesterol, HDL cholesterol, total–HDL cholesterol ratio, and LDL–HDL cholesterol ratio); change in insulin sensitivity (insulin, C-peptide, and homeostasis model index); response rates for exceeding hyperglycemic targets between salsalate and placebo groups; need for rescue therapy; need for discontinuation of study medication; response rates in patients initially treated with lifestyle modification, insulin secretagogue, metformin, or combination therapy; response rates for a reduction in HbA_{1c} levels for obese versus nonobese participants; response rates by baseline high-sensitivity C-reactive protein level; safety and tolerability of salsalate compared with placebo; change in body weight; changes in leukocyte and differential counts, high-sensitivity C-reactive protein levels, other inflammatory markers (interleukin-6, interleukin-1β, tumor necrosis factor-α, plasminogen activator inhibitor-1, adiponectin, serum amyloid A, intercellular adhesion molecule, and vascular cell adhesion molecule), lipoproteins (apolipoproteins A and B), and free fatty acids; and change in liver function (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase), stratified according to baseline liver function, as an index of nonalcoholic steatohepatitis and to assess potential improvements or decline. Outcomes were assessed after the final patient had completed all dosing visits. Lipoproteins and several inflammatory markers have not been analyzed to date, including interleukin-6, interleukin-1β, plasminogen activator inhibitor-1, serum amyloid A, intercellular adhesion molecule, and vascular cell adhesion molecule.

Laboratory Measurements and Calculations

Unless otherwise noted, laboratory measurements were done at Quest Diagnostics. Commercial immunoassays were used according to assay instruction for insulin and C-peptide (Mercodia), adiponectin, cystatin C, high-sensitivity C-reactive protein, and tumor necrosis factor-α (enzyme-linked immunosorbent assay [ELISA] kits from R&D Systems, Minneapolis, Minnesota), and free fatty acids (reagents from VWR International, Philadelphia, Pennsylvania).

The Mercodia Insulin ELISA has low cross-reactivity to C-peptide (<0.001) and total proinsulin ($<0.01\%$), des-31,32 proinsulin ($<0.5\%$), or split des-32,33 proinsulin ($<0.05\%$), but cross-reacts with des-64,65 proinsulin (98%) and split des-65,66 proinsulin (56%), according to manufacture performance characteristics (54). The Mercodia C-peptide ELISA has low cross-reactivity to intact insulin ($<0.001\%$), with the following cross-reactivity to total proinsulin: $<1.8\%$; des-31,32 proinsulin: 3%; or split des-32,33 proinsulin: 2%, des-64,65 proinsulin: 74%, and split des-65,66 proinsulin: 10%, according to manufacture performance characteristics (54).

To estimate the GFR, the Modification of Diet in Renal Disease formula was used: estimated GFR $= 186 \times$ serum creatinine$^{-1.154} \times$ age$^{-0.203} \times$ (1.212 if black) $\times$ (0.742 if female); with creatinine in mg/dL, and age in years. Creatinine levels in μmol/L can be converted to mg/dL by dividing them by 88.4. Serum cystatin C GFR was calculated as the reciprocal of cystatin C (mg/L) multiplied by 86.7 and reduced by subtracting 4.2, as described (2).

Missing Data for the Primary Analysis

Three participants randomly assigned to placebo are missing all data on HbA_{1c} levels. Two withdrew consent from the trial immediately after randomization and before a blood draw, and 1 withdrew consent to have any blood draws, stopped study medication, attended through week 24, then withdrew all consent to participate. Therefore, we do not have results to analyze for these patients.

Secondary Outcomes

The cumulative changes in concomitant diabetes medications by treatment group are shown in **Appendix Table 1**. Concomitant diabetes medications used by participants at the end of the study by treatment group are shown in **Appendix Table 2**. The number of patients reporting dyspepsia or nausea and vomiting were equal between groups (**Appendix Table 3**).

In mixed-model analyses, HbA_{1c} response rates did not differ in patients with baseline obesity (body mass index ≥30 kg/m^2) ($P = 0.725$) or elevated high-sensitivity C-reactive protein levels greater than 285 nmol/L (>3 mg/L) ($P = 0.62$).

In separate exploratory mixed-model analyses to assess the relationship between the change in inflammatory marker or mediators, we found the change in adiponectin inversely correlated with change in both HbA_{1c} levels (β estimate, -0.043 [CI, -0.071 to -0.015]; $P = 0.001$) and fasting glucose levels (β estimate, -2.00 [CI, -3.74 to -0.26]; $P = 0.023$) in the salsalate group but not in the placebo group ($P = 0.88$ for HbA_{1c}; $P = 0.83$ for glucose). Although change in high-sensitivity C-reactive protein levels did not differ between groups (**Table 2**), in the separate exploratory mixed-model analyses there were also statistically significant associations between change in high-sensitivity C-reactive protein and either change in HbA_{1c} levels (β estimate, 0.01 [CI, 0.00 to 0.02]; $P = 0.037$) or fasting glucose levels (β estimate, 0.75 [CI, 0.14 to 1.36]; $P = 0.016$), in the salsalate but not the placebo group ($P = 0.68$ for HbA_{1c}; $P = 0.37$ for glucose).

There were 76 (50%) aspirin users in the salsalate group and 64 (48%) in the placebo group ($P = 0.79$, chi-square). In a mixed-model analysis, there was no interaction between salsalate or placebo and baseline aspirin use ($P = 0.61$).

Plausible reasons why statin use may confound and attenuate the glycemic effect of salsalate include the established anti-inflammatory properties of statins and the association between statins and new-onset diabetes. There was no interaction between group and statin use at baseline in predicting change in fasting glucose ($P = 0.52$) or HbA_{1c} levels ($P = 0.75$). However, in an exploratory analysis using a mixed-model analysis adjusted for group, statin use was an independent predictor of the change in fasting glucose levels ($P = 0.025$), with a trend ($P = 0.072$) toward greater fasting glucose level decreasing in participants randomly assigned to salsalate receiving statins at baseline (-0.98 mmol/L $[-17.66$ mg/dL] [CI, -1.26 to -0.68 mmol/L $\{-22.70$ to -12.25 mg/dL$\}$]; $P < 0.001$) compared with those not receiving statins at baseline (-0.46 mmol/L $[-8.29$ mg/dL] [CI, -0.84 to -0.08 mmol/L $\{-15.14$ to -1.44 mg/dL$\}$]; $P = 0.018$). In contrast, the difference in change in fasting glucose

levels was not significant ($P = 0.34$) for patients randomly assigned to placebo who were receiving statins at baseline (0.10 mmol/L [1.80 mg/dL] [CI, −0.15 to 0.35 mmol/L {−2.70 to 6.31 mg/dL}]; $P = 0.44$) compared with those not receiving statins at baseline (0.29 mmol/L [5.23 mg/dL] [CI, −0.02 to 0.60 mmol/L {−0.36 to 10.81 mg/dL}]; $P = 0.066$). Likewise, greater glycemic-decreasing trends ($P = 0.144$) were numerically similar for change in HbA_{1c} levels for salsalate recipients who were receiving statins at baseline (−0.42% [CI, −0.57% to −0.27%]; $P < 0.001$) compared with those not receiving statins at baseline (−0.21% [CI, −0.40% to −0.02%]; $P = 0.030$). In contrast, the difference in change in HbA_{1c} levels was not significant ($P = 0.58$) for placebo recipients who were receiving statins at baseline (0.03% [CI, −0.01 to 0.16%]; $P = 0.65$) compared with those not receiving statins at baseline (0.08% [CI, −0.07 to 0.24%]; $P = 0.28$). Taken together, these data suggest that the glycemic efficacy of salsalate is greater, not attenuated, in statin users. Differences in statistical significance for interactions between salsalate and statin use in fasting glucose versus HbA_{1c} levels may be due to different time intervals between glycemic assessment captured by fasting glucose and HbA_{1c} levels, contributions of nonfasting glycemia to HbA_{1c} levels, or a type I statistical error. In view of the negative statistical interaction between statins and salsalate, these findings are provocative and interesting but inconclusive.

The interaction between statin use at baseline and treatment group was not statistically significant for the lipid outcomes fasting total cholesterol ($P = 0.124$), HDL cholesterol ($P = 0.57$), LDL_{direct} ($P = 0.106$), or triglyceride levels (log-transformed, $P = 0.93$).

We saw no statistically significant difference in the change in alanine aminotransferase, aspartate aminotransferase, or γ-glutamyltransferase in patients with elevated levels at baseline between the salsalate and placebo groups, using Kruskal–Wallis testing followed by Wilcoxon rank-sum test pairwise comparisons.

54. **Mercodia.** Mercodia Insulin ELISA. Uppsala, Sweden: Mercodia. Accessed at www.mercodia.se/products/human.html on 9 May 2013.

Appendix Table 1. Time to First Adjustment of Concomitant Diabetes Medication*

Medication	8 wk	12 wk	16 wk	24 wk	36 wk	48 wk
Placebo						
Increase	6	7	8	21	28	32
Decrease	0	2	2	2	4	5
Salsalate						
Increase	3	4	5	7	14	15
Decrease	14	16	18	19	21	24

* Cumulative adjustments in concomitant diabetes medications showing number of patients by treatment group. The first adjustment per participant was included, with increases or decreases shown separately.

Appendix Table 2. Use of Concomitant Diabetes Medications at End of Study

Medication	Total, n/N (%)	Placebo, n/N (%)	Salsalate, n/N (%)
Metformin	204/238 (85.7)	104/116 (89.7)	100/122 (82.0)
Insulin secretagogue	115/238 (48.3)	51/116 (44.0)	64/122 (52.5)
Insulin	14/238 (5.9)	9/116 (7.8)	5/122 (4.1)
α-Glucosidase inhibitor	1/238 (0.4)	0/116 (0)	1/122 (0.8)
DPP-4 inhibitor	32/238 (13.4)	16/116 (13.8)	16/122 (13.1)

DPP-4 = dipeptidyl peptidase-4.

Appendix Table 3. Adverse Events Occurring in ≥5% of the Salsalate Group and More Frequently in the Salsalate Group Than in the Placebo Group

Condition	Total, n/N	Placebo, n/N	Salsalate, n/N	P Value*
Tinnitus	23/286	7/140	16/146	0.082
Frequent cough	39/286	19/140	20/146	1.00
Vomiting	21/286	10/140	11/146	1.00
Muscle stiffness	23/286	9/140	14/146	0.39
Dizzy	21/286	10/140	11/146	1.00
Weakness or fatigue	22/286	9/140	13/146	0.51

* Fisher exact test.

Appendix Table 4. Incidence of Gastrointestinal Side Effects, by Treatment Group

Condition	Placebo, n/N	Salsalate, n/N
Heartburn	15/140	15/146
Trouble swallowing	1/140	1/146
Nausea	12/140	8/146
Vomiting	10/140	11/146