Original Article

INITIAL COMBINATION THERAPY WITH METFORMIN AND COLESEVELAM FOR ACHIEVEMENT OF GLYCEMIC AND LIPID GOALS IN EARLY TYPE 2 DIABETES

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ABSTRACT

Objective: To evaluate the efficacy and safety of initial combination therapy with metformin plus colesevelam in patients with early type 2 diabetes.

Methods: In this 16-week, randomized, double-blind, placebo-controlled study, adults with type 2 diabetes (hemoglobin A1c [A1C] values of 6.5% to 10.0%) and hypercholesterolemia (low-density lipoprotein cholesterol [LDL-C] levels ≥100 mg/dL) were randomly assigned (1:1) to colesevelam (3.75 g/d) or placebo in combination with open-label metformin (850 mg/d; uptitrated at week 2 to 1,700 mg/d). The primary efficacy evaluation was change in A1C from baseline to study end (week 16 with last observation carried forward).

Results: In total, 286 patients were randomized: metformin/colesevelam (n = 145) or metformin/placebo (n = 141). Mean A1C was reduced by 1.1% with metformin/colesevelam (from 7.8% at baseline to 6.6% at study end) and by 0.8% with metformin/placebo (from 7.5% to 6.7%), resulting in a treatment difference of −0.3% at study end (P = .0035). In addition, metformin/colesevelam significantly reduced LDL-C (−16.3%), total cholesterol (−6.1%), non-high-density lipoprotein cholesterol (−8.3%), apolipoprotein B (−8.0%), and high-sensitivity C-reactive protein (−17%) and increased apolipoprotein A-I (+4.4%) and triglycerides (+18.6%) versus metformin/placebo (P<.01 for all). The proportions of patients who achieved recommended goals with metformin/colesevelam versus metformin/placebo, respectively, were as follows: A1C <7.0% (67% versus 56% [P = .0092]), LDL-C <100 mg/dL (48% versus 18% [P<.0001]), and composite A1C <7.0% + LDL-C <100 mg/dL (40% versus 12% [P<.0001]). Safety and tolerability were similar between the treatment groups.

Conclusion: Metformin plus colesevelam may be a valid option for initial therapy to achieve glycemic and lipid goals safely in early type 2 diabetes. **(Endocr Pract. 2010;16:629-640)**

Abbreviations:
A1C = hemoglobin A1c; **AEs** = adverse events; **ANCOVA** = analysis of covariance; **apo** = apolipoprotein; **CI** = confidence interval; **FPG** = fasting plasma glucose; **HDL-C** = high-density lipoprotein cholesterol; **hsCRP** = high-sensitivity C-reactive protein; **LDL-C** = low-density lipoprotein cholesterol; **LOCF** = last observation carried forward; **MTT** = meal tolerance test; **TC** = total cholesterol; **TG** = triglycerides

INTRODUCTION

Type 2 diabetes is characterized by hyperglycemia resulting from insulin resistance and progressive impairment of insulin secretion (1,2). Metformin is safe and effective and is the recommended first-line pharmacologic therapy for the management of hyperglycemia in most patients with type 2 diabetes (1,3,4). Often, however, metformin monotherapy is not sufficient to achieve glycemic control, and as the disease progresses, most patients require additional therapy to maintain therapeutic glycemic targets (5,6). In addition, gastrointestinal symptoms are reportedly

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associated with metformin therapy, and this situation may impede adequate dose titration and limit the clinical utility of this medication (7,8).

Colesevelam hydrochloride is a bile acid sequestrant that exerts substantial glycemic and lipid effects in patients with type 2 diabetes (9-12). When added to stable metformin-based therapy, colesevelam further reduced both hemoglobin A1c (A1C) and low-density lipoprotein cholesterol (LDL-C) by 0.5% and 16%, respectively (9). Furthermore, colesevelam therapy significantly lowered high-sensitivity C-reactive protein (hsCRP) levels, had a low incidence of hypoglycemia, and was not associated with weight gain (9-12). Unlike previous clinical studies in which colesevelam was added to existing antidiabetes therapy in patients with inadequate glycemic control, the current study evaluated the combination of metformin plus colesevelam (metformin/colesevelam) in comparison with metformin alone as initial therapy in drug-naïve patients with early or recently diagnosed type 2 diabetes to assess the efficacy, tolerability, and safety. Therefore, the rationale for this study was to evaluate whether a metformin/colesevelam combination as initial therapy significantly improved glycemia and what effects this drug combination had on safety and tolerability (possibly resulting in fewer gastrointestinal symptoms) in comparison with metformin/placebo.

MATERIALS AND METHODS

This 16-week, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 16 sites in the United States, 10 in Mexico, 7 in Colombia, and 5 in India. The study was conducted in compliance with institutional review board regulations, good clinical practice guidelines, and the Declaration of Helsinki. Institutional review board approval was acquired before initiation of the study, and all patients provided written informed consent. The study rationale and design have been reported previously (13).

Patients

This study enrolled adults (18 to 79 years old) with type 2 diabetes (based on American Diabetes Association diagnostic criteria) (1). Inclusion criteria were A1C values of 6.5% to 10.0%, LDL-C levels ≥100 mg/dL, and triglycerides (TG) <500 mg/dL. All patients were drug-naïve, defined as never having received antidiabetes treatment or not having received treatment for ≥3 months before screening. No specific, protocol-directed dietary evaluation or dietary recommendations were made during the course of the study (for example, such as would occur through protocol-directed visits with a dietitian). Patients were excluded from the study for the following factors: body mass index ≥40 kg/m^2; history of type 1 diabetes, metabolic acidosis, pancreatitis, dysphagia, swallowing disorders, intestinal motility disorders, or long-term insulin therapy (except for gestational diabetes); treatment with a bile acid sequestrant or orally administered corticosteroids within 3 months of screening; acute coronary syndrome, coronary intervention, congestive heart failure, or transient ischemic attack within 3 months of screening; considerably abnormal hematologic or blood chemistry values; clinical or laboratory evidence of hepatic disease; or participation in a weight-loss program with ongoing weight loss. Patients receiving maintenance doses of weight-loss medications (including orlistat and sibutramine) whose weight was stable were eligible for participation. Hormones (oral contraceptives and hormone replacement therapy) and lipid-altering drugs (statins, fibrates, niacin, and ezetimibe) were permitted, if a stable dose had been maintained for ≥3 months.

Study Procedures

Each patient was screened by an oral glucose tolerance test and fasting plasma glucose (FPG) measurement. Patients who had a previous diagnosis of type 2 diabetes could qualify with one confirmatory test. Patients who had not been previously diagnosed with type 2 diabetes required a second test to confirm the initial screening test. Eligible patients proceeded to randomization within 1 week after fulfilling all selection criteria.

Patients were randomly assigned (1:1) to open-label metformin plus blinded unmarked colesevelam (metformin/colesevelam) or open-label metformin plus blinded colesevelam-matching placebo (metformin/placebo). Metformin treatment was initiated in all patients with one 850-mg tablet taken with the morning meal. This dosage was maintained for 1 week and then increased to 1,700 mg/d (one 850-mg tablet taken with the morning and evening meals), to be maintained for the remaining 14 weeks. If metformin uptitration was not tolerated, an additional 1 to 2 weeks were allowed; if patients still were unable to tolerate metformin at the dosage of 1,700 mg/d by the end of week 4, they were allowed to remain in the study at a metformin dosage of 850 mg/d. The metformin dosage of 1,700 mg/d was chosen because it was above 1,500 mg/d (clinically significant responses have not been seen with dosages <1,500 mg/d) and within the range of the usual starting doses for this drug (7). Colesevelam (3.75 g/d) or matching placebo was taken either once daily (six 625-mg tablets with the evening meal) or twice daily (three 625-mg tablets with the noon and evening meals); patients chose their preferred dosing schedule but were instructed to maintain the selected schedule for the duration of the study.

During the randomized treatment period, if 3 consecutive self-monitored fasting blood glucose measurements of <60 mg/dL or >275 mg/dL were obtained, a confirmatory FPG test was scheduled. If FPG was <60 mg/dL or >275 mg/dL at a routine visit, and then confirmed within 2 days, or if A1C was ≥10.5% at any visit, the patient was withdrawn from the study.

The primary efficacy variable was change in A1C from baseline to week 16 with use of last observation carried forward (LOCF) analysis. Secondary efficacy end points were also evaluated by using week 16 LOCF analyses and included change in FPG, fasting insulin, fasting C-peptide, post-meal tolerance test (MTT) glucose, post-MTT insulin, post-MTT C-peptide, change and percent change in lipids and apolipoproteins, and hsCRP. The percentages of patients achieving A1C <7.0%, A1C ≤6.5%, LDL-C <100 mg/dL, or LDL-C <70 mg/dL were also evaluated. In addition, A1C, FPG, lipids, and lipid and apolipoprotein ratios were evaluated at intermediate time points by using observed data (non-LOCF).

Laboratory panels were obtained under fasting conditions and evaluated by a certified laboratory (Covance Laboratories, Indianapolis, Indiana, and Singapore). The MTT consisted of two 8-oz cans of Ensure with fiber (contents of each 8-oz can: 42.0 g of carbohydrates, 8.8 g of protein, and 6.1 g of fat plus 24 essential minerals and vitamins). The LDL-C level was calculated by using the Friedewald equation for patients with TG levels <400 mg/dL at baseline and by using the Lipid Research Clinics Beta-Quant method for patients with TG levels of 400 to 500 mg/dL at baseline. The method of LDL-C determination used at screening was maintained throughout the study, regardless of changes in TG level.

Safety assessments included changes in vital signs, findings on physical examinations, occurrence and severity of adverse events (AEs), and clinical laboratory test results. Compliance with the medication regimen was evaluated by tablet count at each study visit.

Statistical Analysis

The randomized population included all patients who signed a consent form and were assigned a randomization number. The intent-to-treat population, which was used for all efficacy analyses, included all patients who had taken at least 1 dose of study medication and had a baseline and ≥1 postbaseline efficacy measurements. The safety population, which was used to evaluate safety, included all patients who had taken at least 1 dose of study medication. At a 2-sided level of significance of .05, with the assumption of a common standard deviation of 1.2% and use of a 2-sample *t* test, a sample size of 113 patients in each treatment group provided ≥80% power to detect a difference of ≥0.45% in the change in A1C value from baseline between the treatment groups. In order to allow for withdrawals, the number of patients was adjusted upward to 130 per treatment group.

An analysis of covariance (ANCOVA) model was used for the primary efficacy analysis, with treatment and country as fixed effects and the baseline efficacy variable value as a continuous covariate. The least-squares mean and 95% confidence interval (CI) for each treatment group and the difference between the treatment groups were calculated. The 2-sided *P* value test for a difference between the treatment groups was also performed. With the exclusion of TG and hsCRP evaluations, comparisons between treatment groups for continuous secondary efficacy variables were performed by using the same model as the primary efficacy analysis. Comparisons between treatment groups for the change and percent change in TG and hsCRP from baseline were performed with use of a nonparametric equivalent of rank ANCOVA, stratified by country (14). The median difference was calculated by using Hodges-Lehmann point estimates and 2-sided 95% CIs calculated with use of the method of Moses, whereas CIs for median changes from baseline were calculated by using the Hahn and Meeker method. The normality assumption of the efficacy data, except for TG and hsCRP, was examined before fitting the ANCOVA model. When significant departure from normality was determined, a nonparametric ANCOVA stratified by country was applied, and median changes from baseline and median differences between treatments were reported.

Goal achievement was assessed by using logistic regression, with treatment, country, and baseline values included. Only patients who did not meet the goal at baseline were considered for inclusion in the goal achievement assessment, in order to assess the achievement of goal attributable to treatment. Achievement of multiple goals was examined in post hoc analyses (composites of A1C <7.0% + LDL-C <100 mg/dL, A1C ≤6.5% + LDL-C <100 mg/dL, or A1C <7.0% + LDL-C <100 mg/dL + hsCRP <3.0 mg/L).

All hypothesis testing was conducted at a 2-sided significance level of .05 except for testing for interaction. The treatment-by-country interaction was evaluated at a significance level of .10. If a significant treatment-by-country interaction was suggested by the data, further analyses were implemented to assess the qualitative or quantitative nature of the interaction.

RESULTS

Patient Disposition and Baseline Characteristics

As part of the screening process, patients identified as having prediabetes were directed into a separate substudy (not reported here) (13), thus accounting for the large number of patients screened (N = 1,668; Fig. 1). In total, 286 patients were randomized in this study: 145 to metformin/colesevelam and 141 to metformin/placebo. The safety population included all randomized patients. Seven patients in the metformin/colesevelam group and 4 in the metformin/placebo group discontinued the study without undergoing any postbaseline efficacy measurements; therefore, the intent-to-treat population comprised 138 patients receiving metformin/colesevelam and 137 receiving metformin/placebo (Fig. 1). Overall, 85% of patients completed the 16-week study. The treatment groups were similar with regard to demographic and baseline characteristics

(Table 1); however, the mean LDL-C level was slightly but significantly lower in the metformin/colesevelam group in comparison with the metformin/placebo group at baseline (P<.05). Baseline A1C was not substantially elevated in either treatment group (7.8% [metformin/colesevelam] and 7.5% [metformin/placebo]), as expected, because a large proportion of patients was recently diagnosed with type 2 diabetes (approximately 60% in each treatment group had been diagnosed for <1 year). At baseline, few patients in either treatment group were receiving statin therapy (8% [metformin/colesevelam] and 6% [metformin/placebo]). By week 4, 121 patients (83%) in the metformin/colesevelam group and 120 patients (85%) in the metformin monotherapy group had completed the uptitration to metformin 1,700 mg/d.

In total, 42 patients discontinued the study—21 from each treatment group (Fig. 1). Of the patients who discontinued participation, 2 withdrew because of diarrhea (1 from each treatment group) and 2 withdrew because of hyperglycemia (1 from each treatment group). Compliance in the metformin/colesevelam group was 98% (metformin) and 92% (colesevelam), whereas compliance in the metformin/placebo group was 97% (metformin) and 92% (placebo).

Efficacy

Glycemic Variables

Treatment with metformin/colesevelam for 16 weeks significantly reduced A1C in comparison with metformin/

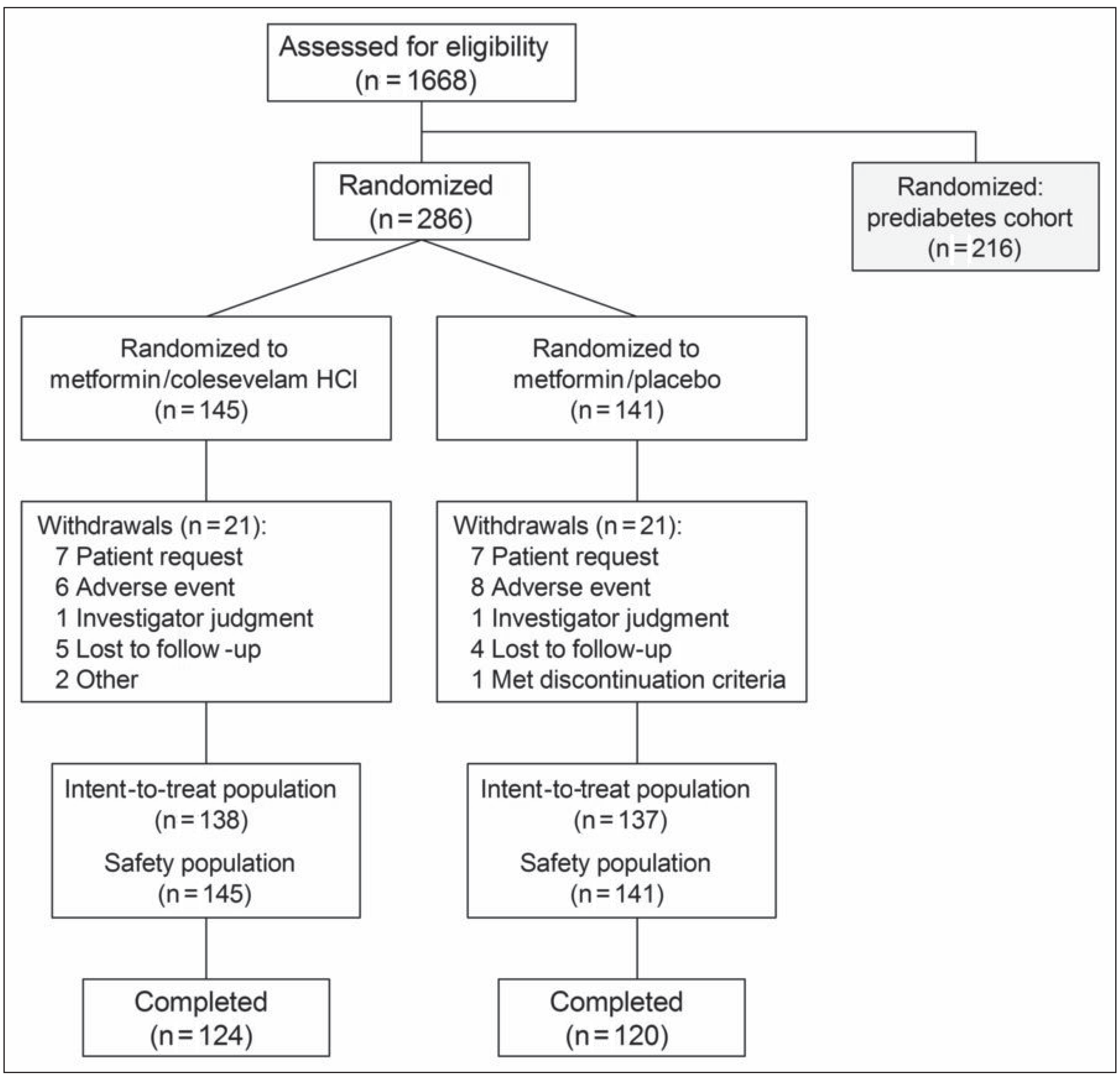

Fig. 1. Patient disposition. *HCl* = hydrochloride.

Table 1
Demographic and Baseline Characteristics (Randomized Population)

Factor	Metformin/ colesevelam HCl (n = 145)	Metformin/ placebo (n = 141)	*P* value
Age, y, mean (SD)	52.7 (11.5)	53.9 (10.1)	NS
Sex, no. (%)			NS
Male	69 (48)	56 (40)	
Female	76 (52)	85 (60)	
Race/ethnicity, no. (%)			NS
White	21 (15)	20 (14)	
Hispanic	89 (61)	90 (64)	
Black	3 (2)	1 (1)	
Asian	32 (22)	30 (21)	
Country, no. (%)			NS
United States	30 (21)	30 (21)	
Mexico	58 (40)	56 (40)	
Colombia	26 (18)	25 (18)	
India	31 (21)	30 (21)	
Height, cm, mean (SD)	162.3 (9.7)	160.6 (10.6)	NS
Weight, kg, mean (SD)	80.8 (15.5)	77.3 (16.2)	NS
Body mass index, kg/m^2, mean (SD)	30.6 (4.7)	29.8 (4.4)	NS
Hemoglobin A1c, %, mean (SD)	7.8 (1.0)	7.5 (0.9)	NS
Fasting plasma glucose, mg/dL, mean (SD)	153.4 (39.0)	145.7 (37.5)	NS
2-h post-meal tolerance test glucose, mg/dL, mean (SD)	234.7 (71.4)	220.3 (58.7)	NS
Low-density lipoprotein cholesterol, mg/dL, mean (SD)	129.1 (23.1)	135.5 (26.7)	.0311
Time since type 2 diabetes diagnosis, no. (%)			NS
Newly diagnosed (at study enrollment)	36 (25)	31 (22)	
<1 y	58 (40)	50 (36)	
1–5 y	37 (26)	44 (31)	
>5 y	14 (10)	16 (11)	
Common concomitant medications, no. (%)			NA
Angiotensin-converting enzyme inhibitors, plain	17 (12)	23 (16)	
Angiotensin II antagonists, plain	12 (8)	18 (13)	
Statins	11 (8)	9 (6)	
Platelet aggregation inhibitors, excluding heparin	32 (22)	28 (20)	

Abbreviations: HCl = hydrochloride; NA = not available; NS = not significant; SD = standard deviation.

placebo from a mean baseline A1C of 7.8% and 7.5%, respectively (baseline A1C values between treatment groups were not statistically significantly different). The least-squares mean A1C change from baseline at week 16 LOCF was −1.1% (metformin/colesevelam) and −0.8% (metformin/placebo), resulting in a mean treatment difference of −0.3% (*P* = .0035; Fig. 2 *A*). At study end, A1C values were 6.6% (metformin/colesevelam) and 6.7% (metformin/placebo). Changes from baseline in A1C that reflect the treatment effect were compared with use of ANCOVA to adjust for baseline differences. Furthermore, a significant treatment difference in A1C was observed as early as week 4 (−0.2%; *P* = .0123; Fig. 2 *B*). In both treatment groups, FPG, fasting C-peptide, and fasting insulin levels were reduced numerically from baseline. At study end, however, the treatment differences were not significant (Table 2).

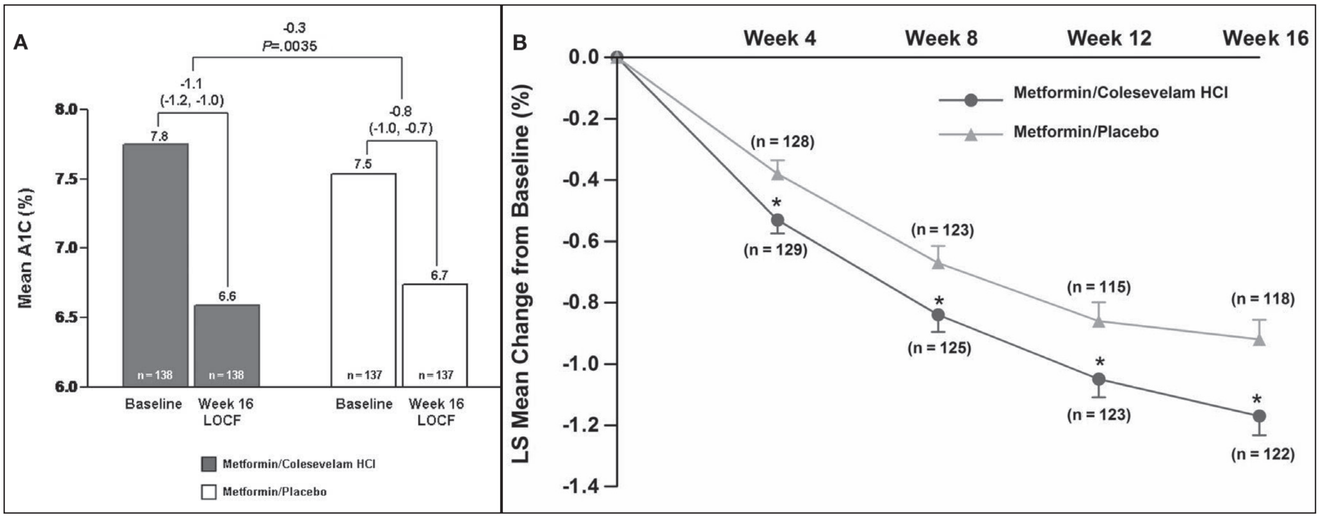

Fig. 2. *A*, Least-squares (*LS*) mean hemoglobin A1c (*A1C*) change from baseline to study end/week 16 last observation carried forward (*LOCF*) (intent-to-treat population). *B*, LS mean A1C change from baseline at weeks 4, 8, 12, and 16 (intent-to-treat population). *P<.05 versus metformin/placebo. *HCl* = hydrochloride.

Lipid Variables

At study end, LDL-C, total cholesterol (TC), and non-high-density lipoprotein cholesterol (non-HDL-C) levels were reduced more significantly with metformin/colesevelam than with metformin alone (P<.001 for all; Fig. 3). A significant treatment-related difference in LDL-C level was apparent by week 8 and was maintained for the duration of the study. The HDL-C level increased from baseline in both treatment groups at study end, although the treatment-associated difference was not significant (Fig. 3). The TG levels increased from baseline with metformin/colesevelam, whereas they were reduced with metformin/placebo; the result was a significant treatment difference at study end (P<.001; Fig. 3). Apolipoprotein (apo) A-I and apo C-III increased significantly whereas apo B decreased significantly from baseline with metformin/colesevelam versus metformin/placebo (P<.001 for all; Fig. 3). In addition, the TC:HDL-C, LDL-C:HDL-C, non-HDL-C:HDL-C, and apo B:apo A-I ratios were significantly improved with metformin/colesevelam versus metformin/placebo (P<.0001 for all).

Inflammatory Markers

The hsCRP value was reduced from baseline by 24% with metformin/colesevelam and by 7% with metformin/placebo at study end. The outcome was a median treatment difference of −17% (P = .0038).

Goal Achievement

At study end, significantly more patients receiving metformin/colesevelam in comparison with metformin/placebo achieved the following goals: A1C <7.0% (67% versus 56% [P = .0092]); A1C ≤6.5% (57% versus 46% [P = .0073]); LDL-C <100 mg/dL (48% versus 18% [P<.0001]); LDL-C <70 mg/dL (13% versus 4% [P = .0439]; Fig. 4); and hsCRP <3.0 mg/L (36% versus 17% [P = .0071]). In post hoc analyses, composite dual glycemic and lipid goals achieved with metformin/colesevelam versus metformin/placebo were the following: A1C <7.0% + LDL-C <100 mg/dL (40% versus 12% [P<.0001]) and A1C ≤6.5% + LDL-C <100 mg/dL (33% versus 8% [P<.0001]; Fig. 4). The composite triple goal of A1C <7.0% + LDL-C <100 mg/dL + hsCRP <3.0 mg/L was achieved in 25% of patients receiving metformin/colesevelam versus 7% of patients in the metformin/placebo group (P<.0001; Fig. 4).

Safety

The frequency of gastrointestinal-related AEs was similar between the metformin/colesevelam and metformin/placebo groups (Table 3). The incidences of upper gastrointestinal complaints in the metformin/colesevelam versus metformin/placebo groups, respectively, were as follows: nausea (12% versus 8%), vomiting (4% versus 1%), gastritis (5% versus 2%), upper abdominal pain (3% versus 2%), and constipation (4% versus 1%). The frequency of diarrhea was 12% among patients receiving metformin/colesevelam versus 18% among those receiving metformin/placebo, whereas the frequency of drug-related diarrhea was 8% in the metformin/colesevelam group versus 14% in the metformin/placebo group. Two severe diarrhea-associated AEs occurred with metformin/placebo. In addition, the incidence of diarrhea among patients who completed the uptitration to metformin 1,700 mg/d was 11% with metformin/colesevelam treatment and 17% with metformin/placebo.

Table 2
Change From Baseline in Glycemic Variables to End of Study, Week 16 Last Observation Carried Forward (Intent-to-Treat Population)

Factor	No. of patients	Baseline mean (SD) or median (IQR)	Change from baseline: LS mean (SE) or median (95% CI)	Treatment difference[a]: LS mean (SE) or median (95% CI); *P* value
Fasting plasma glucose, mg/dL[b]				
Metformin/colesevelam HCl	138	143.5 (126.0, 170.0)	−25.0 (−31.0, −20.0)	−6.0 (−13.0, 0.0); .2370
Metformin/placebo	137	136.0 (124.0, 159.0)	−18.0 (−22.0, −14.0)	
Fasting C-peptide, ng/mL				
Metformin/colesevelam HCl	138	2.757 (1.32)	−0.43 (0.1)	−0.14 (0.1) (−0.32, 0.04); .1146
Metformin/placebo	137	2.733 (1.18)	−0.28 (0.1)	
Fasting insulin, μIU/mL[b]				
Metformin/colesevelam HCl	138	10.12 (6.74, 16.0)	−1.59 (−2.96, −0.86)	−0.060 (−1.25, 1.11); .7798
Metformin/placebo	137	10.30 (6.90, 16.5)	−1.90 (−2.60, −1.13)	
2-h post-MTT glucose, mg/dL				
Metformin/colesevelam HCl	136	233.1 (71.1)	−36.2 (4.1)	−6.6 (5.8) (−17.9, 4.7); .2524
Metformin/placebo	134	221.6 (58.5)	−29.6 (4.2)	
2-h post-MTT C-peptide, ng/mL				
Metformin/colesevelam HCl	137	7.84 (3.27)	−0.14 (0.24)	0.07 (0.33) (−0.58, 0.72); .8319
Metformin/placebo	134	8.55 (3.33)	−0.21 (0.24)	
2-h post-MTT insulin, μIU/mL[b]				
Metformin/colesevelam HCl	136	55.16 (35.94, 76.61)	−9.30 (−11.89, −4.98)	4.300 (−5.960, 10.03); .3578
Metformin/placebo	134	71.85 (35.45, 102.7)	−12.27 (−17.68, −5.24)	

Abbreviations: CI = confidence interval; HCl = hydrochloride; IQR = interquantile range; LS = least-squares; MTT = meal tolerance test; SD = standard deviation; SE = standard error.
[a] Treatment difference = metformin/colesevelam HCl − metformin/placebo.
[b] Reported as median.

DISCUSSION

In this study, initial combination therapy with metformin/colesevelam significantly improved glucose control and benefited lipid and inflammation variables, as shown by significant reductions in A1C, LDL-C, TC, non-HDL-C, apo B, and hsCRP relative to metformin monotherapy in patients with early type 2 diabetes. Initiation of treatment with metformin/colesevelam facilitated better control of both glycemia and lipids and allowed more patients to achieve corresponding therapeutic targets. Although the absolute difference in A1C between the treatment groups may be perceived as small (0.3%), it was statistically significant and clinically may help individual patients achieve

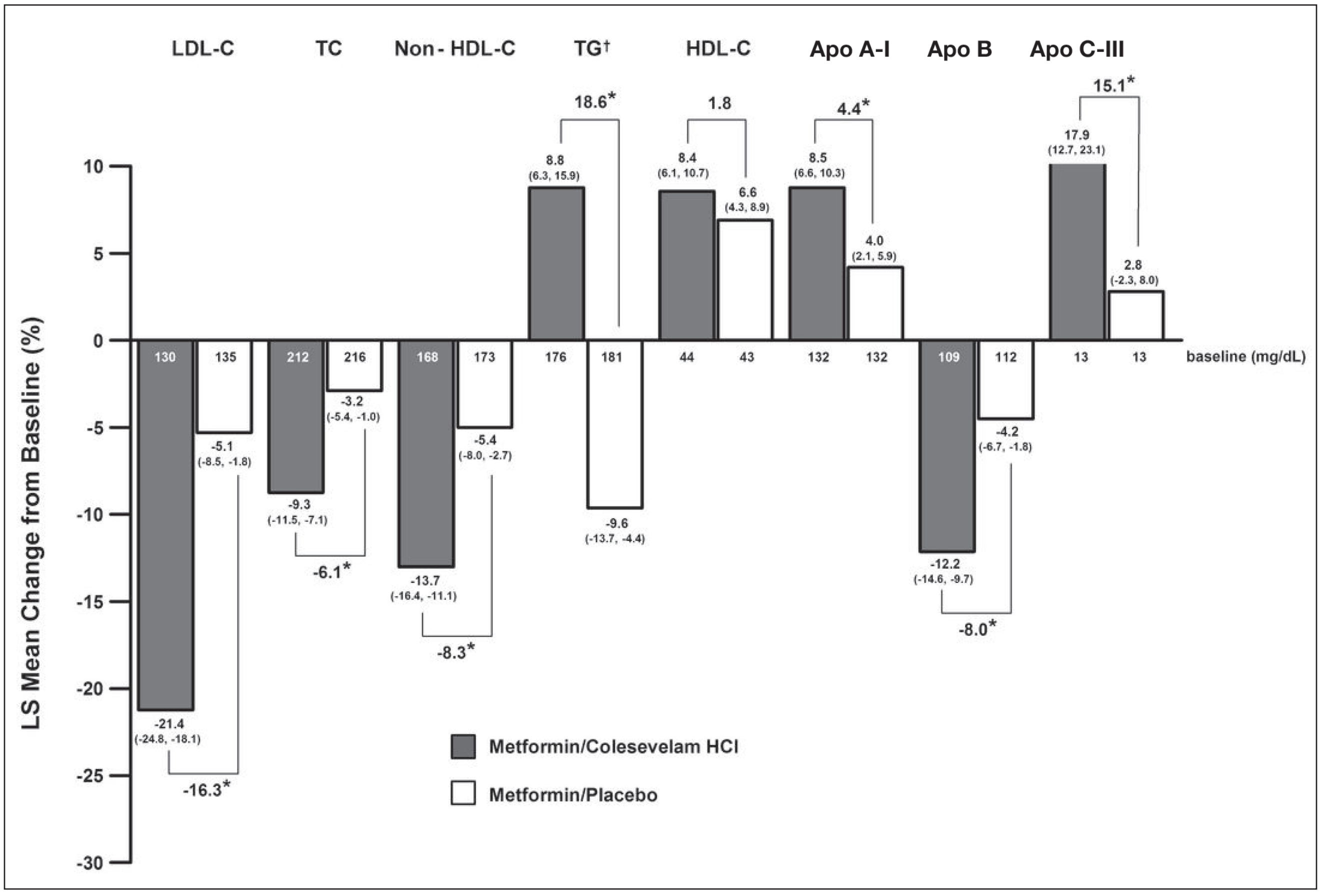

Fig. 3. Least-squares (*LS*) mean change in lipid and apolipoprotein variables from baseline to study end/week 16 last observation carried forward (intent-to-treat population). **P*<.001. †Triglycerides (*TG*) reported as median difference in percent change from baseline. *Apo* = apolipoprotein; *HCl* = hydrochloride; *HDL-C* = high-density lipoprotein cholesterol; *LDL-C* = low-density lipoprotein cholesterol; *TC* = total cholesterol.

therapeutic goals that otherwise may not be achieved with monotherapy alone, while also helping to achieve a goal for LDL-C.

Often, achievement of adequate glycemic control with antidiabetes monotherapy is difficult, and prompt addition of other agents is generally necessary (15). Frequently, however, several factors delay intensification of treatment. Recent clinical studies have suggested that early, aggressive management of hyperglycemia in patients with type 2 diabetes exerts a legacy effect, potentially attributable to metabolic or vascular memory (or both) (16,17). In a follow-up of the United Kingdom Prospective Diabetes Study, although glycemic differences between aggressive and conventional therapy were lost after the first year, relative risk reductions for any diabetes-related end point, microvascular disease, myocardial infarction, and death persisted at 10 years with early, aggressive therapy (16). After 5 years of follow-up in the Action in Diabetes and Vascular Disease study, aggressive therapy targeting A1C <6.5% resulted in a 10% relative reduction in the combined outcome of major macrovascular and microvascular events (17). Thus, delaying treatment may have important long-term adverse consequences. Some organizations have proposed treatment algorithms for type 2 diabetes encouraging early combination therapy to minimize exposure to prolonged hyperglycemia (4,18,19). Specifically, the American Association of Clinical Endocrinologists Road Map for the pharmacologic management of type 2 diabetes recommends the addition of colesevelam if glycemic control is not achieved within 2 to 3 months with metformin monotherapy (in patients with an initial A1C value of 6.5% to 7.5%) (4).

Intensive treatment of hyperglycemia, hypercholesterolemia, and inflammation is important for reduction of complications in patients with type 2 diabetes. The current study was unique in that it assessed patients with hypercholesterolemia (LDL-C levels ≥100 mg/dL), a criterion not often included in studies investigating the efficacy of antidiabetes therapy. Of note, metformin/colesevelam reduced LDL-C, non-HDL-C, apo B, and hsCRP (effects not attributable to statins because ≤8% of patients were receiving statin therapy) and resulted in a significant increase in

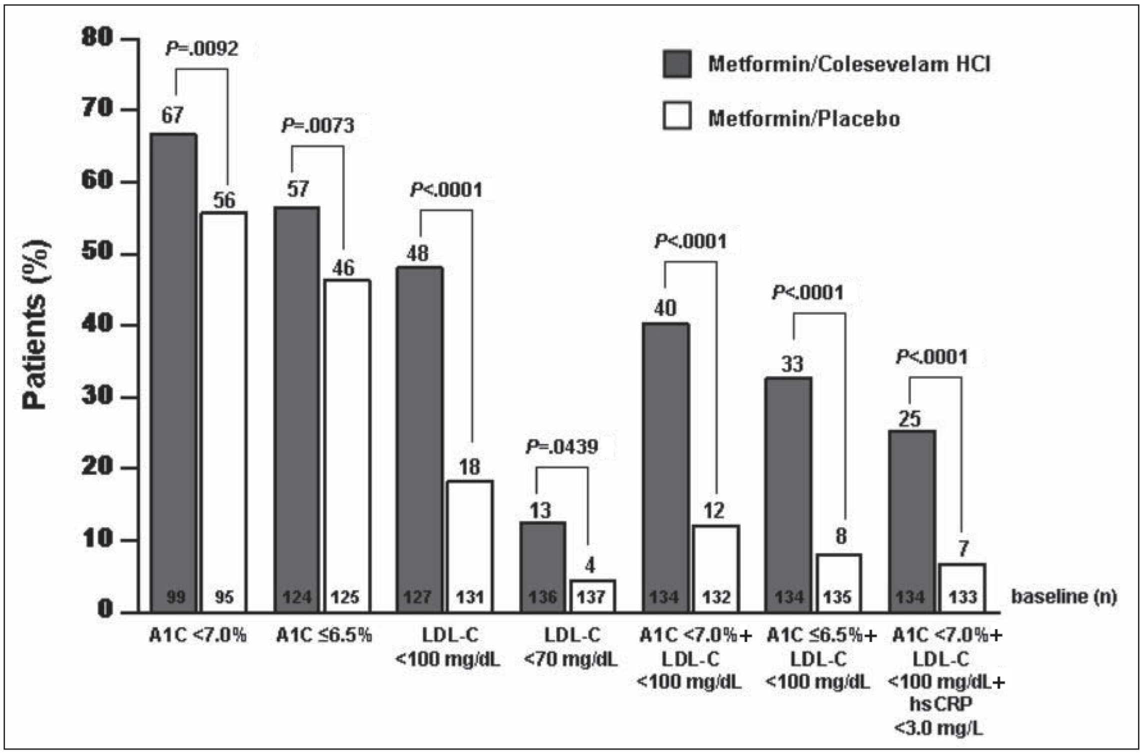

Fig. 4. Hemoglobin A1c (*A1C*) and low-density lipoprotein cholesterol (*LDL-C*) goal attainment at study end/week 16 last observation carried forward (intent-to-treat population). Only patients who did not meet the goal at baseline (*n*) were considered for inclusion. *HCl* = hydrochloride; *hsCRP* = high-sensitivity C-reactive protein.

apo A-I. The low use of statins in this study was surprising and may be ascribed to the large number of patients outside the United States. Most, if not all, patients included in this study should have been receiving statin therapy to reduce their elevated baseline LDL-C levels because studies such as the Heart Protection Study (20) and the Collaborative Atorvastatin Diabetes Study (21) have shown the beneficial effects of these agents in patients with type 2 diabetes. Nevertheless, this situation allowed us to evaluate the specific lipid effects of colesevelam without the influence of statins as commonly used in clinical practice. In this study, TG and apo C-III levels significantly increased with metformin/colesevelam treatment relative to metformin alone. An increase in TG levels has also been observed in other clinical trials with bile acid sequestrants, including colesevelam (9-11), and its clinical significance remains unclear. Colesevelam, however, should be used with caution in patients with TG levels >300 mg/dL and should be avoided in patients with TG levels >500 mg/dL.

Aggressive treatment in early type 2 diabetes could potentially increase the risk of hypoglycemia. Metformin/colesevelam treatment, however, did not increase the incidence or severity of hypoglycemia relative to metformin alone, despite the achievement of a mean A1C of 6.6% at study end. This was an important observation, in light of the low baseline A1C levels of 7.8% and 7.5% in the metformin/colesevelam and metformin/placebo groups, respectively.

Despite the association of metformin with gastrointestinal side effects, particularly diarrhea, the overall incidence of gastrointestinal-related AEs and tolerability was similar between the treatment groups in this study. Unfortunately, the incidence, severity, and type of AEs reported during this study were not evaluated on the basis of the dosing schedule for colesevelam (once daily versus twice daily), which is a limitation. Additional studies are needed to determine whether the combination of metformin and colesevelam confers improved tolerability over metformin alone.

The mechanism by which colesevelam lowers glucose levels is under investigation. Bile acids, now recognized as signaling molecules, may modulate glucose metabolism by interacting with the farnesoid X receptor and a G-protein-coupled receptor, TGR5. Bile acid sequestrants may have a role in the modulation of bile acid composition and pool size, which may be altered in type 2 diabetes (22).

CONCLUSION

Type 2 diabetes is a complex disease, and in order to prevent complications, multiple surrogate markers beyond glucose alone need to be addressed to improve achievement

Table 3
Summary of Adverse Events (Safety Population)

Factor	Metformin/ colesevelam HCl (n = 145)	Metformin/ placebo (n = 141)
Patients reporting an adverse event, no. (%)	97 (67)	97 (69)
Severity of adverse events, no. (%)		
Mild	55 (38)	47 (33)
Moderate	34 (23)	44 (31)
Severe	8 (6)	6 (4)
Patients with adverse events, no. (%)		
Drug-related	49 (34)	53 (38)
Serious	2 (1)	1 (1)
Drug-related serious	0 (0)	0 (0)
Patient withdrawal from study, no. (%)		
Due to adverse events	5 (3)	9 (6)
Due to drug-related adverse events	3 (2)	5 (4)
Due to serious adverse events	1 (1)	1 (1)
Patients with diarrhea-associated adverse events, no. (%)	17 (12)	26 (18)
Deaths, no. (%)	0 (0)	0 (0)
Gastrointestinal adverse events, no. (%)		
Abdominal distention	4 (3)	5 (4)
Abdominal pain	6 (4)	8 (6)
Abdominal pain, upper	5 (3)	3 (2)
Constipation	6 (4)	2 (1)
Diarrhea	17 (12)	26 (18)
Dyspepsia	5 (3)	5 (4)
Flatulence	3 (2)	4 (3)
Gastritis	7 (5)	3 (2)
Nausea	18 (12)	11 (8)
Vomiting	6 (4)	2 (1)
Adverse events occurring in ≥5% of patients, no. (%)		
Back pain	0 (0)	8 (6)
Dizziness	9 (6)	5 (4)
Headache	12 (8)	14 (10)
Hypertension	2 (1)	8 (6)
Influenza	12 (8)	9 (6)
Pyrexia	2 (1)	7 (5)
Urinary tract infection	3 (2)	7 (5)

Abbreviation: HCl = hydrochloride.

of appropriate goals. In this study, initial treatment with the combination of metformin/colesevelam in patients with type 2 diabetes provided synergistic effects, lowering both A1C and LDL-C levels. This combination therapy may be particularly beneficial for patients with recently diagnosed type 2 diabetes, helping them to achieve the glycemic and lipid goals associated with overall risk reduction. Additional studies are needed, however, to evaluate whether colesevelam preserves β-cell function in patients with type 2 diabetes and whether it improves cardiovascular outcomes in these patients.

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