



# Goal achievement of HbA1c and LDL-cholesterol in a randomized trial comparing coleselam with ezetimibe: GOAL-RCT

Harpreeet S. Bajaj MD<sup>1,2</sup> | Ruth E. Brown PhD<sup>1</sup> | Dishay Jiandani MSc<sup>1</sup> |  
Karri Venn RD<sup>1</sup> | Hani Al-Asaad MD<sup>1</sup> | Hasnain Khandwala MD<sup>1</sup> |  
Oren Steen MD<sup>1</sup> | Suzan Abdel-Salam MD<sup>1</sup> | Ronnie Aronson MD<sup>1</sup>

<sup>1</sup>LMC Diabetes & Endocrinology, Toronto, Ontario, Canada

<sup>2</sup>Leadership Sinai Center for Diabetes, Mount Sinai Hospital, Toronto, Ontario, Canada

## Correspondence

Harpreeet S. Bajaj, MD, MPH, LMC Diabetes & Endocrinology, 2979 Bovaird Drive East, Brampton, Ontario L6S 0C6, Canada.  
Email: harpreet.bajaj@lmc.ca

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## Abstract

**Aim:** To compare the efficacy and safety of coleselam and ezetimibe as second-line low density lipoprotein-cholesterol (LDL-c)-lowering options in type 2 diabetes (T2D).

**Materials and Methods:** GOAL-RCT is a 24-week, open-label, randomized, pragmatic clinical trial. Subjects with T2D with uncontrolled HbA1c (7.1%-10%) and LDL-c (>2.0 mmol/L) were randomized 1:1 to coleselam 3.75 g or ezetimibe 10 mg daily. The primary composite outcome was the proportion of participants achieving an LDL-c target of ≤2.0 mmol/L and HbA1c target of ≤7.0%. Intention to treat analysis was performed.

**Results:** Two hundred subjects were enrolled: mean age 59 ± 10 years; mean HbA1c 8.0%; mean LDL-c 2.5 mmol/L; 97% on statin therapy. The primary composite outcome was achieved by similar proportions of participants with coleselam (14.6%) and ezetimibe (10.5%) ( $P_{\text{non-inferiority}} < .001$ ,  $P_{\text{superiority}} = .41$ ). LDL-c reduction from baseline was less with coleselam compared with ezetimibe (14.0% vs. 23.2%,  $P < .01$ ), as was the proportion of subjects achieving an LDL-c target of ≤2.0 mmol/L (47.6% and 67.0%, respectively;  $P = .007$ ). Mean HbA1c was reduced with coleselam ( $-0.26 \pm 0.10\%$ ), while no change was observed with ezetimibe (difference  $P = .06$ ). Adverse events and discontinuation rates were higher for coleselam (20.2% and 31.1%) compared with ezetimibe (7.2% and 6.2%), respectively.

**Conclusions:** Among subjects with T2D, the initiation of coleselam or ezetimibe led to similar achievement of primary composite outcome (LDL-c and HbA1c within target), with ezetimibe recording a greater LDL-c reduction and better tolerability than coleselam.

## KEY WORDS

cardiovascular prevention, cholesterol, HbA1c, LDL-c, lipid, randomized trial

## 1 | INTRODUCTION

Type 2 diabetes (T2D) is considered a coronary artery disease risk equivalent.<sup>1</sup> Low density lipoprotein-cholesterol (LDL-c) reduction with a target of <2.0 mmol/L, with 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor (statin) medications as the first-line option, is recommended by global guidelines to lower the risk of cardiovascular (CV) morbidity and mortality in the high-risk population, including those with T2D.<sup>2–5</sup>

Despite the widespread availability, efficacy and cost benefit of statins, a care gap persists in achieving recommended LDL-c targets at a population level.<sup>6,7</sup> Similarly, target LDL-c achievement in T2D lags behind guideline recommendations, with 40%–60% achieving levels of <2.0 mmol/L according to available Canadian data.<sup>8–10</sup> Non-achievement of target LDL-c, despite high-intensity statin medications or because of statin intolerance, necessitates a consideration of second-line LDL-c-lowering medications. The concept of 'lower is better' in terms of LDL-c for major adverse cardiovascular events reduction has been further fuelled recently by positive CV outcomes observed in three recent trials where non-statin medications (ezetimibe, evolocumab and alirocumab) were added on in high-risk populations.<sup>11–13</sup> Interestingly, in subgroup analyses, those with T2D had a greater absolute risk reduction of CV endpoints within each of these three trials utilizing second-line LDL-c-lowering medications.<sup>14–16</sup>

Comparative LDL-c-lowering efficacy, safety and cost-effectiveness are important determinants for guideline recommendations for the hierarchical or stepwise use of these second-line agents. Oral LDL-c-lowering agents (ezetimibe or bile acid sequestrants [BAS]) are generally preferred as second-line agents in clinical practice over injectable and costly proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitor therapies. Ezetimibe is a cholesterol absorption inhibitor that is thought to impair intestinal absorption of dietary cholesterol and hepatically excreted biliary cholesterol via the inhibition of a transporter protein.<sup>17</sup> BAS agents are thought to form a non-absorbable complex with bile acids in the intestine, preventing reabsorption and increasing faecal excretion of bile acids. The resultant depletion of the endogenous bile acid pool increases bile acid synthesis, which in turn diverts circulating LDL-c into bile acids, thereby reducing plasma LDL-c.<sup>18,19</sup> In separate randomized trials, both ezetimibe and colesevvelam (a BAS agent) have shown comparable reductions in LDL-c ranging from 15% to 25%.<sup>20–23</sup> The data gap for comparative evidence is even more evident in T2D, where initiation of colesevvelam to antidiabetes agents has been associated with glycaemic benefits, with a modest reduction of 0.3%–0.5% HbA1c levels from baseline.<sup>22–24</sup> However, no randomized controlled trial to date has directly compared the efficacy and safety of ezetimibe with colesevvelam in T2D. Hence, the objective of the GOal achievement of HbA1c and LDL-c in a Randomized trial comparing Colesevvelam with ezetimibe as add-on to baseline statin Therapy (GOAL-RCT) trial was to compare the safety and efficacy of ezetimibe and colesevvelam in subjects with T2D not achieving target LDL-c and HbA1c levels.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and participants

GOAL-RCT was a 24-week, randomized, open-label, parallel-group, investigator-initiated, multi-centre, pragmatic clinical trial (clinicaltrials.gov NCT02682680). All patients provided written informed consent before participating in the study. The study complied with the Declaration of Helsinki and the study protocol was approved by local ethics review boards in Ontario and Alberta.

Study participants were enrolled from seven LMC Diabetes & Endocrinology (LMC) sites in Ontario and one LMC site in Calgary, Alberta, from January to October. LMC Diabetes & Endocrinology is a Canadian, referral-based, specialist practice. Trial participants had a clinical diagnosis of T2D >6 months, HbA1c of 7.1% to 10.0%, LDL-c >2.0 mmol/L, stable diabetes medications for at least 3 months (with the exception of allowance for change in insulin dose), and a stable dose of statin (or alternative lipid-lowering) therapy for a minimum of 3 months. Patients were excluded for: a triglycerides level of ≥5.0 mmol/L or an incalculable LDL-c, creatine kinase (CK) or alanine aminotransferase (ALT) ≥3 times the upper limit of normal, females who were pregnant or breastfeeding, chronic kidney disease stage IV-V (i.e. an estimated glomerular filtration rate of <30 mL/min/1.73 m<sup>2</sup>), a history of severe gastroparesis or significant bowel resection, or current use of an investigational product.

### 2.2 | Procedures

Patients were assessed for study eligibility and randomized in a 1:1 ratio to either colesevvelam 3.75 g daily (tablets or sachets) or ezetimibe 10 mg daily, with an instruction to begin treatment on the day of randomization. Patients randomized to colesevvelam were instructed to take colesevvelam once or twice daily with a meal, while patients randomized to ezetimibe were instructed to take ezetimibe with or without a meal at the same time once every day. The following laboratory tests were measured at baseline, 12 ± 4 and 24 ± 4 weeks: HbA1c, LDL-c, fasting plasma glucose (FPG), high density lipoprotein-cholesterol (HDL-c), non-HDL-c, triglycerides, ALT, CK and high sensitivity C-reactive protein (hs-CRP) (LifeLabs International Reference Laboratory, Toronto, Canada). Weight, body mass index (BMI), waist circumference and blood pressure were measured in clinic at the same time points. Sociodemographic information (age, gender, ethnicity, education and income level) and medical history (duration of diabetes, microvascular and macrovascular complications) were extracted from the patients' electronic medical records. Diabetes therapies (with the exception of insulin dose) and lipid-lowering therapies were to remain stable throughout the 24-week follow-up period.

### 2.3 | Outcomes

The primary endpoint was the proportion of patients who achieved a composite of LDL-c ≤2.0 mmol/L and HbA1c ≤7.0% by 24 weeks (last

observation carried forward [LOCF]). Secondary endpoints included the proportion of subjects who achieved the primary composite outcomes in the subgroup of subjects on sodium-glucose co-transporter-2 inhibitor (SGLT2i) therapy; change from baseline to 24 weeks in LDL-c, HbA1c, FPG and non-HDL-c; change from baseline to 24 weeks in LDL-c, HbA1c, FPG and non-HDL-c in the subgroup of trial participants on SGLT2i therapy; and change from baseline to 24 weeks in HDL-c, triglycerides, hs-CRP, weight, BMI, waist circumference and blood pressure. Additional secondary endpoints included the proportion of patients who achieved HbA1c  $\leq 7.0\%$  ( $<53$  mmol/mol), with no reported hypoglycaemia and no weight gain, the proportion of patients with a  $\geq 0.3\%$  reduction in HbA1c and  $\geq 10\%$  reduction in LDL-c at 24 weeks, and the proportion of patients with a  $\geq 0.5\%$  reduction in HbA1c and  $\geq 15\%$  reduction in LDL-c at 24 weeks. Mean dose of colesevelam was evaluated at 12 and 24 weeks. Secondary safety endpoints included the change in ALT and CK from baseline to 24 weeks, total hypoglycaemia at 12 and 24 weeks, and severe hypoglycaemia at 12 and 24 weeks. The proportion of patients who discontinued study medication and the reasons for discontinuation were summarized.

## 2.4 | Statistical analysis

The original sample size calculation yielded a sample size of 200 for  $\geq 99\%$  power to establish non-inferiority and  $>80\%$  power to establish superiority of colesevelam for the primary composite endpoint, with a non-inferiority margin of 20%, and a predicted 10% non-completion rate. However, a sample size of 440 participants was originally chosen based on the key secondary outcome of analysing the primary outcome in the SGLT2i subgroup, with the use of this antidiabetes therapy class projected at 20%. This sample size of 440 subjects would provide  $>99\%$  power to establish non-inferiority and  $>80\%$  power to establish the superiority of colesevelam for the primary composite endpoint within the SGLT2i subgroup.

After 116 subjects were enrolled, an interim, blinded analysis of baseline medication data indicated close to 50% SGLT2i use in the study population. Hence, the original projection of 20% SGLT2i use was modified to 45%, with the revised sample size of 200 randomized subjects (100 per arm). This would provide  $\geq 99\%$  power to establish non-inferiority of the colesevelam arm in the total study population as well as in the SGLT2i subgroup. The protocol amendment was approved by local ethics review boards.

The primary and secondary efficacy endpoints were analysed using a modified intention to treat (mITT) population and included all randomized patients who received at least one dose of the study treatment and had a baseline and follow-up HbA1c and LDL-c measurement. The primary endpoint was also analysed in the per-protocol (PP) population, who remained on study treatment until 24 weeks. The safety population included all randomized subjects who took at least one dose of the study medication. Missing data were not replaced. Alpha was considered statistically significant at  $P < .05$  and all analyses were performed with SAS version 9.4 (Cary, NC, USA).

Baseline characteristics for all randomized subjects were summarized as mean (standard deviation) for continuous variables and frequencies (percentages) for categorical variables. The primary endpoint of the proportion of patients achieving HbA1c  $\leq 7.0\%$  and LDL-c  $\leq 2.0$  mmol/L (or non-HDL-c  $\leq 2.6$  mmol/L) at  $24 \pm 4$  weeks was tested using a chi-square test. Analysis of covariance (ANCOVA) models with treatment status as fixed effects and baseline value as a covariate were used to evaluate the treatment effect for the secondary endpoints of change from baseline to 24 weeks. The proportions of patients achieving secondary composite endpoints were compared with chi-square tests.

## 3 | RESULTS

From January to October 2016, 200 subjects were randomized (98 to colesevelam and 102 randomized to ezetimibe), of whom 186 (89 randomized to colesevelam and 97 randomized to ezetimibe) initiated the medication. The main reason reported for not initiating the prescribed study medication in the 14 patients was the cost of the medication. During follow-up, seven colesevelam and two ezetimibe patients were lost to follow-up. Therefore, the mITT population consisted of 82 patients randomized to colesevelam and 95 patients randomized to ezetimibe (Figure S1).

Baseline characteristics are presented in Table 1. In both treatment groups at baseline, mean HbA1c was 8.0% (64.0 mmol/mol), mean LDL-c was 2.5 mmol/L and 97% of patients were using a statin. The majority were using metformin; just over half of the patients were on an SGLT2i; 55% injected insulin; there were no differences between treatment arms.

During the trial period, there were no changes in statin dose for any patient. One subject discontinued background fenofibrate during the trial period because of myalgia. One subject switched their SGLT2i to another SGLT2i because of insurance coverage. All other patients had unchanged lipid-lowering and diabetes medications.

The proportion of participants who achieved the primary composite endpoint of LDL-c  $\leq 2.0$  mmol/L and HbA1c  $\leq 7.0\%$  by 24 weeks (LOCF) in the colesevelam arm (14.6%) was non-inferior, but not superior, to the proportion of patients in the ezetimibe arm (10.5%), with a between-group difference in proportions of 4.1% (95% CI -5.7 to 13.9,  $P_{\text{non-inferiority}} < .001$ ;  $P < .41$  for superiority; Figure 1). Similarly, non-inferiority for the primary composite outcome was confirmed in the PP population (15.4% colesevelam, 10.0% ezetimibe, between-group difference in proportions of 5.4% [95% CI -5.0% to 15.5%,  $P_{\text{non-inferiority}} < .001$ ]). In the subgroup using SGLT2is, the proportion of patients who achieved the primary composite endpoint in the colesevelam arm (9.8%) was non-inferior to the proportion of patients in the ezetimibe arm (10.6%), with a between-group difference in proportions of -0.9% (95% CI -0.128 to 0.110,  $P_{\text{non-inferiority}} = .004$ ).

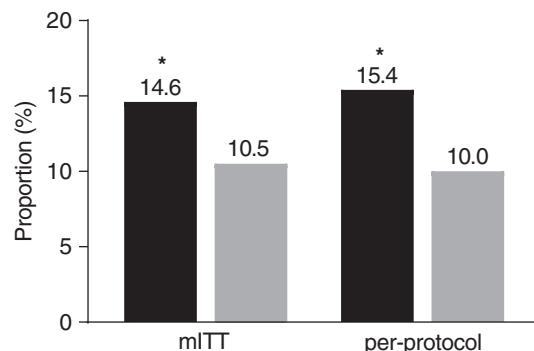
Both treatment groups had significant reductions in LDL-c at 24 weeks from baseline (14% for colesevelam vs. 23.2% for ezetimibe), with a significantly greater reduction observed in ezetimibe (between-

**TABLE 1** Baseline characteristics of all randomized patients

|                                                                  | Colesevelam  | Ezetimibe    |
|------------------------------------------------------------------|--------------|--------------|
| N                                                                | 98           | 102          |
| Age                                                              | 59.9 ± 10.2  | 59.0 ± 10.3  |
| Males, N (%)                                                     | 45 (45.9)    | 52 (51.0)    |
| Duration of diabetes (years)                                     | 14.0 ± 9.1   | 14.5 ± 8.8   |
| History of CVD                                                   | 22 (22.5)    | 10 (9.8)     |
| HbA1c (%)                                                        | 8.0 ± 0.9    | 8.0 ± 0.8    |
| HbA1c (mmol/Mol)                                                 | 64 ± 10      | 64 ± 9       |
| FPG (mmol/L)                                                     | 8.0 ± 2.2    | 7.9 ± 2.2    |
| FPG (mg/dL)                                                      | 145 ± 40     | 140 ± 40     |
| LDL-c (mmol/L)                                                   | 2.53 ± 0.63  | 2.50 ± 0.55  |
| LDL-c (mg/dL)                                                    | 97.8 ± 24.3  | 96.7 ± 21.3  |
| Non-HDL-c (mmol/L)                                               | 3.3 ± 0.7    | 3.2 ± 0.7    |
| Non-HDL-c (mg/dL)                                                | 127.6 ± 27.1 | 123.7 ± 27.1 |
| Weight (kg)                                                      | 80.9 ± 19.0  | 81.1 ± 16.9  |
| BMI (kg/m <sup>2</sup> )                                         | 29.7 ± 6.1   | 29.9 ± 7.2   |
| Ethnicity, N (%)                                                 |              |              |
| Caucasian                                                        | 34 (34.7)    | 20 (19.6)    |
| Asian                                                            | 38 (38.8)    | 55 (53.9)    |
| Other                                                            | 16 (16.3)    | 10 (9.8)     |
| Declined                                                         | 10 (10.2)    | 17 (16.7)    |
| Concomitant lipid therapies, N (%)                               |              |              |
| Rosuvastatin                                                     | 51 (52.0)    | 71 (69.6)    |
| Atorvastatin                                                     | 35 (35.7)    | 21 (20.6)    |
| Fluvastatin                                                      | 4 (4.1)      | 2 (2.0)      |
| Pravastatin                                                      | 3 (3.1)      | 3 (2.9)      |
| Simvastatin                                                      | 2 (2.0)      | 2 (2.0)      |
| Fibrates                                                         | 0            | 1 (1.0)      |
| No lipid-lowering therapy                                        | 3 (3.1)      | 2 (2.0)      |
| Concomitant AHA therapies, N (%)                                 |              |              |
| Metformin                                                        | 85 (86.7)    | 94 (92.2)    |
| Sulphonylurea                                                    | 29 (29.6)    | 32 (31.4)    |
| SGLT2 inhibitors                                                 | 52 (53.1)    | 53 (52.0)    |
| DPP-4 inhibitors                                                 | 62 (63.3)    | 64 (62.8)    |
| GLP-1 RA                                                         | 11 (11.2)    | 11 (10.8)    |
| Insulin                                                          | 54 (55.1)    | 56 (54.9)    |
| Mean number of total AHA                                         | 3.2 ± 1.1    | 3.2 ± 1.0    |
| Mean number of oral AHA                                          | 2.3 ± 1.0    | 2.4 ± 1.0    |
| Mean number of oral AHA in patients not using injectable therapy | 2.5 ± 1.0    | 2.7 ± 0.9    |

Abbreviations: AHA, antihyperglycaemic agents; BMI, body mass index; CVD, cardiovascular disease (defined as a history of coronary artery disease, peripheral vascular disease, myocardial infarction, stroke or heart surgery as per electronic medical record); DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LDL-c, low density lipoprotein-cholesterol; non-HDL-c, non-high density lipoprotein-cholesterol; SGLT2, sodium-glucose co-transporter-2.

All data are expressed as mean ± standard deviation or as count (percentage).



**FIGURE 1** Proportion of patients achieving the primary endpoint in the colesevelam and ezetimibe arms in the modified intention to treat (mITT) population and in the per-protocol population. Black bar = colesevelam arm; grey bar = ezetimibe arm. \* = non-inferiority of colesevelam ( $P < .001$ )

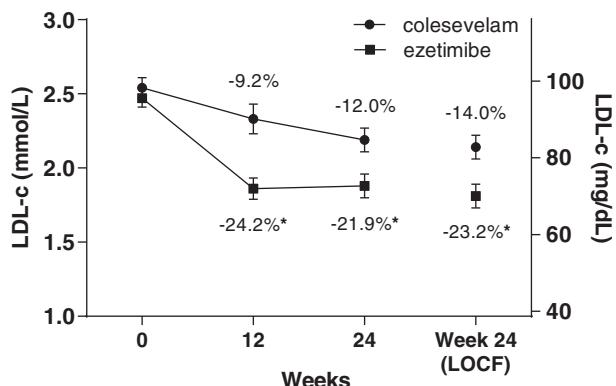
group least squares [LS] means LOCF reduction in LDL-c at 24 weeks  $0.26 \pm 0.11$  mmol/L [ $P = .01$ ]; Figure 2). The proportion of participants achieving the LDL-c target of  $\leq 2.0$  mmol/L was also less with colesevelam (47.6%) versus ezetimibe (67.0%;  $P = .009$ ).

The colesevelam group had a significant reduction in HbA1c at 12 and 24 weeks, while there was no change in the ezetimibe arm (between-group LS means LOCF reduction in HbA1c at 24 weeks  $-0.2\% \pm 0.1\%$ ,  $P = .06$ ; Figure 3). The proportion of patients in the colesevelam arm who achieved target HbA1c ( $\leq 7.0\%$ ) was 26.8%, which was significantly greater than the 14.7% of patients who achieved target HbA1c in the ezetimibe arm ( $P = .04$ ).

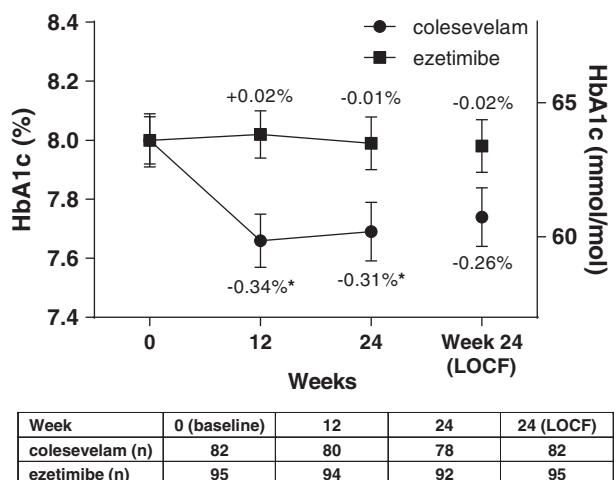
Both treatment groups had significant reductions in non-HDL-c at 24 weeks, with a greater comparative reduction observed with ezetimibe (Table S1). There were no significant differences for changes in FPG, HDL-c, triglycerides, hs-CRP, ALT, CK, body weight, BMI, waist circumference or blood pressure at 24 weeks. Additionally, change from baseline to 24 weeks in secondary endpoints of LDL-c, HbA1c, FPG and non-HDL-c in the subgroup of trial participants on SGLT2i therapy changed by the same magnitude, approximately, as those not on SGLT2i therapy, and were not statistically different between colesevelam and ezetimibe treatment arms (Table S1).

In patients with baseline LDL-c of 2.0–2.5 mmol/L, both arms had significant reductions in LDL-c (colesevelam  $-0.22 \pm 0.11$  mmol/L,  $-7.9\%$ ,  $P = .04$ ; ezetimibe  $-0.33 \pm 0.10$  mmol/L,  $-15.1\%$ ,  $P < .01$ ; between-group difference  $P = .34$ ) (Figure S2). Both treatment groups had significant reductions in LDL-c in patients whose baseline LDL-c was  $\geq 2.5$  mmol/L (colesevelam  $-0.65 \pm 0.13$  mmol/L,  $-20.6\%$ ; ezetimibe  $-1.08 \pm 0.12$  mmol/L,  $-35.1\%$ ), with a significantly greater LDL-c reduction observed with ezetimibe ( $P = .01$ ).

Among subgroup analyses for baseline HbA1c, neither treatment led to a significant change for those with an HbA1c of 7.0%–8.0% (Figure S3). The colesevelam arm had a significant reduction in HbA1c ( $-0.4\% \pm 0.2\%$ ;  $P = .02$ ) only among the subgroup of patients whose baseline HbA1c was between 8.0% and 10% (difference  $P = .17$ ).



**FIGURE 2** Low density lipoprotein-cholesterol (LDL-c) over 24 weeks in the colesevelam and ezetimibe arms. Closed circles = colesevelam arm; closed squares = ezetimibe arm. \* = significantly different compared with ezetimibe ( $P < .05$ ). LOCF, last observation carried forward



**FIGURE 3** HbA1c over 24 weeks in the colesevelam and ezetimibe arms. Closed circles = colesevelam arm; closed squares = ezetimibe arm. \* = significantly different compared with ezetimibe ( $P < .05$ ). LOCF, last observation carried forward

The proportion of patients who achieved the composite endpoint of  $\text{HbA1c} \leq 7.0\%$  ( $\leq 53 \text{ mmol/mol}$ ), with no hypoglycaemia and no weight gain at 24 weeks, was significantly greater in the colesevelam arm (18.0%) compared with the ezetimibe arm (6.4%;  $P = .02$ ), as was the proportion of patients who achieved the composite endpoint of  $\text{HbA1c}$  reduction  $\geq 0.3\%$  and  $\text{LDL-c}$  reduction  $\geq 10\%$  at 24 weeks (35.4% and 18.1%, respectively;  $P = .004$ ). However, the proportion of patients who achieved the composite endpoint of  $\text{HbA1c}$  reduction  $\geq 0.5\%$  and  $\text{LDL-c}$  reduction  $\geq 15\%$  at 24 weeks in colesevelam (22.0%) compared with ezetimibe (13.8%) did not reach statistical significance ( $P = .06$ ).

During the trial, at least one episode of hypoglycaemia occurred in 22.0% of patients in the colesevelam group and 16.8% of patients in the ezetimibe group ( $P = .36$ ). There was no reported severe hypoglycaemia, and no serious adverse events or deaths during the trial.

The proportion of patients who discontinued study treatment was greater in the colesevelam arm (31.1%) compared with the ezetimibe arm (6.2%) ( $P < .001$ ). More patients in the colesevelam arm (20.2%) experienced at least one adverse event compared with ezetimibe (7.2%) ( $P = .009$ ). The most commonly reported adverse events for the colesevelam arm were gastrointestinal symptoms (Table S2).

#### 4 | DISCUSSION

GOAL-RCT is the first randomized controlled trial comparing ezetimibe and colesevelam in subjects with T2D. The primary composite endpoint ( $\text{LDL-c}$  and  $\text{HbA1c}$  target attainment), achieved in a low proportion of subjects, was similar between the two treatment groups. However, initiation of ezetimibe led to a much greater reduction in  $\text{LDL-c}$ , and a significantly higher proportion of subjects achieving target  $\text{LDL-c}$  levels, compared with colesevelam. The greater  $\text{LDL-c}$  reduction efficacy of ezetimibe was observed consistently, independent of baseline  $\text{LDL-c}$  subgroups. In addition, both tolerability and persistence of therapy were much better for ezetimibe compared with colesevelam. A modest, non-statistically significant  $\text{HbA1c}$  reduction was observed only in the colesevelam arm.

The difference in magnitude of  $\text{LDL-c}$  reduction observed in this head-to-head randomized trial between ezetimibe and colesevelam is unexpected. Although a head-to-head comparison of these therapies in diabetes has not been previously reported, comparable  $\text{LDL-c}$ -lowering efficacy has been observed in randomized trials where either ezetimibe or colesevelam was added separately to background statin therapy.<sup>20-23</sup> Variations in study inclusion criteria, specifically differences in baseline mean  $\text{LDL-c}$  levels within individual colesevelam and ezetimibe trials, could potentially explain this discrepancy between the published literature and our findings. It is also plausible that various types of biases (selection, assessment, attrition or outcome reporting bias) could have influenced the previously published literature. Furthermore, as GOAL-RCT was conducted entirely in a T2D sample, another possible explanation is that the two agents have differential  $\text{LDL-c}$  reduction efficacy in this population. In addition to the greater  $\text{LDL-c}$ -lowering efficacy, tolerability and persistence of treatment were better for ezetimibe in the GOAL-RCT trial compared with colesevelam. Poor adherence has been previously reported with earlier generations of bile acid-binding therapies.<sup>25</sup>

Differences in both  $\text{LDL-c}$  reduction efficacy and tolerability within the GOAL-RCT trial are important novel results in clinical decision-making for non-statin add-on therapy options in favour of ezetimibe. Based on the findings of lower efficacy and tolerability, colesevelam should not receive priority in recommendation as a second-line lipid-lowering option. Currently, some researchers have advocated for such a priority, in patients with the metabolic syndrome

and/or T2D, because of their dual effect on HbA1c together with efficacious LDL-c reduction.<sup>26</sup> Of note, current guidelines range in their recommendations for oral add-on LDL-c reduction therapy options, with Canadian lipid guidelines somewhat silent on the choice between BAS and ezetimibe,<sup>3</sup> while the American College of Cardiology expert panel has expressed a preference for ezetimibe.<sup>27</sup> In the GOAL-RCT trial, coleselam led to a reduction in HbA1c of 0.3% among the overall trial population, with a 0.4% reduction among the baseline-elevated HbA1c subgroup (HbA1c 8.0% to 10%), comparable in magnitude with the published literature.<sup>22–24</sup> However, the clinical significance of this modest glucose reduction by itself, and its effect on macrovascular complications, is debatable.<sup>28,29</sup> Overall, because of the dual glycaemic and LDL-c reduction benefit observed in this trial with coleselam, when added to a baseline of several antihyperglycaemic agents and statin medications, the BAS class of agents may continue to be a valid therapeutic option for those individuals who can tolerate and persist with this therapy.

Despite the published literature suggesting an increase in LDL-c with SGLT2is,<sup>30–32</sup> with an unclear mechanism, GOAL-RCT did not find any significant differences between the two treatment arms on primary or secondary outcomes in participants using SGLT2is at baseline, with a similar overall trend for LDL-c and HbA1c reduction noticeable for the overall study population.

The main strengths of this pragmatic, real-world trial include well-matched baseline characteristics between the treatment groups, together with standardized trial conduct and procedures. Background medical care was provided within clinics affiliated with a single-specialty diabetes centre. Additionally, the majority of subjects were treated with standard-of-care CV protection strategies, including 97% statin utilization at baseline.

The open-label design of this randomized trial may be considered a study limitation. However, no medication or dose changes were made in cholesterol-lowering medications during the trial period, except for one subject who discontinued background fenofibrate because of myalgias. A nationwide shortage of prescription coleselam affected the medication persistence for a few trial participants. This temporary gap in treatment was fortunately small (affecting five subjects) and did not lead to permanent treatment discontinuation. In a sensitivity analysis excluding the five subjects who were temporarily affected by this shortage, no change in the magnitude of LDL-c-lowering was observed in the coleselam group. Because of the pragmatic real-world nature of this trial, adherence to therapy or to medication instructions (including avoidance of drug-drug interactions) was not monitored beyond the routine clinical paradigm. Finally, generalizability of GOAL-RCT trial findings to populations without diabetes is limited.

In conclusion, GOAL-RCT suggests favourable LDL-c reduction, tolerability and therapy persistence for ezetimibe compared with coleselam in T2D. These results may help inform clinicians, and guidelines, on comparative metabolic efficacy as well as tolerability of coleselam and ezetimibe, and guide them in the choice of appropriate second-line cholesterol-lowering therapy in people with T2D who are not achieving their target LDL-c levels on statin medications.

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## CONFLICT OF INTEREST

H.S.B. reports personal fees for lectures and research funding for serving as principal investigator on clinical trials paid to LMC Healthcare from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk and Sanofi; he serves as an editor for the *Canadian Journal of Diabetes* and as a columnist for Medscape. K.V. has received consulting fees from Sanofi. O.S has received research support from AstraZeneca, Eisai, Eli Lilly, Gilead, Janssen, Kowa, Lexicon, Novartis, Novo Nordisk, Pfizer, Sanofi, Bausch and Zealand; has received speaking honoraria from AstraZeneca, Eli Lilly, Janssen, Merck, Novo Nordisk and Sanofi; and has received consulting fees from Amgen, Eli Lilly, Merck, Novo Nordisk and Sanofi. R.A. reports personal fees and research support outside the submitted work from Novo Nordisk, Janssen, Sanofi, AstraZeneca, Eli Lilly, and research support from Merck and Boehringer Ingelheim. R.E.B., D.J., H.A-A., H.K. and S.A-S. have no conflicts of interest to declare. H.S.B. is the guarantor of this article and takes responsibility for the contents of this article.

## AUTHOR CONTRIBUTIONS

H.S.B. designed/conducted the study and co-wrote the manuscript. R.E.B. and D.J. performed the data collection, statistical analyses and co-wrote the manuscript. K.V., H.A-A., H.K., O.S. and S.A-S. assisted in study design and conducting the study. R.A. provided critical revisions to the manuscript.

## DATA-SHARING STATEMENT

Data from this trial will not be made available to others.

## ORCID

Harpreet S. Bajaj  <https://orcid.org/0000-0002-1461-1465>

Ronnie Aronson  <https://orcid.org/0000-0002-8976-2321>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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