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CLINICAL PRACTICE UPDATE IN
DIABETES & ENDOCRINOLOGY

Clinical Controversies in Diabetes Management:

An Interactive Evening for Endocrinologists at Vascular 2013
Thursday, October 17, 2013, Montreal, Quebec

Part 1 – Dyslipidemia Management in the Diabetes Patient
Targeting LDL-C and A1C in Type 2 Diabetes: The Role of Colesevelam

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At Vascular 2013 in Montreal, Quebec, endocrinologists spent an evening discussing clinical controversies in diabetes management. One of the issues discussed related to the role of the bile-acid sequestrant colesevelam as not only an LDL-C lowering agent, but also as an anti-hyperglycemic agent. The discussants included Dr. Jacques Genest, cardiologist at Royal Victoria Hospital, Montreal, and Dr. Ron Goldenberg, endocrinologist at LMC Diabetes & Endocrinology in Thornhill.

Introduction:

Achieving both A1C and LDL-C targets is an ongoing challenge in the management of type 2 diabetes. The DM-SCAN Survey of 5,123 patients with type 2 diabetes in Canada demonstrated that an A1C ≤ 7.0% was met by 50% and an LDL-C ≤ 2.0 mmol/L by 57%. While metformin and statins are first-line therapies for targeting glycemia and LDL-C, a wide range of approaches exist for second-line options when targets are not achieved with first-line therapies.

Case Study Synopsis:

A 50 year old male with type 2 diabetes for 7 years is being treated with metformin 1000 mg bid and a high-dose of an efficacious statin. A1C is 7.5% and LDL-C= 2.4 mmol/L.

Question for discussion:

In order to improve the LDL-C and A1C, which of the following approaches would you consider:

A. Add a second antihyperglycemic agent and ezetimibe
B. Add colesevelam

Targeting LDL-C in Diabetes Patients

Dr. Genest briefly reviewed the CCS 2012 Lipid Guidelines, reminding the audience that individuals with diabetes are at high risk for cardiovascular events if they meet any of the following criteria: documented atherosclerosis; microvascular disease; hypertension plus 3 risk factors; ≥40 years of age; ≥30 years of age and diabetes duration over 15 years; Framingham 10 year risk score ≥ 20%. Consider treating all high-risk individuals with the primary target being an LDL-C < 2 mmol/L or a 50% reduction in LDL-C from baseline.

While statins are the agents of choice for LDL-C lowering, many individuals will not reach LDL-C targets with statin monotherapy, as illustrated in the case description. While most individuals do well with statin therapy, some individuals are intolerant to statins and others may only tolerate lower doses. Physicians need to be aware of non-statin lipid-lowering strategies, especially agents that lower LDL-C, such as ezetimibe and bile-acid sequestrants, such as colesevelam. Niacin has fallen out of favour due to the lack of cardiovascular benefit in recent trials and poor tolerability.

Colesevelam as an Antihyperglycemic Agent

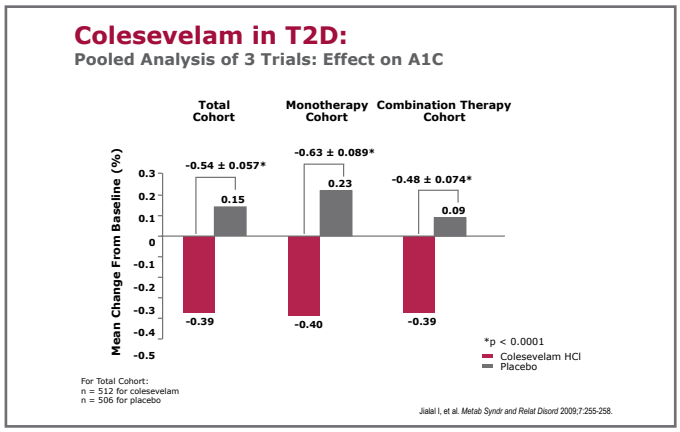
Dr. Goldenberg presented data with the bile-acid sequestrant (BAS) colesevelam, highlighting its association with both LDL-C and A1C lowering, and stressing that it is an ideal agent to consider when a patient with type 2 diabetes needs further LDL-C and A1C lowering despite statin and metformin therapy, as presented in the case scenario.

In a pooled analysis of 3 colesevelam studies in type 2 diabetes patients, Jialal et al reported placebo-corrected A1C reductions from baseline of -0.48% with background monotherapy and -0.63% in the combination therapy cohort (Figure 1). A meta-analysis of 8 colesevelam trials showed a -0.59% reduction in A1C versus placebo.

While there are no head-to-head studies, the A1C reduction with colesevelam as an add-on to metformin is similar or perhaps just slightly less than that seen with commonly used antihyperglycemic agents such as DPP-4 inhibitors or sulfonylureas.

Dr. Goldenberg described a network meta-analysis of add-on to metformin trials where the placebo corrected A1C lowering for oral antihyperglycemic agent therapies ranged from -0.66% to -0.82%. Colesevelam is currently not approved as a glucose lowering therapy for type 2 diabetes in Canada, but does have this indication in the U.S.A.

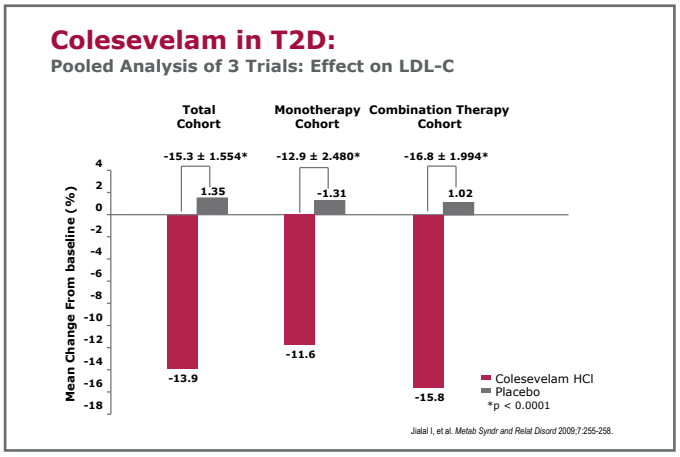
FIGURE 1: POOLED ANALYSIS OF 3 TRIALS: EFFECT ON A1C



LDL-C Lowering with Colesevelam

Colesevelam's indication is for LDL-C lowering in Canada, and it lowers LDL-C by 15% to 20% when used as monotherapy or as add-on to statin therapy and has been shown to be effective for LDL-C lowering in type 2 diabetes patients on various background antihyperglycemic therapies (Figure 2).

FIGURE 2: POOLED ANALYSIS OF 3 TRIALS: EFFECT ON LDL-C

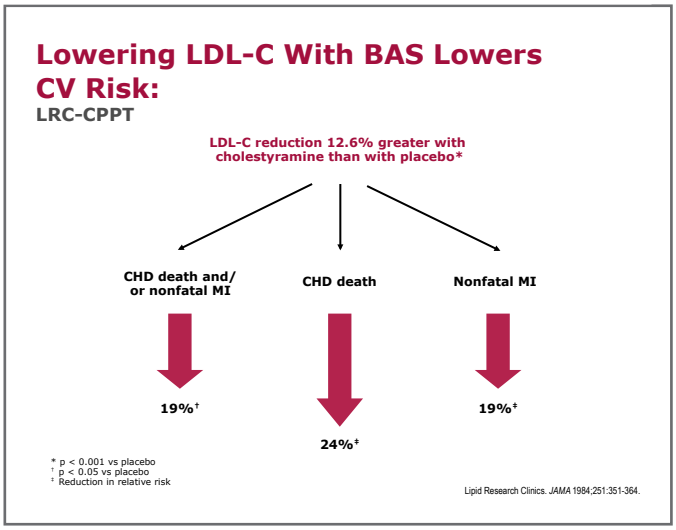


The BAS cholestyramine was associated with cardiovascular event risk reduction in the LRC-CPPT trial published in 1984 (Figure 3). Colesevelam, due to its unique polymer structure, has enhanced specificity and a higher capacity for binding bile acids compared to conventional bile acid sequestrants such as cholestyramine. It has a low risk of adverse events and an excellent safety profile, with constipation rates only slightly higher than those reported with placebo.

It also has a low rate of drug interactions, but can inhibit the absorption of levothyroxine, glyburide and oral contraceptives, which should be dosed four hours prior to colesevelam.

Colesevelam is usually dosed at 6 tablets (625 mg each) once daily or 3 tablets twice daily.

FIGURE 3:
CARDIOVASCULAR RISK REDUCTION WITH BILE ACID SEQUESTRANT THERAPY



Targeting LDL-C and A1C with a Single Agent: The Role of Colesevelam

In the case scenario provided, **it is likely that both metabolic targets – A1C and LDL-C – would be achieved by the simple addition of colesevelam therapy to the already established treatment** with statin and metformin (Table 1).

TABLE 1: Advantages of Adding Colesevelam versus Another Antihyperglycemic Agent Plus Ezetimibe

- A single agent is used to treat 2 problems – less polypharmacy
- Likely to achieve your LDL-C target and your A1c target
- Well-tolerated
- Long, established safety profile

Using it in this clinical setting will lessen polypharmacy, as all other LDL-C lowering options would require the addition of another antihyperglycemic agent for improving glycemia. In fact, Dr. Goldenberg pointed out that amongst all the second-line lipid-lowering agents, only colesevelam is associated with both LDL-C and A1C lowering (Figure 5).

The lively evening discussion that ensued

left an audience consensus:
Colesevelam should be considered in type 2 diabetes patients when LDL-C is not at target despite statin therapy or when statins are not tolerated, as the dual benefit on LDL-C and A1C offers a unique management approach.

Effect	Colesevelam	Ezetimibe	Fibrate	Niacin
LDL Lowering	✔	✔	✗	✔
A1C Lowering	✔	✗	✗	✗

FIGURE 5: SECOND-LINE LIPID LOWERING AGENTS: LDL-C AND A1C LOWERING EFFICACY

Alternative Approaches to Dual A1C and LDL-C Lowering Add-on Therapy

Dr. Goldenberg was also asked to act as the devil's advocate and present an opposing point of view in this clinical setting. He pointed out that adding ezetimibe in this situation would likely lead to a further 15% drop in LDL-C, similar to that seen with colesevelam. However, there would likely be a slight drop in triglycerides with add-on ezetimibe therapy but a rise in triglycerides with colesevelam. In fact, colesevelam should be used with caution in those with triglycerides > 3.4 mmol/L.

He showed a small study by Zema et al, where add-on ezetimibe therapy lowered LDL-C 7% more than add-on colesevelam. He stated that when A1C and LDL-C are above target with metformin and statin therapy, switching the metformin to fixed-dose combination with a DPP-4 inhibitor would be an efficacious way to lower A1C without increasing the pill burden and then adding in ezetimibe will help get the LDL-C to target without having to be concerned about the rise in triglycerides with the colesevelam approach. He did conclude by stating that clinical judgment and cost and coverage will ultimately drive the decision about which agent to consider for further LDL-C and A1C lowering.

Case Study Summary

In the case under discussion, the A1C was above target despite metformin monotherapy and the LDL-C above target despite efficacious statin therapy. While the traditional approach in this setting would be the addition of both an anti-hyperglycemic and lipid-lowering agent, the availability of colesevelam now allows for a newer and practical approach. The addition of a single agent (colesevelam) has the potential to improve both the LDL-C and the A1C. Adding colesevelam to background statin and antihyperglycemic agent therapy in type 2 diabetes should help improve the percent of patients achieving target LDL-C ≤ 2.0 mmol/L and A1C ≤ 7.0 mmol/L.

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