

Advances in the Combined Management of Hyperglycemia and Dyslipidemia in Type 2 Diabetes

a report by

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Diabetes and Cardiovascular Disease

The increased incidence of premature coronary heart disease (CHD) continues to present a major challenge in the care of patients with type 2 diabetes. While there has been a significant decline in mortality from CHD in the US due to recently described reductions in other coronary risk factors, these reductions in mortality have been offset by the increasing prevalence of obesity and diabetes.¹ In another large population study, based on increased rates of premature myocardial infarction (MI), diabetes was shown to be equivalent to a 15-year acceleration in aging.² Moreover, mortality from cardiovascular disease (CVD) continues to be higher in patients with diabetes following recovery from MI, despite advances in treatment. In a recent analysis of 11 large studies encompassing more than 62,000 patients presenting with acute coronary syndromes—of whom 10,600 (17%) had known diabetes—the 30-day and one-year mortality rates were increased by 40 and 33%, respectively, in those with diabetes compared with those without, after adjustments for other multiple risk factors and covariates.³ The precise reasons underlying these differences are not known. However, the low rate of early diagnosis of diabetes (resulting in prolonged periods of metabolic derangements), suboptimal control of hyperglycemia, hypercholesterolemia, and other risk factors unique to diabetes are likely contributory. In the Nurses' Health Study, the risk of MI or stroke during 20-year follow-up of 117,000 women was 2.8-fold greater during the pre-diabetes phase in those who subsequently developed diabetes.⁴ There is also ample evidence for a markedly increased prevalence of undiagnosed diabetes and pre-diabetes—impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)—in patients with a recent acute coronary event. In a prospective, 3.2-year follow-up of over 8,000 patients with MI at a mean age of 59 years and with no diabetes at baseline, 62% were diagnosed with new-onset diabetes or pre-diabetes.⁵ These staggering observations raise the possibility that early diagnosis of hyperglycemia and greater attention to the other risk factors might help reduce the burden of CVD in such individuals.



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Dyslipidemia and Cardiovascular Disease in Diabetes

The dyslipidemia of type 2 diabetes and the well-known cardio-metabolic syndrome is characterized by a number of inter-related atherogenic abnormalities, including increased levels of triglyceride-rich lipoproteins (very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and remnant particles), low levels of high-density lipoproteins (HDL), and increased levels of small, dense LDL, as well as non-HDL cholesterol. Since the mid-1990s, a plethora of randomized, controlled trials with 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) have established the efficacy of LDL-lowering agents in reducing cardiovascular outcomes. In a recent meta-analysis of 16 randomized trials of statin therapy, encompassing 90,056 individuals from various parts of the world, a mean LDL cholesterol reduction of 1mm (~40mg/dl) over five years resulted in a 23% reduction in MI or coronary death ($p < 0.0001$), a 17% reduction in stroke, ($p < 0.001$), and a 12% reduction in all-cause mortality ($p < 0.0001$).⁶ These benefits were seen regardless of the presence of diabetes ($n = 18,686$) or components of metabolic syndrome (HDL, triglycerides, hypertension), although the absolute risk of events was greater in those with hypertriglyceridemia, low HDL, or hypertension. In view of the markedly increased risk of subsequent cardiovascular events (CHD and stroke) in patients with pre-existing CHD, the current update of the adult treatment panel (ATP) III guidelines recommends an LDL goal of < 70 mg/dl in all patients in this category.⁷ A recent meta-analysis included four trials of intensive LDL-lowering therapy in patients with acute coronary syndromes—Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT), Aggrastat to Zocor (A to Z)—or stable coronary artery disease (CAD)—Treating to New Targets Study (TNT), Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL)—involving 27,548 patients.⁸ Of these, 4,379 patients had diabetes. The mean LDL-cholesterol (LDL-C) achieved by intensive therapy was 75mg/dl compared with 101mg/dl by standard treatment. This analysis revealed a 16% risk reduction (RR) in coronary death or MI ($p < 0.0003$) and an 18% RR in stroke ($p = 0.012$). Similar outcomes were observed in patients with diabetes. Since the absolute baseline risk in patients with diabetes is greater, the benefit in such patients with similar decrease in lipid levels is greater, especially in secondary prevention.

Hyperglycemia and Cardiovascular Disease

There is increasing evidence for the cardiovascular benefits of glycemic lowering, although thus far such evidence has been less strong compared with LDL lowering, possibly due to the fact that optimal glycemic control has never really been achieved in any clinical trial in patients with type 2 diabetes. In the largest trial—the UK Prospective Diabetes Study (UKPDS)—there was a 14% reduction in MI for each 1% reduction in glycated hemoglobin (HbA_{1c}).⁹ A similar 18% increase in CVD events for each 1% increase in HbA_{1c} was

Table 1: Look-AHEAD—Changes in Selected Parameters at One Year¹⁶

Measure	ILI	DSE	p value
n	2,496	2,463	
Use of diabetes medicines (%)			
Baseline	86.5±0.7	86.5±0.7	0.93*
Year 1	78.6±0.8	88.7±0.6	<0.001*
Change	-7.8±0.6	2.2±0.5	<0.001†
Fasting glucose (mg/dl)			
Baseline	151.9±0.9	153.6±0.9	0.21‡
Year 1	130.4±0.8	146.4±0.9	<0.001‡
Change	-21.5±0.9	7.2±0.9	<0.001‡
HbA_{1c} (%)			
Baseline	7.25±0.02	7.29±0.02	0.26‡
Year 1	6.61±0.02	7.15±0.02	<0.001‡
Difference	-0.64±0.02	-0.14±0.02	<0.001‡
Use of lipid-lowering medicines (%)			
Baseline	49.4±1.0	48.4±1.0	0.52*
Year 1	53.0±1.0	57.8±1.0	<0.001*
Change	3.7±0.8	9.4±0.8	<0.001†
LDL cholesterol (mg/dl)			
Baseline	112.2±0.4	112.4±0.6	0.78‡
Year 1	107.0±0.6	106.7±0.7	0.74‡
Change	-5.2±0.6	-5.7±0.6	0.49‡
HDL cholesterol (mg/dl)			
Baseline	43.5±0.2	43.6±0.2	0.80‡
Year 1	46.9±0.3	44.9±0.2	<0.001‡
Change	3.4±0.2	1.4±0.1	<0.001‡
Triglycerides (mg/dl)			
Baseline	182.8±2.3	180.0±2.4	0.38‡
Year 1	152.5±1.8	165.4±1.9	<0.001‡
Change	-30.3±2.0	-14.6±1.8	<0.001‡

Data are means ±SE or % ±SE. *Logistic regression with adjustment for clinical site. †Mantel-Haenszel test with adjustment for clinical site. ‡ANCOVA, with adjustment for clinical site.

found in a meta-analysis of 13 observational studies.¹⁰ The best evidence of the salutary effects of glycemic control on CVD outcomes came from the Epidemiology of Diabetes Interventions and Complications (EDIC) Study, a 15-year extended follow-up of the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes.¹¹ In this cohort, a 42–57% reduction in major CVD events was reported in patients in the original intensive versus standard therapy subgroup (mean HbA_{1c} at the end of 6.5 years: 7.2 versus 9%, respectively). The results of a long-term trial investigating the role of near-normal glycemic control in type 2 diabetes—Action to Control Cardiovascular Risk in Diabetes (ACCORD)—are currently awaited.

Interventions to Achieve Both LDL and Glycemic Control

Non-pharmacological Strategies

The lipid and glycemic goals striven for in type 2 diabetes frequently remain unmet. According to a recent National Health and Nutrition Examination Survey (NHANES), fewer than 40% of patients with type 2 diabetes are at the HbA_{1c} goal of <7%; this is also often the case regarding cholesterol and blood-pressure goals.¹² Based on the clinical trial evidence, the current LDL-C goals were updated by the ATP III and adopted by the American Diabetes Association (ADA).^{7,13} These recommendations advocate a minimum goal of LDL-C of <100mg/dl in most patients with type 2 diabetes, and a goal of LDL-C <70mg/dl in those with CVD. In addition, it is recommended that treatment-lowering strategies should aim to reduce LDL-C by at least 30–40% from

Table 2: Look-AHEAD—Participants Meeting Goals at One Year¹⁶

Measure	ILI	DSE	p value
HbA_{1c} (<7%)			
Baseline	46.3±1.0	45.4±1.0	0.50*
Year 1	72.7±0.9	50.8±1.0	<0.001*
Difference	26.4±1.0	5.4±1.0	<0.001†
Blood pressure (<130/80 mmHg) (%)			
Baseline	53.5±1.0	49.9±1.0	0.01*
Year 1	68.6±0.9	57.0±1.0	<0.001*
Change	15.1±1.1	7.0±1.2	<0.001†
LDL cholesterol (<100 mg/dl) (%)			
Baseline	37.1±1.0	36.9±1.0	0.87*
Year 1	43.8±1.0	44.9±1.0	0.45*
Change	6.7±1.0	8.0±1.0	0.34†
All three goals			
Baseline	10.8±0.6	9.5±0.6	0.13*
Year 1	23.6±0.8	16.0±0.7	<0.001*
Change	12.8±0.9	6.5±0.8	<0.001†

Data are % ± SD. *Logistic regression with adjustment for clinical site. †Mantel-Haenszel test with adjustment for clinical site.

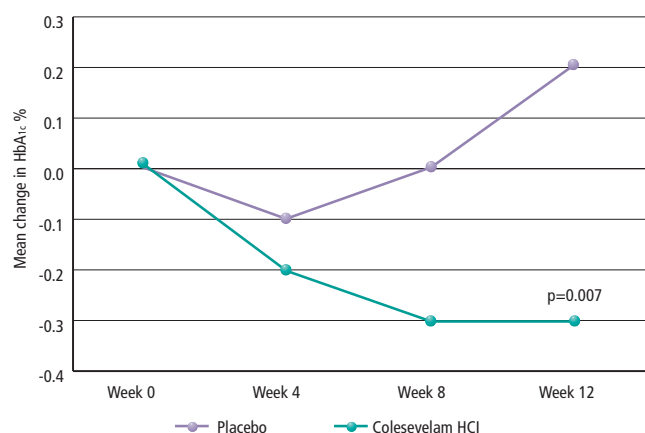
baseline in order to influence clinical outcomes. These goals can rarely be achieved by therapeutic lifestyle interventions alone. Dietary interventions may result in a reduction in LDL-C of 10–15% at best in most patients.¹⁴ Since most patients with type 2 diabetes are overweight or obese, a common myth among patients and physicians is that weight reduction might cause significant LDL reduction. The fact is that weight reduction, in the absence of specific qualitative dietary changes aimed at lowering serum cholesterol, rarely results in LDL reduction. For example, weight reduction of 5–7% in the intensive lifestyle arm (n=1,079) of the Diabetes Prevention Program (DPP) resulted in no significant change in total or LDL-C after three years, although triglyceride levels were reduced by 15% and HDL-C increased by a meager 0.25%.¹⁵ Similarly, in the ongoing Action for Health in Diabetes (Look-AHEAD) trial in patients with type 2 diabetes, 2,496 subjects in the Intensive Lifestyle Intervention (ILI) group lost an average of 8.6% of bodyweight at one year; however, LDL-C declined by only 5.2%, identical to the control group,¹⁶ despite significant changes in HbA_{1c}, triglycerides, and HDL-C (see Table 1). Furthermore, in Look-AHEAD there was no difference in the percentage of patients achieving the LDL-C goal of <100mg/dl compared with controls, while there were significant differences in the percentage of patients achieving HbA_{1c} and blood-pressure goals (see Table 2). Finally, even a marked weight loss of up to 25% of initial bodyweight achieved by bariatric surgery over 10 years in a large cohort of morbidly obese subjects resulted in no significant change in LDL-C, while many other metabolic and clinical parameters, including glycemic control, improved.¹⁷ Thus, pharmacological interventions remain the primary mode for achieving success in LDL-lowering strategies.

Pharmacological Strategies

While statin drugs are the drugs of choice for achieving LDL-C reduction, many patients need up-titration to near maximal dose in order to reach recommended goals. This is often not performed, and is frequently ineffective since each doubling of statin dose leads only to approximately 5–6% additional reduction in LDL-C.¹⁸ Another limitation of statins is the significant increase in liver transaminases or myalgia at the high-dose statins, as shown in clinical trials and meta-analyses.^{8,19,20} An effective alternative to overcome these limitations of statins is to combine them with another drug to improve efficacy and safety. The pharmacological approach best suited to achieving this goal is

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Figure 1: Glucose-lowering Effect of WelChol Study—Change in HbA_{1c}



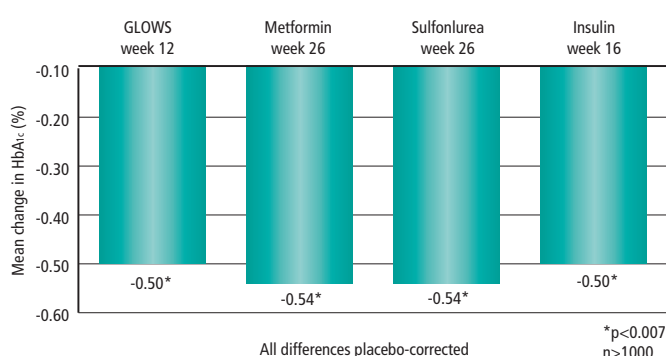
Source: Zieve FJ et al., *Clin Ther*, 2007.²⁹

to combine a statin with a cholesterol absorption inhibitor such as ezetimibe²¹ or a bile-acid sequestrant (BAS).^{22,23} BAS were the drugs of choice for LDL reduction in the pre-statin era, reducing LDL by up to 30%. In a large primary prevention clinical trial, the Lipid Research Clinic's Coronary Primary Prevention Trial (LRC-CPPT), a mean 13% reduction in cholestyramine was associated with a significant 19% reduction in CHD death and non-fatal MI.²⁴ Of much interest was the serendipitous finding in an eight-week controlled trial in patients with type 2 diabetes where cholestyramine, compared with placebo, led to a significant 20mg/dl decline in fasting plasma glucose (p=0.003) and a 0.5% drop in HbA_{1c} (p=0.17).²⁵ In another short-term observational study with another BAS, Colestimide, in Japan, an HbA_{1c} reduction of 0.9% (7.7–6.9%) and a 12mg/dl reduction in plasma glucose (p=0.08) was reported.²⁶ No significant glycemic effects have been reported for the cholesterol absorption inhibitor ezetimibe, which works by a different mechanism.

Pivotal Clinical Trials with Colesevelam Exploring Lipid and Glycemic Efficacy and Safety

Colesevelam, a newer BAS with a better safety profile, is well known for its better tolerability and safety in LDL lowering, both as monotherapy and in combination with statins.^{27,28} Prompted by the initial report with Cholestyramine in type 2 diabetes in 1994, Colesevelam has recently been studied in several clinical trials in relation to its lipid-lowering and glycemic effects. In a 12-week pilot study in 65 patients with type 2 diabetes on metformin ± sulfonylurea therapy (mean age 56 years, HbA_{1c} 8.0%), there

Figure 2: Effects of Colesevelam on HbA_{1c} Levels in Add-on Therapy Trials—≥0.50% Reductions



Sources: Zieve FJ et al., *Clin Ther*, 2007;²⁹ Bays H et al. Abstracts of the 16th Annual AACE Meeting and Clinical Congress, April 11–15, 2007, Seattle, Washington. Abstract 204:18;³⁰ Fonseca VA et al., Abstracts of the 16th Annual AACE Meeting and Clinical Congress, April 11–15, 2007, Seattle, Washington. Abstract 409:10; Goldberg RB and Truitt K, AHA Scientific Sessions, November 12–15, 2006, Chicago, Illinois. Poster 1581.

was a 0.5% reduction in HbA_{1c} (p=0.007) with colesevelam 3.8g compared with placebo (see Figure 1).²⁹ Following this trial, several additional randomized clinical trials have been carried out in patients with type 2 diabetes, totaling >1,000 patients, with similar design and background therapy based on either metformin ± sulfonylurea (n=316), sulfonylurea ± metformin (n=461), or insulin with or without oral drug combinations (n=287).^{30–32} Of interest is that the mean placebo-corrected reductions in HbA_{1c} in all of these studies were consistently at 0.5% (p<0.01 or less). There were expected lipid effects with predominant effects on LDL (approximately 15–17% reduction), with non-significant, minimal effects on triglycerides and HDL-C. In a metformin-based trial, a significant 13% reduction was also seen in mean C-reactive protein (CRP) levels,³⁰ with a similar trend being demonstrated in a sulfonylurea-based trial. Figure 2 summarizes the HbA_{1c} outcomes (p<0.007) in these pivotal trials with Colesevelam. The review of safety data revealed excellent tolerability with mild to moderate increase in gastrointestinal side effects, no serious adverse effects, and no increase in rates of hypoglycemia compared with placebo.^{29–32} On the basis of these trials and the safety data, Colesevelam was approved by the FDA in January 2008, with the dual indication for the improvement in hyperglycemia as well as reduction of LDL-cholesterol in patients with type 2 diabetes. The mechanism underlying the glycemic effects of BAS is currently under intense scrutiny. Current hypotheses include effects of bile-acid metabolites on nuclear receptor signaling and consequent potential effects on gluconeogenesis, insulin sensitivity, and lipid synthesis in the liver.^{33–34} ■

- Ford ES, et al., *N Engl J Med*, 2007; 356(23):2388–98.
- Booth GL, et al., *Lancet*, 2006;368(9529):29–36.
- Donahoe SM, et al., *AMA*, 2007;298(7):765–75.
- Hu FB, et al., *Diabetes Care*, 2002;25(7):1129–34.
- Mozaffarian D, et al., *Lancet*, 2007;370(9588):667–75.
- Baigent C, et al., *Lancet*, 2005;366(9493):1267–78.
- Grundy SM, et al., *Circulation*, 2004;110(2):227–39.
- Cannon CP, et al., *J Am Coll Cardiol*, 2006;48(3):438–45.
- UK Prospective Diabetes Study (UKPDS) Group, *Lancet*, 1998; 352(9131):854–65.
- Selvin E, et al., *Ann Intern Med*, 2004;141(6):421–31.
- Nathan DM, et al., *N Engl J Med*, 2005;353(25):2643–53.
- Saydah SH, et al., *JAMA*, 2004;291(3):335–42.
- Standards of medical care in diabetes—2007, *Diabetes Care*, 2007;30(Suppl. 1):S4–S41.
- Executive Summary of The Third Report of The National

- Cholesterol Education Program (NCEP), *JAMA*, 2001;285(19):2486–97.
- Ratner R, et al., *Diabetes Care*, 2005;28(4):888–94.
- Pi-Sunyer X, et al., *Diabetes Care*, 2007;30(6):1374–83.
- Sjostrom L, et al., *N Engl J Med*, 2004;351(26):2683–93.
- Illingworth DR, *Drugs*, 1988; 36(Suppl. 3):63–71.
- Alsheikh-Ali AA, et al., *J Am Coll Cardiol*, 2007;50(5):409–18.
- Insull W, Jr., *South Med J*, 2006; 99(3):257–73.
- Gagne C, et al., *Am J Cardiol*, 2002; 90(10):1084–91.
- The Lipid Research Clinics Coronary Primary Prevention Trial results. I. *JAMA*, 1984;251(3):351–64.
- Armitage J, *Lancet*, 2007; 370(9601):1781–90.
- The Lipid Research Clinics Coronary Primary Prevention Trial results. II. *JAMA*, 1984;251(3):365–74.
- Garg A, Grundy SM, *Ann Intern Med*, 1994;121(6):416–22.
- Kobayashi M, et al., *Diabetes*, 2007;56(1):239–47.

- Bays HE, et al., *Am J Cardiol*, 2006;97(8):1198–1205.
- Knapp HH, et al., *Am J Med*, 2001;110(5):352–60.
- Zieve FJ, et al., *Clin Ther*, 2007;29(1):74–83.
- Bays H, et al., Abstracts of the 16th Annual AACE Meeting & Clinical Congress, April 11–15, 2007, Seattle, Wash. Abstract 204:18.
- Ganda OP, Abby S, Truitt K, et al., XVI International Symposium on Drugs Affecting Lipid Metabolism (DALM) International Atherosclerosis Society, New York, Oct 4–7, 2007, abstract # 399.
- Jones MR, Abby S, Truitt K, XVI International Symposium on Drugs Affecting Lipid Metabolism (DALM) International Atherosclerosis Society, New York, Oct 4–7, 2007, abstract # 400.
- Claudel T, et al., *Arterioscler Thromb Vasc Biol*, 2005;25(10): 2020–30.
- Bays HE, Cohen DE, *Curr Med Res Opin*, 2007;23(7):1673–84.