

Management of Dyslipidemia in the Diabetic Patient

Abstract

Diabetic patients remain at significantly increased risk for vascular disease but until recently we had limited evidence that improving the lipid profile in the diabetic patient improves outcome. Prior to 2002, the only data available was subgroup analyses from the major lipid outcome trials which included relatively small numbers of diabetic subjects. In general, however, the coronary risk reduction in people with diabetes was virtually identical relative to those without diabetes.

The largest statin study completed to date was the Heart Protection Study (HPS). Amongst the 20,536 patients were 5963 with diabetes of whom 1978 had a history of coronary heart disease and 3985 did not. Furthermore, about 10% of the diabetic subjects had type 1 diabetes, and HPS remains the only completed statin trial to include them. Overall the study showed about a 24-25% risk reduction for both coronary disease and stroke. The more recently published results of the diabetic subset of HPS showed a virtually identical risk reduction for both major coronary events and stroke in people with diabetes versus those without. In addition, the risk reduction was similar irrespective of type of diabetes (type 1 vs. type 2), A1c, duration of diabetes, presence or absence or pre-existing coronary heart disease or baseline LDL-C levels (below vs. above 3.0 mmol/L).

CARDS (Collaborative Atorvastatin Diabetes Study) is the first completed statin study done exclusively in patients with diabetes without known coronary heart disease. Its aim was to evaluate the effectiveness and safety of atorvastatin 10 mg daily versus placebo in the primary prevention of cardiovascular disease in patients with type 2 diabetes with “normal cholesterol levels”. A total of 2,838 patients with type 2 diabetes mellitus were randomly assigned to atorvastatin 10 mg daily or placebo. The relative risk reduction for the primary composite end point of major coronary events (acute coronary heart disease death, nonfatal MI including silent MI, hospitalized unstable angina, resuscitated cardiac arrest, coronary revascularization and stroke) was 37% (95% confidence interval(CI) 17-52, p=0.001) and for stroke was 48% (CI 11-69).

More recently, subgroup analyses from a number of “LDL-lower is better” studies including REVERSAL, PROVE-IT, and TNT have shown similar benefits in the diabetic subsets as in the overall study populations associated with more aggressive LDL-C lowering.

There is also some evidence on the potential benefits of other lipid modifying therapies. In the VA-HIT study, treatment with gemfibrozil was associated with similar benefit in subjects with and without diabetes with stable coronary disease and relatively isolated low HDL-C. In the FIELD study, however, treatment with fenofibrate relative to placebo was associated with a non significant 11% reduction in the primary endpoint of non-fatal MI and CHD death in 9795 subjects with type 2 diabetes.

The 2006 Canadian Diabetes Association Lipid Guidelines recommend that most adults with type 1 or type 2 diabetes should be considered at high risk for vascular disease. The exceptions are younger adults with type 1 or type 2 diabetes with shorter duration of disease and without complications of diabetes (including established CVD) and without other CVD risk factors. Adults at high risk of a vascular event should be treated with a statin to achieve the primary target of an LDL-C ≤ 2.0 mmol/L, with clinical judgment used as to whether additional LDL-C lowering is required for adults with an on-treatment LDL-C of 2.0 to 2.5 mmol/L. If the

secondary target of TC/HDL-C ratio is ≥ 4.0 , strategies to achieve a TC/HDL-C ratio < 4.0 should be considered. These include improved glycemic control, intensification of lifestyle (weight loss, physical activity, smoking cessation) and, if necessary, pharmacologic interventions. Finally, in adults with serum TG > 10.0 mmol/L despite best efforts at optimal glycemic control and other lifestyle interventions (e.g. weight loss, restriction of refined carbohydrates and alcohol), a fibrate should be prescribed to reduce the risk of pancreatitis.

In summary, coronary risk is extremely high in diabetic subjects but we now have evidence that benefits of modification of lipids in intervention trials also apply to individuals with diabetes. As a result, the new Canadian Diabetes Association Guidelines, now recommend treatment with a statin to achieve a target LDL-C \leq for the vast majority of our diabetic patients.

References

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Dyslipidemia in Adults with Diabetes. *Can J Diab* 2006; 30(3):230-240.

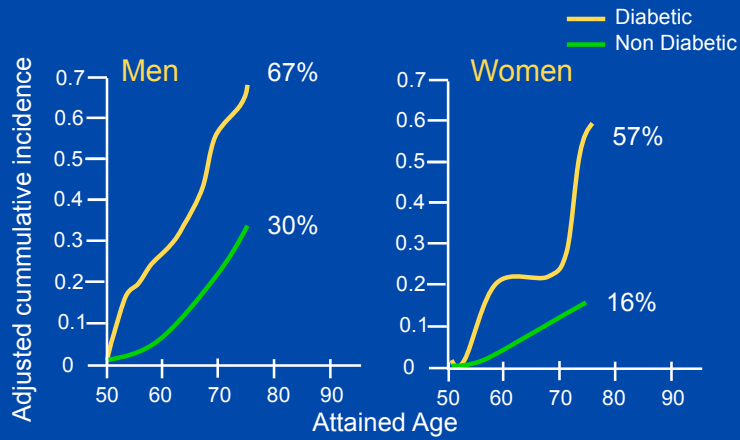
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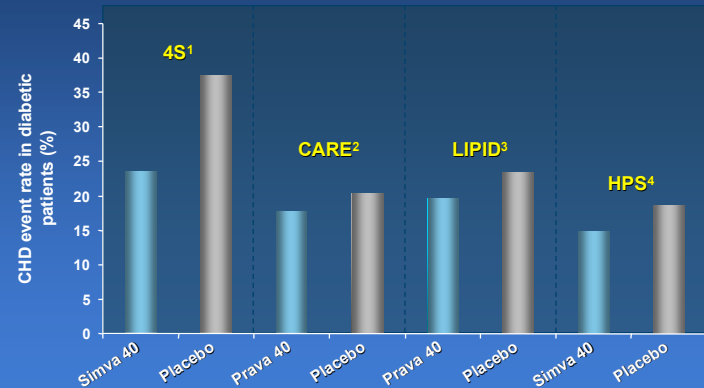
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Diabetes and Lifetime Risk for CHD



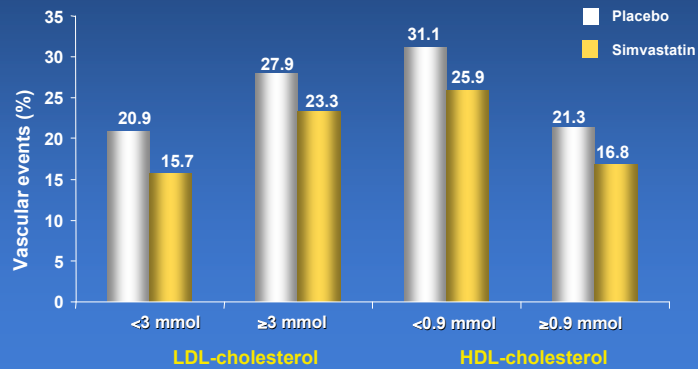
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LDL-C Lowering in Diabetes: "Early" Statin Trials

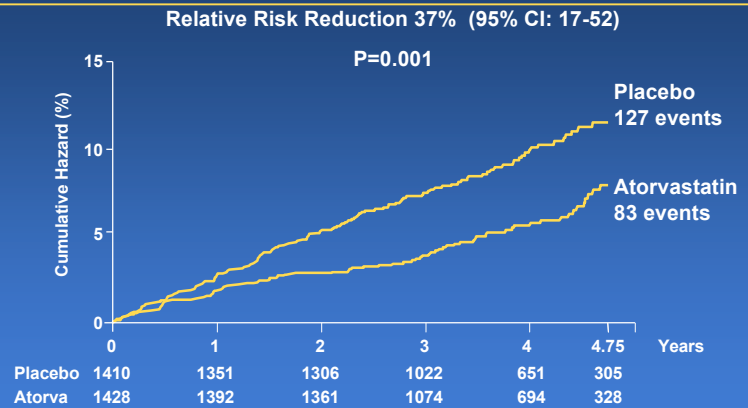


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HPS: Diabetic Cohort Benefits of Simvastatin by Baseline LDL and HDL-cholesterol

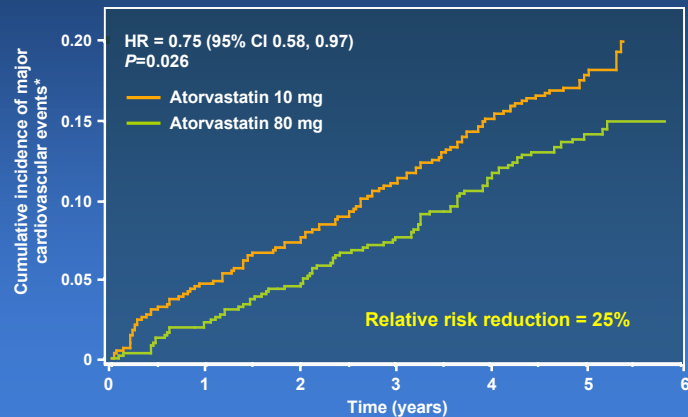


CARDS: Cumulative Hazard for Primary Endpoint



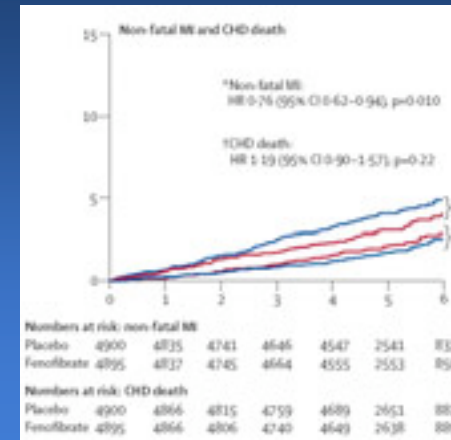


Time to First Major Cardiovascular Event in Patients With Diabetes



*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

FIELD: Non-fatal MI and CHD Death



FIELD Study Investigators. *The Lancet*. 2005. Published online.

2003 Clinical Practice Guidelines
for the Prevention and Management
of Diabetes in Canada

DYSLIPIDEMIA IN ADULTS WITH DIABETES*

*Updated in 2006. Leiter LA, et al for the CDA CPG Expert Committee. *Can J Diabetes*. 2006;30:230-240.



LIPID TARGETS

LIPID TARGETS FOR ADULTS WITH DM AT HIGH RISK FOR CVD

| INDEX | TARGET VALUE |
|----------------------------------|--------------|
| Primary target: LDL-C | ≤2.0 mmol/L |
| Secondary target: TC/HDL-C ratio | <4.0 |

Clinical judgment should be used to decide whether additional LDL-C lowering is required for patients with an on-treatment LDL-C of 2.0 to 2.5 mmol/L.

CDA CPG Expert Committee. *Can J Diabetes*. 2006;30:230-240



DYSLIPIDEMIA

- Achieving an LDL-C of ≤ 2.0 mmol/L is the primary goal of therapy.
- Once the LDL-C goal has been attained, consideration to achieving the secondary target of an TC/HDL-C ratio of < 4.0 .
- The vast majority of patients will be able to attain the LDL-C goal on statin therapy.
- Although not formal goals of therapy, optimal TG is < 1.5 mmol/L and apo B is 0.9 g/L
- Lifestyle modification should be seen as an important adjunct to, not substitution for, pharmacologic therapy.

CDA CPG Expert Committee. *Can J Diabetes*. 2006;30:230-240

