

## Combination lipid-lowering therapy in type 2 diabetes mellitus: A review of the evidence

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Current lipid-lowering guidelines have stringent targets for LDL-cholesterol (LDL-C), triglyceride (TG), and HDL-cholesterol (HDL-C) levels in patients with type 2 diabetes mellitus (DM). It is often difficult to meet all the targets with antilipemic monotherapy and combination therapy is potentially attractive for several reasons:

- the dyslipidemia associated with DM, together with low LDL-C targets, often mean that more than one lipid target needs to be met
  - no currently available agent targets all 3 lipids to the degree required
  - although mortality is reduced with monotherapy, it still remains at a significant level.
- In addition, there may be a lower risk of side effects using 2 agents at lower doses compared to 1 agent at a much higher dose. This issue of *Endocrinology Rounds* reviews the evidence for the benefits and risks associated with the use of combination lipid-lowering therapy in DM.

### The challenge

DM has a prevalence of 5% in the general North American population. DM, impaired glucose tolerance, and impaired fasting glucose are all associated with insulin resistance, an abnormal lipid profile, and an increased risk of atherosclerosis. The incidence of macrovascular disease is 2- to 5-fold higher in patients with DM than in nondiabetic patients. In one study, the risk of a first myocardial infarction (MI) was shown to be as great in a diabetic population with no known cardiac disease, as a recurrent MI in a nondiabetic population that had already suffered an MI.<sup>1</sup> The dyslipidemia and glucose intolerance associated with DM consists of elevated TG levels and low HDL-C levels. LDL-C levels are generally similar to that in non-diabetic patients,<sup>2</sup> but the LDL exists in a small, dense form that renders it more atherogenic. Hypertriglyceridemia may represent an independent cardiovascular risk factor,<sup>3</sup> but levels of LDL-C and HDL-C may be more significant.<sup>4</sup> Finally, triglyceride levels >10 mmol/L predispose the patient to the development of pancreatitis.

Because of the evidence cited above, recent lipid guidelines in Canada<sup>5</sup> have recommended targeting LDL-C at <2.5 mmol/L, TG at <2 mmol/L, and total cholesterol:HDL-C ratio at <4. These targets are equivalent to those for patients with known cardiovascular disease. American guidelines (NCEP-ATP III<sup>6</sup>, ADA<sup>7</sup>) are just as aggressive. These targets are often difficult to achieve with lifestyle modification, glycemic control, and one hypolipidemic agent. The NHANES and L-TAP studies found that in patients with 2 or more CV risk factors, 55%-63% failed to reach these targets, and in patients with known CAD, 82% failed to meet these targets.<sup>8,9</sup>

Monotherapy often fails to achieve targets in patients with the following lipid profiles:

- patients with mixed dyslipidemia (since the best lipid-lowering agents do not target all lipid abnormalities), and
- less commonly, in DM patients with LDL-C that is above target after monotherapy.



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## **The tools: Diet, exercise, and glucose-lowering agents**

Besides restriction of saturated fat, cholesterol, total calories, and simple carbohydrates, any action that improves glycemic control in patients with type 2 diabetes is associated with a reduction in the incidence of hypertriglyceridemia.<sup>10</sup> A detailed description of the impact of various oral antihyperglycemic agents on plasma lipids was reviewed by DeFronzo.<sup>11</sup> Generally, metformin and TZDs have a favourable impact on lipids, while acarbose, sulphonylureas, and meglitinides are lipid-neutral.

### **Lipid-lowering agents**

The literature on the therapeutic effects of various lipid-lowering agents used as monotherapy has been reviewed extensively.<sup>12</sup> Statins, fibrates, nicotinic acid, bile acid sequestrants, fish oil and, in the near future, ezetimibe are all potential candidates for monotherapy and for combination therapy. There are many studies examining the impact of monotherapy on secondary outcomes (ie, impact on the various lipid parameters) in subjects with DM. In general, their impact on patients with diabetes mellitus is similar to that in the general population.

### **The evidence**

#### **Monotherapy: The general population with diabetic subgroup analyses**

Multiple, large, randomized, controlled trials have examined, as primary endpoints, the reduction in cardiovascular events and total mortality in high-risk subjects (both primary and secondary prevention). These trials have targeted the lowering of LDL-C, and/or raising of HDL-C using simvastatin, pravastatin, lovastatin, atorvastatin, and gemfibrozil. In post-hoc analyses of the diabetic subgroups, the primary prevention trials showed trends towards reduction in cardiovascular events. These reductions reached statistical significance in the secondary prevention trials. The 4S,<sup>13</sup> LIPID,<sup>14</sup> CARE,<sup>15</sup> HPS,<sup>16</sup> GREACE,<sup>17</sup> and VA-HIT<sup>18</sup> all showed a relative reduction of 19%-45% in cardiovascular events in diabetic subjects, but lacked the power to examine overall mortality. These studies generally excluded patients with hypertriglyceridemia and were post-hoc analyses, so the true impact of lipid-lowering agents on the general population of patients with diabetes is still not proven.

#### **Combination therapy: General population with diabetic subgroup analysis**

The HDL-C-lowering Atherosclerosis Treatment Study (HATS)<sup>19</sup> used a statin-niacin combination. One hundred and sixty subjects with angiographically-proven coronary artery disease were followed for 3 years and randomized to 1 of 4 treatment arms:

- placebo
- niacin (2-4 g/d) and simvastatin (10-20 mg/d)

- antioxidants plus placebo
- antioxidants plus simvastatin-niacin.

Initial lipids were as follows: HDL-C < 0.9 mmol/L, LDL-C < 3.7 mmol/L, and triglycerides < 4.5 mmol/L. The combination of simvastatin-niacin led to an LDL-C decrease of 35%, HDL-C increase of 30% and a TG fall of 34%.

There were two primary outcomes of the study: angiographic mean change in percent stenosis and a primary clinical endpoint composed of cardiovascular events. A plaque regression of 4% was seen in the niacin/simvastatin/no antioxidant arm of the trial versus progression in the other arms of the study. Clinical events were relatively reduced by 87% in the same arm compared to placebo. Only 10% of subjects had DM; the results from this subgroup have not been published.

### **Combination therapy in DM**

The ACCORD study is a large, ongoing, NIH-funded trial with primary clinical endpoints. All patients in the lipid substudy receive a statin and in addition, are randomized to receive a fibrate or placebo. The purpose is to study the additional benefit of raising HDL-C and lowering TG in subjects who have desirable LDL-C levels and good glycemic control.

To date, all trials using combination therapy in diabetes have been small and have studied secondary endpoints (lipid lowering). Most have combined statins with either fibrates or niacin since the statins are the most effective agents available to reduce LDL-C, while the fibrates are the most effective to reduce TG and niacin is the most effective to raise HDL-C. Other studies in non-DM subjects have studied the following additional combinations: statins + bile acid sequestrants, statins + ezetimibe, statins + fish oil, statin + stanol/sterol ester, statins + statins, nicotinic acid + bile acid sequestrants, and fibrates + nicotinic acid.

### **Targeting mixed dyslipidemia in DM**

#### **Statin + niacin combination: Lipid benefits**

The 5 studies using this combination generally had small sample sizes and were not randomized controlled trials (Table 1). The most common study design was open-labelled, nonrandomized, non-placebo-controlled, and used sequential therapy. Different types of niacin were used including: niacin, acipimox (a niacin analog), and niaspan (an extended-release form). Two of the 5 studies examined niacin in combination with pravastatin.

Tsalamandris et al<sup>20</sup> included a subgroup of 11 subjects with DM. The combination of pravastatin 40 mg/d and niacin 1.5 g/d resulted in a further reduction in triglyceride levels and an increase in HDL-C, compared with pravastatin alone. LDL-C and triglyceride levels were further reduced compared to niacin alone. HbA<sub>1c</sub> increased from 7.3 to 7.9 in subjects who received niacin, with or without pravastatin (this was not statistically

**TABLE 1: Combination therapy: Statins and niacin/acipimox/niaspan in DM.**

Values shown are the percentage change in the lipid in each arm from baseline. Note: No studies used a placebo.							
Drugs	No subjects, Baseline lipids	Duration of treatment	Tchol	LDL	HDL	TG	Concerns
Pravastatin 40 mg/d OR Niacin 1.5 g/d THEN Pravastatin 40 mg/d + niacin 1 g/d (Tsalamandris <sup>20</sup> )	N=11	12 weeks each period	↓25% ↓10% ↓23%	↓32% ↓17% ↓27-36%	↑16% ↑31% ↑34%	↓28% ↓32% ↓39%	21% withdrew due to niacin intolerance • ↑HbA <sub>1c</sub> from 7.3 to 7.9% for niacin alone and in combination • 1 statin patient withdrew due to nausea
Pravastatin 20 mg/d THEN, if needed: Pravastatin 20 mg/d + niacin 1.5 g/d (Gardner <sup>21</sup> )	16 TG < 5.7 LDL > 4	4 weeks each period	↓21% ↓27%	↓23% ↓33%	NS ↑14%	↓13% ↓22%	LDL-C was the only significant change with combination over statin alone • 3 withdrew due to niacin
Lovastatin 40 mg/d THEN Lovastatin 40 mg/d + acipimox 750 mg/d (Ko <sup>22</sup> )	33: ↑TG > 2.8 Tchol > 6.2	12 weeks, each period	↓21%	↓5.5%	↑11.6% ↑ to 25%	↓32%	Well-tolerated
Simvastatin 20 mg/d + gemfibrozil 1.2 g/d + acipimox 0.5-1.5 g/d (sequentially added) (Kanters <sup>23</sup> )	N=95 LDL 3.6	30 weeks					• Tried to attain lipid targets by adding agents until maximum tolerated dose or targets met • 30% withdrew
	Type 1:		↓24%	↓34%	↑14-24%	↓42%	
	Type 2:		↓30%	↓35%	NS	↓50%	
Atorvastatin 80 mg/d OR niaspan 3 g/d OR Both (Van <sup>24</sup> )	53	6 weeks		↓50% ↓20% ↓69%	NS ↑42% ↑42%	↓31% ↓47% ↓55%	

Tchol = total cholesterol, LDL = LDL-cholesterol, HDL = HDL-cholesterol, TG = triglycerides, DM = diabetes mellitus, PBO = placebo, CV = cardiovascular, RCT = randomized controlled trial.

significant). Twenty-one per cent of patients on niacin withdrew secondary to nausea and flushing.

The second study<sup>21</sup> was only 4 weeks in duration, with 16 subjects. It demonstrated an improvement in LDL-C when niacin was added to a lower dose of pravastatin (20 mg/d). There were trends towards lower TG and higher HDL-C levels. Three subjects withdrew secondary to niacin intolerance. There was no change in glycemic control as measured by fasting plasma glucose and fructosamine.

The other 3 studies used acipimox or niaspan; however, neither is available in Canada. When acipimox was added to lovastatin in patients with mixed dyslipidemia,<sup>22</sup> all lipid profiles changed favourably, but the only statistically significant parameter was the rise in HDL-C. The combination was well tolerated with no myopathy and no change in glycemic control.

Kanters et al<sup>23</sup> studied the feasibility of an intensive lipid-lowering strategy to achieve lipid targets. Patients were treated with simvastatin or gemfibrozil and then, if necessary, both were used in combination. Finally, acipimox was added and titrated up to a maximum of 1.5 g/d, if required, to achieve lipid targets. Of 95 subjects, 49 reached target with a fibrate, a statin, or both. A further 14 reached target when acipimox was added. Ten

patients did not reach target despite using all 3 drugs and 15 subjects who were taking all 3 drugs dropped out. The mean HbA<sub>1c</sub> was unchanged throughout the study. One patient dropped out due to unstable plasma glucose.

Another study<sup>24</sup> compared atorvastatin 80 mg/d, niaspan 3 g/d, and their combination. All lipid parameters improved for the 3 groups, except for HDL-C, which was unchanged with atorvastatin alone. The combination of atorvastatin and niaspan resulted in improved LDL-C when compared to niaspan alone, and better HDL-C and TG levels compared to atorvastatin alone. Side effects and drop-outs were not reported.

**Side effects:** In the above studies, no patients were reported to have elevated liver enzymes or myopathy. Three studies had high dropout rates of 20%-30% due to flushing on niacin. One study reported an increase in HbA<sub>1c</sub> from 7.3% to 7.9% with niacin, while the others did not report a change in HbA<sub>1c</sub>. Of note, the sample sizes were small and many studies were of short duration.

**Summary:** While the above studies were not ideal for the reasons indicated above, the combination of statin + niacin does appear to provide additional lipid benefits compared to monotherapy, resulting in improvements in all 3 lipid parameters compared to baseline pre-treatment levels.

**Table 2: Statins plus fibrates in DM**

Values shown are the percentage change in the lipid in each arm from baseline pretreatment lipids. Note: only studies that had placebo are indicated as PBO.							
Drugs	No subjects, Baseline lipids	Duration of treatment	Tchol	LDL	HDL	TG	Concerns
RCT: Atorvastatin 20 mg/d OR Micronized fenofibrate 200 mg/d OR Both (Athyros <sup>25</sup> )	N = 120	24 weeks	↓31%	↓40%	↑9%	↓30%	
			↓16%	↓15%	↑16%	↓41%	
			↓37%	↓46%	↑22%	↓50%	
Bezafibrate SR 400 mg/d OR Simvastatin 20 mg/d THEN Both (Gavish <sup>26</sup> )	N = 148 Avg lipids: TG 4.4 LDL 4.5 HDL 0.9	6 months then 12 months	↓22%	↓32%	NS	NS	<ul style="list-style-type: none"> <li>• ↓CV event rate from 9.5% to &lt; 2%</li> <li>• 3 patients had myopathy (2 were on combination)</li> </ul>
			↓4%	↓4%	↑25%	↓39%	
			↓23%	↓29%	↑25%	↓42%	
RCT: PBO vs gemfibrozil 1.2 g/d THEN Gemfibrozil vs gemfibrozil + lovastatin 40 mg/d (Garg <sup>27</sup> )	N = 10 with TG > 5.6	28 days each part	Part 1: ↓17% Part 2: ↓37%	↑42% NS	↑23% ↑27%	↓52% ↓56%	
	6 with TG 2.8-5.6	28 days each part	Part 1: NS Part 2: ↓24%	NS ↓16%	NS NS	↓31% ↓40%	
Simvastatin 20 mg/d + gemfibrozil 1.2 g/d + acipimox 0.5-1.5 g/d (sequentially added) (Kanters <sup>23</sup> )	N = 95 LDL 3.6	30 weeks					<ul style="list-style-type: none"> <li>• Tried to attain lipid targets by adding agents until maximum tolerated dose or targets met</li> <li>• 30% withdrew</li> </ul>
	Type 1:		↓24%	↓34%	↑14-24%	↓42%	
	Type 2:		↓30%	↓35%	NS	↓50%	

Tchol = total cholesterol, LDL = LDL-cholesterol, HDL = HDL-cholesterol, TG = triglycerides, DM = diabetes mellitus, PBO = placebo, CV = cardiovascular, RCT = randomized controlled trial.

In addition, it was reasonably well tolerated. Glycemic control should be closely monitored since patients may require additional glucose-lowering therapy.

### Statin + fibrate combination: Lipid benefits

There are 4 trials studying a statin + fibrate combination in subjects with DM (Table 2).

- Athyros et al<sup>25</sup> examined 120 subjects with moderate dyslipidemia (total cholesterol 6.5 mmol/L, TG 3.1 mmol/L, LDL-C 4.2 mmol/L, and HDL-C 0.9 mmol/L). Subjects were randomized to atorvastatin 20 mg/d, micronized fenofibrate 200 mg/d, or both for 24 weeks. As expected, the combination of drugs had the greatest impact on lipids: LDL-C fell 46%, HDL-C rose 22% and TG fell 50%. Ninety-seven per cent of subjects reached American Diabetes Association lipid targets and no patient withdrew from the study.

- In a longer, nonrandomized, sequential study, Gavish et al<sup>26</sup> placed 148 subjects on monotherapy with simvastatin 20 mg/d or bezafibrate SR 400 mg/d for 6 months, then combination therapy for 1 year.

Again, favourable responses were seen in LDL-C, HDL-C and TG profiles. Three patients (2 in the combination group and 1 in the simvastatin alone group) were reported to have myopathy (how this was defined is unreported). The cardiovascular event rate was reduced from 9.5 % (with monotherapy) to < 2% with combination therapy.

- Garg et al<sup>27</sup> studied 10 subjects with elevated TG (> 5.6 mmol/l). The hypertriglyceridemia responded to gemfibrozil, but LDL-C levels became elevated. LDL-C was reduced to baseline with the addition of lovastatin 40 mg/d.

- Kanters' intensive lipid-lowering strategy<sup>23</sup> (using 3 drugs if required) is described above. Of the 49 subjects who reached target with a fibrate, statin, or both:

- 14 were on a statin alone
- 33 were on combination therapy
- only 2 were on a fibrate alone
- 3 patients withdrew due to myalgia (2 were on fibrates, 1 was on combination therapy, and all had normal creatine kinase levels).

**Side effects:** Shek et al<sup>28</sup> reviewed 36 published trials and 29 case reports studying the risks associated with statin+fibrate therapy in the general population. He found an increased risk of myopathy ( $\geq 0.12\%$ ) in subjects on the combination. This study, which examined the risk in trials, may have underestimated the risk in clinical practice. Care must be taken in patients with renal or liver impairment and in those who are on medications that may decrease clearance of certain statins. In the studies reported above, only 1 reported myopathy (in 3 of 148 subjects). These studies in DM used only moderate doses of statins.

**Summary:** The combination of a statin+fibrate favourably affects lipid profiles for TG, HDL-C, and LDL-C in subjects with DM and mixed dyslipidemia. The exact risk of myopathy is unknown, but does not seem to be excessive if patients are carefully screened for contraindications and monitored for symptoms.

### Targeting LDL-C reduction

While the above combinations also have an LDL-C lowering effect, a reduction in LDL-C is best achieved with the following two combinations.

#### Statin + bile acid sequestrant

In monotherapy, the bile acid sequestrant, cholestyramine (16 g/day) reduced LDL-C by 28% and increased TG levels by 13% in subjects with DM.<sup>29</sup> This LDL-C lowering effect is additive when used with statins in the general population. The major side effects with bile acid sequestrants are bloating, cramping, and constipation. As well, these agents can interfere with the absorption of other medications. The increase in TG levels often seen with bile acid sequestrants may also limit their use.

#### Statin + ezetimibe

Ezetimibe, in doses of 5-10 mg once daily, inhibits the intestinal absorption of cholesterol from both dietary and endogenous sources. It reduces LDL-C by 17%, with a small rise in HDL-C (3%) and an 11% reduction in TG.<sup>30</sup> When ezetimibe is used with a statin, the reduction in LDL-C is additive to that produced by the statin.<sup>31</sup> There are no pharmacokinetic drug interactions between ezetimibe and lovastatin, simvastatin, fluvastatin, or fenofibrate. No side effects have been documented in studies. There have been no studies to date using ezetimibe specifically in patients with diabetes mellitus, but subgroup analyses have shown a similar effect on LDL-C lowering in DM.

### Conclusion

Patients with DM are at significantly increased risk of macrovascular disease. Multiple lipid targets may need to be addressed and often, these cannot be achieved with monotherapy alone. In the large, randomized, controlled trials, the diabetic subgroups show a reduction in macrovascular events in subjects taking statins or fibrates, depending on initial lipid abnormalities. The best evidence for combination therapy is the HATS trial that demonstrated regression of coronary lesions and a reduction in cardiovascular events in subjects on simvastatin and niacin. The data on the diabetic subgroup, however, have not been published. The ACCORD trial will provide valuable information about primary outcomes for the combination of a statin + a fibrate versus a statin alone in subjects with DM. Therefore, the evidence for combination therapy in DM is from nonrandomized trials with secondary outcomes (ie, changes in lipids). Currently available studies have examined two combinations: statin + niacin and statin + fibrate. Both combinations appear to improve LDL-C, TG, and HDL-C over pretreatment levels (caveat: no placebo). They also appear to improve at least one lipid target compared to monotherapy and the risks appear reasonable. Patients on niacin require careful monitoring of their glycemic control. Patients on the statin + fibrate combination need to be monitored for symptoms of myopathy. In cases where patients on statins require more LDL-C-lowering, the addition of bile acid sequestrants (or ezetimibe in the future) can be considered.

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