Diabetes is a strong risk factor for cardiovascular (CV) events and death. It is associated with a two-to-four-fold increased risk of cardiovascular disease (CVD), causing up to 80% of deaths in people with diabetes.

The control of blood glucose, blood pressure and lipids is among the 2003 Canadian Diabetes Guidelines' highest-priority mandated measures for vascular protection. Those patients who are young, with shorter duration of diabetes, no other CVD risk factors and no other complications of diabetes may be considered at moderate risk (Table 1).

The primary abnormality of metabolic syndrome is the liver’s over-production of very low-density lipoprotein (VLDL), the major TG-carrying particles and precursor of the more cholesterol-enriched LDL. The breakdown of TG by the enzyme called lipoprotein lipase may also be partially impaired, contributing to elevated TG. The VLDL in the circulation interacts with HDL and LDL, which may then become more atherogenic. The enzyme converting TG to cholesterol, called cholesterol-ester transfer protein, may also be deficient, leading to lower HDL-C. The TG in LDL is also broken down by HL, transforming them into small, dense LDL. Small, dense LDL is cleared more slowly by the liver through the LDL receptor, more readily enters arterial walls, induces more endothelial dysfunction and is more susceptible to oxidation. This vicious cycle creates the atherogenic triad of small, dense LDL, high TG and low HDL.

Three classes of medications are commonly used to treat dyslipidemia in patients with diabetes: HMG-CoA reductase inhibitors (statins), fibric acid derivatives and niacin.

**Statins**

The most rigorous evidence supports targeting LDL lowering by using statins; statins remain the first-line therapy in the treatment of dyslipidemia in
Dyslipidemia

Diabetes. This class of medication impairs HMG-CoA reductase, an essential enzyme used in cholesterol synthesis. By impairing the liver cells’ ability to synthesize cholesterol, LDL receptor-mediated uptake of circulating LDL is increased, thereby lowering the LDL level in the blood.

A number of large, well-conducted, randomized, controlled trials in the 1990s demonstrated that statin medications reduced major CV events and death both in primary and secondary prevention. Most of these trials included patients with diabetes and subgroup analyses from these trials suggested a similar benefit (Table 2).

More recently, the Heart Protection Study (HPS) and the Collaborative Atorvastatin Diabetes Study (CARDS) confirmed the benefit conferred by these agents in patients with diabetes. HPS showed a 22% reduction in all major CV endpoints with statin therapy and CARDS showed a 37% relative risk reduction in major CV endpoints, translating to an absolute risk reduction of 3.7% over four years. These trials form the cornerstone of current dyslipidemia therapy in patients with diabetes and suggest that a statin medication be used in all those at sufficient risk for CVD, regardless of baseline cholesterol level.

Fibrates

Treatment with statin monotherapy does not address the mixed dyslipidemia profile of high TG and low HDL. Fibric acid derivatives (fibrates) have significant TG-lowering effects, primarily through increasing the breakdown of TG in VLDL by lipoprotein lipase. They also raise serum HDL levels and therefore have the potential to reverse the major lipid abnormalities seen in diabetes patients.

Three major trials have examined the effect of these agents on clinical endpoints in those with mixed dyslipidemia. The Helsinki Heart Study assessed gemfibrozil’s role in primary prevention; though the overall trial was positive, the diabetes subgroup showed a non-significant reduction of CV events (3.4% vs. 10.5%) because of the small number of events (p = 0.19). The Veterans’ Affairs High-density lipoprotein Intervention Trial was a secondary prevention study with gemfibrozil and showed a 32% risk reduction in CV events and a 41% reduction in death from CAD. However, another secondary prevention trial with bezafibrate was negative in reducing CV events.

Overall, the evidence regarding the use of fibrates alone in diabetes is unclear and will be elucidated by the ongoing Fenofibrate Intervention and Event Lowering in Diabetes study (randomizing over 9,000 patients with diabetes to fenofibrate versus placebo).

Using statins and fibrates in combination is a logical option for patients with diabetes and mixed dyslipidemia. Several moderately sized studies have looked at the lipid-lowering effects of this

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Table 1

<table>
<thead>
<tr>
<th>Risk level</th>
<th>LDL-C</th>
<th>TC/HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (most patients with diabetes)</td>
<td>&lt; 2.5 mmol/L and</td>
<td>&lt; 4.0 mmol/L</td>
</tr>
<tr>
<td>Medium (young age, short duration of diabetes, no other complications of diabetes and no other risk factors of vascular disease)</td>
<td>&lt; 3.5 mmol/L and</td>
<td>&lt; 5.0 mmol/L</td>
</tr>
</tbody>
</table>

Optimal TG < 1.5 mmol/L
Optimal apo B < 0.9 g/L for high risk; < 1.05 g/L for moderate risk

LDL-C: Low-density lipoprotein cholesterol
TC: Total cholesterol
HDL-C: High-density lipoprotein cholesterol
TG: Triglyceride
apo B: Apolipoprotein B

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About the authors...

Dr. Fung is an Endocrinology Fellow, University of Toronto, Toronto, Ontario.

Dr. Ng is a Staff Endocrinologist/Scientist, St. Michael’s Hospital and an Assistant Professor of Medicine, University of Toronto, Toronto, Ontario.
combination therapy in Type 2 diabetes. Not surprisingly, the combination studies of simvastatin, atorvastatin or rosuvastatin with fenofibrate have shown additional benefits in lowering TG and raising HDL versus statin therapy alone. Moreover, combination statin-fibrate therapy has been shown to decrease the proportion of small, dense LDL, thereby increasing the percentage of larger, more buoyant LDL particles, which may be less atherogenic. However, there has been no large, randomized, controlled trial that examines clinical endpoints with a statin-fibrate combination. One arm of the Action to Control Cardiovascular Risk in Diabetes trial will compare the randomization of patients to a statin alone versus a statin-

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>No.</th>
<th>CHD Risk Reduction (overall)</th>
<th>CHD Risk Reduction (patients with diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>Lovastatin</td>
<td>155</td>
<td>37%</td>
<td>43% (NS)</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>3985</td>
<td>24%</td>
<td>26% (p&lt;0.00001)</td>
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<tr>
<td>CARDS</td>
<td>Avostatin</td>
<td>2838</td>
<td>37%</td>
<td>37% (p=0.001)</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>Simvastatin</td>
<td>483</td>
<td>32%</td>
<td>42% (p=0.001)</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin</td>
<td>782</td>
<td>25%</td>
<td>19%</td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin</td>
<td>586</td>
<td>23%</td>
<td>25% (p=0.05)</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>1978</td>
<td>24%</td>
<td>unreported</td>
</tr>
</tbody>
</table>

CHD: Coronary heart disease  
AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study  
HPS: Heart Protection Study  
CARDS: Collaborative Atorvastatin Diabetes Study  
4S: Scandinavian Simvastatin Survival Study  
LIPID: Long-term Intervention with Pravastatin in Ischaemic Disease  
CARE: Cholesterol And Recurrent Events  
NS: Non-significant
Dyslipidemia

Fibrate combination, shedding light on whether or not combination therapy has further clinical benefit over statin monotherapy alone.

No significant adverse effects have been noted in using a statin-fenofibrate combination in relatively small and short-duration studies. By contrast, gemfibrozil is well-known to increase the risk of myositis when used in combination with statins (especially cerivastatin). This was recently discovered to be due to the inhibitory effect of gemfibrozil in the glucuronidation pathway of statins.

**Niacin**

Niacin has the unique ability to favourably affect TG, LDL and HDL. Niacin decreases VLDL production from the liver, enhances its clearance from the circulation by lipoprotein lipase and also decreases clearance of HDL.

Two studies of niacin plus colestipol resulted in significant reductions in the progression of atherosclerosis, measured by angiography. The secondary prevention study Coronary Drug Project evaluated niacin monotherapy in men from 1966 to 1974. While there was a significant reduction in CV events after six years of followup, a total mortality reduction was found after an additional nine years of post-trial followup.

More recently, niacin has been studied in combination with simvastatin in patients with low HDL and average LDL levels. Niacin-simvastatin therapy resulted in a mean regression of 0.4% in coronary stenosis compared with a mean 3.9% increase in the placebo group. The composite primary endpoint of CV event, death and revascularization was reduced by 60% vs. placebo (p = 0.02).
Dyslipidemia

The use of niacin, however, has been limited due to numerous side-effects, including:

- flushing, pruritus and dyspepsia, more common with immediate-release (IR) niacin,
- liver toxicity, more common with long-acting (LA) niacin and
- a hyperglycemic effect with niacin in general.

The difference in the side-effect profile of the IR versus LA niacin lies in its metabolism. IR niacin is preferentially metabolized through the conjugation pathway, forming metabolites that cause prostaglandin-mediated vasodilation and flushing. LA niacin is mostly metabolized through the nicotinamide pathway, leading to metabolites that are associated with hepatotoxicity. An intermediate-acting niacin has just become available in Canada that has a more balanced metabolism, resulting in less flushing and risk of hepatotoxic effects at daily doses of 2 g or less.

The hyperglycemic effect of up to 3 g of niacin per day has been studied in patients with diabetes. Significant, small increases in hemoglobin A1c (HbA1C) were seen in those patients with diabetes, but the levels subsequently returned to baseline after the patients achieved a stable dose of niacin. Adjustments in the insulin dose made in 13% of patients with diabetes may have accounted for the return of glucose to baseline; however, no significant increase in insulin dose was found overall. Therefore, the effect of niacin on glycemic control in diabetes seems to be limited and manageable.

Concluding thoughts

Treatment with statin monotherapy currently has the best evidence for the prevention of CVD. Thus far, in the limited numbers of patients studied for short durations, fenofibrate-statin and niacin-statin combinations have been safe. Caution and careful assessment of risks and benefits must be applied when using these combination therapies while awaiting the results of large, randomized, controlled trials.

Resources


Further references available—contact Perspectives in Cardiology at cardio@sta.ca.