

## ***Therapeutic approaches to reducing residual vascular risk***

Statin therapy is the cornerstone of cholesterol management, supported by extensive evidence from large prospective clinical trials. However, despite effective low-density lipoprotein cholesterol (LDL-C) lowering treatment, significant cardiovascular (CV) risk persists. The relative CV risk reduction with statin monotherapy is typically in the range of 25% to 35%.<sup>1</sup> Further reduction of LDL-C with maximal doses of statins does not eliminate this residual risk.<sup>2,3</sup> Atherogenic dyslipidemia, defined as low high-density lipoprotein cholesterol (HDL-C) levels and elevated triglycerides (TG), was clearly implicated as significantly contributing to this residual risk.

In patients with type 2 diabetes, even aggressive multifactorial therapy (statins, blood pressure-lowering agents, anti-diabetic agents) did not prevent the development or progression of microvascular complications (diabetic eye disease, kidney disease and lower-limb disease) in up to 50% of patients (STENO 2).<sup>4</sup>

This unmet need in macrovascular (i.e., cardiovascular) and microvascular prevention with statin monotherapy could be bridged by adopting strategies that target various modifiable components of atherogenic dyslipidemia, in which triglycerides and high-density (HDL-C) play a central role. These strategies include lifestyle modifications and other lipid-modifying agents.

### ***Lifestyle modifications***

Adoption of a healthy diet, weight loss, frequent exercise and smoking cessation are important first steps in reducing residual vascular risk, even in statin-treated patients. Large studies have shown that 68% of heart attacks in statin-treated men could be prevented by following this approach.<sup>5</sup> However, many patients cannot achieve the full potential of lifestyle changes to prevent vascular events, and consequently pharmacotherapy may be required.

### ***Pharmacological approaches***

While treatment guidelines identify LDL-C as the primary target for cardiovascular prevention, they recognize HDL-C and elevated TG as important secondary targets and recommend adding a fibrate, niacin or omega-3 fatty acids to statin treatment (see table).<sup>6-8</sup> The most recent European guidelines, and the recently updated NICE guidelines, recommend the use of fibrates when CV risk is high, as is usual in people with type 2 diabetes, if TG levels remain in the range 2.3–4.5 mmol/L (approx 200-400 mg/dL) despite statin therapy.<sup>9</sup>

These guidelines are supported by clinical studies showing significantly greater improvements in triglycerides and HDL-C with fibrates versus statins.<sup>6,7,10</sup> Fibrates also significantly improve cardiovascular outcomes in patients with low HDL-C and/or elevated triglycerides.<sup>11-14</sup>

<b>ATP Guidelines (2004)<sup>15</sup></b>	<ul style="list-style-type: none"> <li>For type 2 diabetic and non diabetic patients: although the evidence base to support fibrate therapy is not as strong as that for statins, fibrates may have an adjunctive role in the treatment of patients with high TG/low HDL-C, especially in combination with statins</li> </ul>
<b>IDF Guidelines (2005)<sup>16</sup></b>	<ul style="list-style-type: none"> <li>The guidelines require access to measurement of a full lipid profile and supporting biochemistry and to aspirin, statins and fibrates as a minimum</li> <li>Once LDL-C is as optimally controlled as possible with a statin, add fenofibrate where serum TG &gt;2.3 mmol/L (&gt;200 mg/dL)</li> <li>Consideration of other lipid-lowering drugs (ezetimibe, sustained-release nicotinic acid, concentrated omega-3 fatty acids) in those who fail to reach lipid-lowering targets or are intolerant to conventional drugs</li> </ul>
<b>ESC/EASD Guidelines (2007)<sup>17</sup></b>	<ul style="list-style-type: none"> <li>In diabetic patients with hypertriglyceridemia &gt;2 mmol/L (178 mg/dL) remaining after having reached LDL-C target with statins, statin therapy should be increased to reduce the secondary target of non HDL-C</li> <li>Combination therapy with ezetimibe, nicotinic acid or fibrates may be considered</li> </ul>
<b>NICE Guidelines (2008)<sup>9</sup></b>	<ul style="list-style-type: none"> <li>Prescribe a fibrate (fenofibrate as first-line) if TG levels remain above 4.5 mmol/L (400 mg/dL) despite attention to other causes</li> <li>If CV risk is high (as is usual in people with type 2 diabetes), consider adding a fibrate to statin therapy if TG levels remain in the range 2.3–4.5 mmol/L (200-400 mg/dL) despite statin therapy</li> </ul>
<b>ADA Guidelines (2008)<sup>18</sup></b>	<ul style="list-style-type: none"> <li>Combination therapy, with a statin and a fibrate or statin and niacin, may be efficacious for treatment of all three lipid fractions, but this combination is associated with an increased risk for abnormal transaminase levels, myositis or rhabdomyolysis</li> <li>The risk of rhabdomyolysis is higher with higher doses of statins and with renal insufficiency, and seems to be lower when statins are combined with fenofibrate than gemfibrozil</li> </ul>

## **Fibrates**

### ***Effect on lipid profile***

The major effect of fibrates is a reduction in TG from between 20 and 50% and an increase in HDL-C levels of between 10 and 35% according to the type of dyslipidemia and the drug used.<sup>19</sup>

### ***Safety***

Fibrate monotherapy is associated with an increased risk of myopathy compared with statins,<sup>20</sup> although the absolute risk with either drug class is low. Safety data from the US Food and Drug Administration's (FDA) Adverse Events Reporting System database (1998–2002) showed that the muscle disorder rhabdomyolysis was 15-fold more prevalent with the combination of gemfibrozil and a statin (excluding the discontinued cerivastatin) than fenofibrate plus a statin.<sup>21</sup> This difference is most likely due to competition between statins and gemfibrozil for major hepatic enzymes involved in each drug's metabolism.

### ***Impact on macrovascular events***

Several large randomized outcome trials with fibrates have been conducted. In the Helsinki Heart Study (HHS)<sup>22</sup> and the Veterans Affairs HDL Intervention Trial (VA-HIT),<sup>23</sup> there was a significant reduction in the risk of coronary heart disease. The Bezafibrate Infarction Prevention (BIP) study<sup>24</sup> and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study<sup>8</sup> did not show a significant effect on their respective primary study outcomes, although in the FIELD trial, fenofibrate significantly reduced total cardiovascular events (pre-defined secondary endpoint).<sup>8</sup>

Interestingly, post-hoc analyses of these trials (HHS, VA-HIT, BIP and FIELD) consistently showed that the relative risk reduction for CVD events was statistically significant and larger in patients with features of the metabolic syndrome, such as atherogenic dyslipidemia (high TG, low HDL-C or both), metabolic syndrome or type 2 diabetes.<sup>8,11-14</sup>

Given its demonstrated lipid-modifying efficacy, the combination of statin-fibrate therapy may provide additional clinical benefit. The macrovascular benefits of simvastatin-fenofibrate versus simvastatin monotherapy are being tested in the prospective ACCORD trial.

### ***Impact on microvascular complications***

The FIELD study showed a significant beneficial effect of fenofibrate on microvascular risk with a reduction in the progression of microalbuminuria, in the development and progression of diabetic eye disease,<sup>25</sup> and in the risk of lower-limb amputations.<sup>26</sup>

The benefit of combination statin-fibrate on microvascular risk and specifically on diabetic retinopathy is further being prospectively evaluated in the ACCORD-Eye sub-study.

## **Niacin**

### ***Effect on lipid profile***

Niacin raises HDL-C typically between 15-25 %.<sup>27</sup> Niacin also lowers LDL-C by 10-15 % and TG by 15-25 %. Combining niacin with a statin further improves LDL-C, HDL-C and TG levels.<sup>6,28</sup>

### ***Safety***

Flushing is a common side effect of niacin and has a substantial impact on patient's acceptability and adherence to treatment.<sup>29</sup> Niacin also increases blood glucose by reducing insulin sensitivity<sup>30</sup> and may lead to new-onset diabetes in people with metabolic syndrome.<sup>31</sup> Uncommon adverse effects include hepatotoxicity and gout.

### ***Impact on macrovascular events***

In the Coronary Drug Project (CDP) study published in 1975, niacin significantly reduced coronary death or non-fatal MI by 14% over five years in patients with previous MI.<sup>32</sup> Extended follow-up showed that niacin significantly reduced all-cause mortality by 11%, mainly due to a 12% reduction in CHD mortality.<sup>33</sup>

Two small angiographic imaging studies showed that niacin combined with colestipol (FATS)<sup>34</sup> or with a statin (HATS)<sup>29</sup> slowed coronary atherosclerosis progression compared with placebo. However, neither study had a statin monotherapy arm for comparison.<sup>32,34</sup> The macrovascular benefits of a combination therapy of niacin-statin are being prospectively evaluated in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial.

The Heart Protection Study 2 - Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial is also investigating the macrovascular benefits of niacin/laropiprant in about 20,000 patients with a history of MI, stroke or peripheral arterial disease and whose LDL-C levels are optimized with statins.<sup>35</sup>

### ***Impact on microvascular complications***

There are no data to date on niacin's effect on microvascular complications.

## **Omega-3 fatty acids**

### ***Effect on lipid profile***

Omega-3 fatty acids lower elevated TG and atherogenic remnant lipoproteins associated with atherogenic dyslipidemia.<sup>36,37</sup> Lipid-modifying benefits have also been observed when omega-3 fatty acids are added to statin therapy.<sup>38</sup>

### ***Impact on macrovascular events***

Omega-3 fatty acids significantly reduced the risk of total and cardiovascular mortality, non-fatal myocardial infarction (MI) and non-fatal stroke in patients with previous MI (GISSI-Prevenzione trial).<sup>45</sup> The recently published GISSI-HF study (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) has also shown that supplementation with omega-3 fatty acids (1g daily) provides a small yet significant beneficial prognostic benefit on mortality and cardiovascular hospitalization in patients with heart failure.<sup>39</sup>

It was hypothesized that the benefit of treatment observed in large prospective studies with omega-3 fatty acids probably relates to effects on cardiac rhythm<sup>40,41</sup> rather than on reduction of lipids or blood pressure. In contrast, the Japan EPA lipid intervention study (JELIS) showed that the combination of omega-3 fatty acids (1,800 mg daily) and a low dose statin compared with statin therapy alone reduced major coronary events without altering rates of sudden cardiac death.<sup>42</sup>

### ***Impact on microvascular complications***

There are no data to date on the effect of omega-3 fatty acids on microvascular complications.

## Other lipid-modifying agents

### *CETP inhibitors and Endocannabinoid type 1 receptor blockers*

Cholesteryl ester transfer protein (CETP) promotes the transfer of plasma cholesterol from HDL-C to LDL-C and the transfer of TG from LDL-C to HDL-C. The first CETP inhibitor submitted to clinical testing, torcetrapib, increased HDL-C by 72% but its development was terminated due to significant excess of mortality and cardiovascular events in combination with atorvastatin.<sup>43</sup> Clinical development of other CETP inhibitors is ongoing. Further clinical outcome data are not expected before 2011.

Selective endocannabinoid type 1 receptor blockers raise HDL-C levels, lower TG and reduce body weight. The first of this class, rimonabant, has had mixed results in clinical trials.

However, concerns about the increased risk of neurological and psychiatric adverse events with rimonabant have been raised, and marketing of the drug was not granted by the FDA in the US. Recently, the EMEA has suspended the marketing authorization of rimonabant in Europe and<sup>44</sup> sanofi-aventis has announced it was discontinuing the ongoing clinical trials with rimonabant, including the CRESCENDO (Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes) trial, investigating the macrovascular benefits of rimonabant.

The development of another endocannabinoid type 1 receptor blocker, taranabant, was also recently discontinued by Merck.

There are no data to date on the effect of CETP inhibitors and type 1 endocannabinoid receptor blockers on microvascular complications.

#### **Recommendations of the R<sup>3</sup>i to reduce residual vascular risk**

- Initiate lifestyle modification as a first step
- Normalize glycosylated hemoglobin (HbA<sub>1c</sub>) and blood pressure
- Improve all lipid parameters. The addition of a fibrate, niacin or omega 3 fatty acids to statin therapy may be useful.
- Earlier intervention in the natural history of the disease is warranted with lifestyle modification and drug therapy

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