

# The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in dyslipidaemic patients

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A CONDENSED POSITION PAPER BY THE RESIDUAL RISK REDUCTION INITIATIVE (R<sup>3</sup>I)\*

## Abstract

**D**espite current standards of care aimed at achieving targets for low-density lipoprotein (LDL) cholesterol, blood pressure and glycaemia, dyslipidaemic patients remain at high residual risk of vascular

events. Atherogenic dyslipidaemia, specifically elevated triglycerides and low levels of high-density lipoprotein (HDL) cholesterol, often with elevated apolipoprotein B and non-HDL cholesterol, is common in patients with established cardiovascular disease, type 2 diabetes, obe-

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\*The Residual Risk Reduction Initiative (R<sup>3</sup>I) is an independent non-profit educational organisation of basic and clinical scientists, cardiologists, endocrinologists and diabetologists that has been formed to address this issue. It is registered in Switzerland under its legal jurisdiction to ensure that the scientists will set the direction and have control of the activities. The current funders are Solvay Pharmaceuticals and Abbott Laboratories.

sity or metabolic syndrome and is associated with macrovascular and microvascular residual risk. The Residual Risk Reduction Initiative (R<sup>3</sup>I) was established to address this important issue.

This position paper aims to highlight evidence that atherogenic dyslipidaemia contributes to residual macrovascular risk and microvascular complications despite current standards of care for dyslipidaemia and diabetes, and to recommend therapeutic intervention for reducing this, supported by evidence and expert consensus. Lifestyle modification is an important first step. Additionally, pharmacotherapy is often required. Adding niacin, a fibrate or omega-3 fatty acids to statin therapy improves achievement of all lipid risk factors. Outcomes studies are evaluating whether these strategies translate to greater clinical benefit than statin therapy alone. In conclusion, the R<sup>3</sup>i highlights the need to address with lifestyle and/or pharmacotherapy the high level of residual vascular risk among dyslipidaemic patients who are treated in accordance with current standards of care.

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**Key words:** lifestyle, macrovascular, microvascular, pharmacotherapy, residual risk.

**Background: defining the problem**

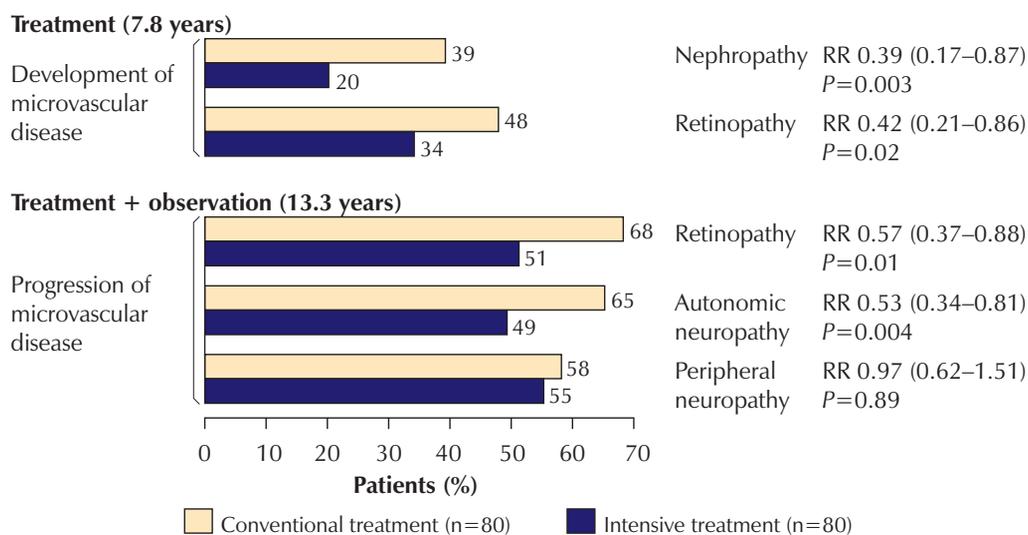
The gains made in cardiovascular disease (CVD) prevention over the last four decades are now being seriously challenged by the impact of global epidemics of obesity, metabolic syndrome and type 2 diabetes.<sup>1</sup> Recent data even raise the prospect of a rever-

sal in heart disease mortality rates, especially in younger men and women.<sup>2,3</sup> These trends will undoubtedly impact on the cost of managing CVD, currently estimated at about \$450 billion per annum in the US,<sup>4</sup> and \$300 billion in Europe.<sup>5</sup>

Current standards of care for CVD prevention emphasise the importance of multifactorial intervention to achieve recommended targets for low-density lipoprotein (LDL) cholesterol, blood pressure and glycaemic control.<sup>6–11</sup> Type 2 diabetes itself is also associated with increased CVD risk.<sup>6</sup> However, as illustrated in the STENO-2 study, multifactorial intervention is insufficient to prevent the development or progression of microvascular disease in up to 50% of patients with type 2 diabetes (figure 1).<sup>12,13</sup> Although statin therapy is the cornerstone of dyslipidaemia management, supported by extensive evidence from large prospective clinical trials, significant CVD risk persists despite effective LDL cholesterol-lowering treatment. Data from a recent meta-analysis including 90,056 subjects (18,686 with diabetes) in 14 randomised trials show that one in seven treated patients experienced events over five years.<sup>14,15</sup> Further lowering of LDL cholesterol with maximal doses of statins does not eliminate this residual risk (figure 2).<sup>16,17</sup>

There is clearly an urgent need for renewed focus on effective interventions that are capable of reducing the residual risk of cardiovascular events and microvascular complications in dyslipidaemic patients receiving optimal therapy in accordance with current standards of care. Management of atherogenic dyslipidaemia (strictly speaking, atherogenic dyslipoproteinaemia) that is typically encountered in patients with metabolic abnormalities falls well short of optimal and is the focus of this paper.

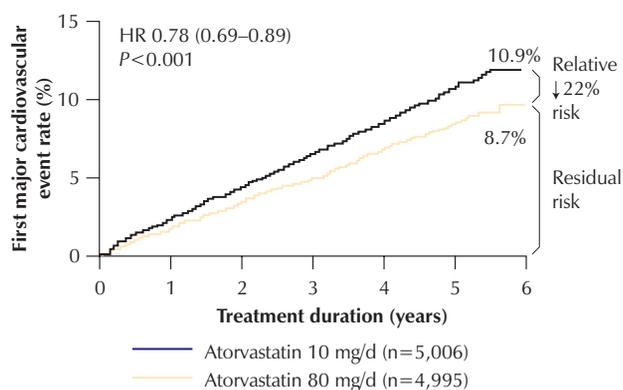
**Figure 1. In the STENO-2 study, intensive multifactorial intervention significantly reduced the development or progression of diabetes-related microvascular disease, but failed to prevent this in many patients<sup>12,13</sup>**



**Key:** RR = relative risk (95% confidence interval)

Diabetic nephropathy was defined as urinary albumin excretion >300 mg per 24 hours in two of three sterile urine specimens. Diabetic retinopathy was graded according to the 6-level grading scale of the European Community-funded Concerted Action Programme into the Epidemiology and Prevention of Diabetes by two independent ophthalmologists who were unaware of treatment assignment. Peripheral neuropathy was measured with a biothesiometer. Autonomic neuropathy was diagnosed based on measurement of the RR interval on an ECG during paced breathing and an orthostatic hypotension test conducted by a laboratory technician who was unaware of patients' treatment assignment.

**Figure 2. In the TNT study,<sup>16</sup> lowering LDL cholesterol beyond current targets with high-dose atorvastatin therapy left a high level of residual risk of major cardiovascular events**



**Key:** TNT = Treating to New Targets; LDL = low-density lipoprotein; HR = hazard ratio. Major cardiovascular events were defined as a composite of coronary heart disease death, non-fatal, non-procedural myocardial infarction, resuscitation after cardiac arrest, and fatal or non-fatal stroke

**Table 1. Dyslipidaemia associated with type 2 diabetes and the metabolic syndrome**

**Major independent\* CVD risk factors**

- ↓ in HDL cholesterol level
- ↓ in apolipoprotein A-I
- ↑ in TG and TG-rich lipoprotein
- ↑ in non-HDL cholesterol
- ↑ in apolipoprotein B

**Other associated risk factors<sup>†</sup>**

- ↑ in postprandial TG
- ↑ in LDL particle numbers (measured by NMR)
- ↑ in apolipoprotein CIII

**Other lipoprotein manifestations**

- Small, dense LDL
- Small HDL, prebeta-1 HDL, alpha-3 HDL

**Key:** CVD = cardiovascular disease; HDL = high-density lipoprotein; TG = triglyceride; LDL = low-density lipoprotein; NMR = nuclear magnetic resonance; \* Independent of other principal lipid and non-lipid risk factors, as shown in many large studies; † Independent of other principal lipid and non-lipid risk factors, but with a less extensive database

**Atherogenic dyslipidaemia: a common feature of dyslipidaemic patients**

Dyslipidaemia may play a role in residual vascular risk, as indicated by the INTERHEART study, which found it to be responsible for more than 50% of population-attributable risk. However, LDL cholesterol is not the sole lipid that defines this risk.<sup>18</sup> Atherogenic dyslipidaemia, characterised by elevated triglycerides (TG) and a low plasma concentration of high-density lipoprotein (HDL) cholesterol, often with elevated apolipoprotein B (apoB) and non-HDL cholesterol, is prevalent in patients with type 2 diabetes, metabolic syndrome and/or established CVD (table 1).<sup>19,20</sup> The risk associated with atherogenic dyslipidaemia is uncorrelated with, and additive to, that of LDL cholesterol.

**Atherogenic dyslipidaemia and macrovascular risk**

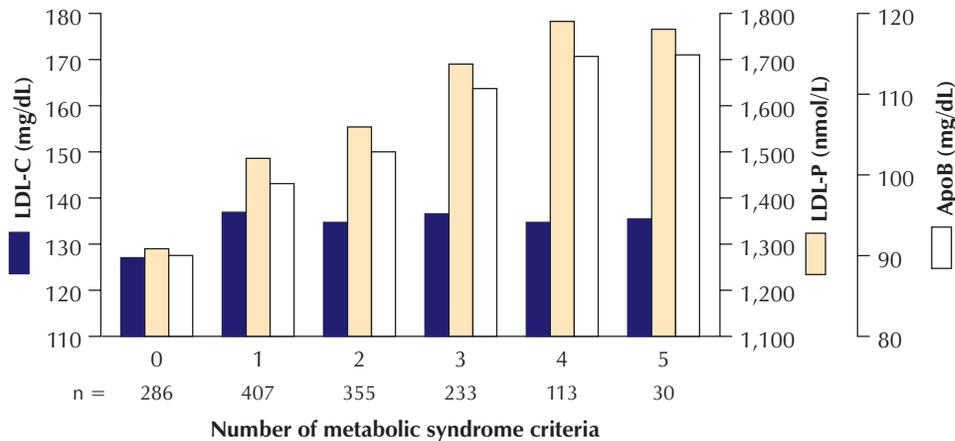
Extensive evidence shows that elevated TG and low HDL cholesterol are both predictors for CVD, independent of LDL cholesterol.<sup>21-23</sup> Non-fasting TG levels, measured 2–4 hours postprandially, may be of even greater relevance to CVD risk since atherogenic lipoprotein remnants secreted by the liver and intestine postprandially circulate in higher concentrations than in the fasting state, as supported by evidence from clinical studies.<sup>24,25</sup> Furthermore, as shown by the Prospective Cardiovascular Münster (PROCAM) study, the ratio of total/HDL cholesterol also needs to be taken into account. One in seven subjects in the PROCAM study with the combination of a high total to HDL cholesterol ratio (> 5.0), low HDL cholesterol (< 35 mg/dL, 0.90 mmol/L) and elevated TG (≥ 200 mg/dL, 2.26 mmol/L) experienced a myocardial infarction (MI).<sup>26</sup>

While LDL cholesterol levels are often normal or only modestly elevated in patients with diabetes and/or metabolic syndrome, apoB concentration may be increased.<sup>27</sup> ApoB concentration represents the sum of concentrations of atherogenic particles (very low-density lipoproteins [VLDL],

intermediate-density lipoproteins [IDL], IDL remnants, LDL and lipoprotein(a)) since each VLDL, IDL and LDL particle carries one molecule of apoB. It is not surprising therefore that substantial evidence supports apoB concentration as a better predictor for coronary heart disease (CHD) risk than LDL cholesterol.<sup>28-35</sup> ApoB (or LDL concentration, estimated by nuclear magnetic resonance [NMR]) was also more strongly correlated with an increasing number of components of the metabolic syndrome (figure 3).<sup>36</sup> Additionally, while there tend to be more LDL particles of small size with reduced cholesterol content associated with the metabolic syndrome, small LDL particle size in itself has not proved to be an independent predictor of CHD, beyond TG, HDL cholesterol or apoB.<sup>37,38</sup> The recent American Diabetes Association/American College of Cardiology (ADA/ACC) consensus statement for lipoprotein management<sup>39</sup> highlights the need to address apoB levels as a component of residual risk since measurement of LDL cholesterol levels under-represents the atherogenic burden of apo-B carrying particles. However, the lack of clinical trial data presents a therapeutic dilemma since it is not known whether this is best achieved by intensification of statin therapy or by augmenting statin therapy with a fibrate or niacin.

Apolipoprotein C-III (apoCIII), a component of some VLDL and LDL that are TG-enriched, has also been shown to be a strong, independent predictor of CVD.<sup>40-48</sup> Plasma levels of apoCIII are elevated in patients with atherogenic dyslipoproteinaemia, hypertriglyceridaemia, metabolic syndrome, insulin resistance and type 2 diabetes.<sup>41,47,49,50</sup> ApoCIII may have a special pathological role in diabetes, being implicated in beta-cell dysfunction and microvascular complications,<sup>51-53</sup> via direct activation of pro-inflammatory and atherogenic mechanisms in vascular endothelial cells and monocytes.<sup>54-56</sup> Other apolipoproteins in VLDL and LDL

**Figure 3. Data from 2,993 Framingham Heart Study participants show a significant increase in apolipoprotein B levels ( $p < 0.0001$  for trend) and LDL particle concentration ( $p < 0.0001$  for trend) with an increasing number of components of the metabolic syndrome. There was much less change in LDL cholesterol levels<sup>36</sup>**



Key: apoB = apolipoprotein B; LDL = low-density lipoprotein

have been implicated with CVD risk, although supportive evidence for these is less well developed than for apoCIII. ApoA-I and apoA-II, the principal apolipoproteins in HDL, are both associated with potentially atheroprotective effects and reduced CVD.<sup>57,58</sup>

In lipid treatment trials, the combination of lipid and lipoprotein abnormalities characteristic of the metabolic syndrome is associated with residual CVD risk.<sup>59</sup> Statin therapy, even at higher doses, incompletely addresses this residual risk. Even if LDL cholesterol levels are  $< 70$  mg/dL (1.81 mmol/L), vascular risk remains up to 40% higher in the presence of low HDL cholesterol ( $< 35$  mg/dL, 0.90 mmol/L)<sup>60</sup> or elevated TG ( $\geq 200$  mg/dL, 2.26 mmol/L).<sup>61</sup>

#### Atherogenic dyslipidaemia and microvascular risk

Dyslipidaemia is also implicated in the pathogenesis of diabetic microvascular disease.<sup>62</sup> Elevated serum total and LDL cholesterol<sup>63-65</sup> and TC<sup>65</sup> may have causative roles in the development of retinal hard exudates and diabetic maculopathy, and high TG levels were also linked with increased risk for proliferative diabetic retinopathy.<sup>66</sup> In a report from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC), the severity of retinopathy was positively associated with TG and negatively associated with HDL cholesterol. As well, there were positive associations between small and medium size VLDL (identified by NMR) and Early Treatment Diabetic Retinopathy Study (ETDRS) score (a measure of retinopathy severity), and an inverse association between large HDL and ETDRS score. In men, retinopathy was also positively associated with apoB and LDL concentrations.<sup>67</sup>

Elevated levels of TG and TG-rich VLDL appear to be associated with progression of albuminuria, a marker of nephropathy.<sup>68</sup> In the United Kingdom Prospective Diabetes Study (UKPDS), elevated TG were independently associated with incident microalbuminuria in patients with type 2 diabetes (hazard ratio 1.13, 95% CI 1.07–1.19,  $p < 0.0001$ ) and

macroalbuminuria (1.19, 95% CI 1.11–1.27,  $p < 0.0001$ ).<sup>69</sup> Additional data suggest that higher HDL cholesterol levels may be protective against nephropathy.<sup>70-72</sup> Finally, abnormal lipids, specifically elevated TG, higher levels of total and LDL cholesterol and lower HDL cholesterol, have been implicated in the development of diabetic neuropathy.<sup>73,74</sup>

#### Atherogenic dyslipidaemia and inflammation

Atherogenic dyslipidaemia is also associated with a pro-inflammatory state which contributes to residual vascular risk. Experimental studies show that TG-enriched VLDL particles activate nuclear factor kappa B (NF- $\kappa$ B) signalling, which plays a key role in activating a spectrum of pro-inflammatory genes, in turn leading to endothelial dysfunction and oxidative stress.<sup>75,76</sup> ApoCIII also exerts direct adverse effects on vascular endothelial and monocytic cells, activating pro-inflammatory and pro-atherogenic cytokines.<sup>54-56</sup> VLDL and LDL isolated from people with type 2 diabetes or metabolic syndrome have increased susceptibility to lipolysis by circulating and subendothelial secretory phospholipase A<sub>2</sub> group V,<sup>77</sup> leading to increases in non-esterified fatty acids and lysophosphatidylcholine in the lipoproteins, which contribute to a pro-inflammatory state. Increased systemic levels of markers of chronic low-grade inflammation factors (e.g. high-sensitivity C-reactive protein) and inflammatory cytokines are also implicated in driving qualitative changes in HDL, leading to attenuation of atheroprotective functions, including protection of LDL against oxidative modification.<sup>78,79</sup>

Furthermore, elevated TG are also associated with activation of the coagulation cascade and suppression of fibrinolysis. Postprandial TG-enriched lipoproteins activate factor VII,<sup>80,81</sup> a risk factor for CHD.<sup>82,83</sup> Additionally, plasminogen activator inhibitor-1 (PAI-1) activity, associated with risk for MI,<sup>84</sup> has been shown to correlate positively with levels of TG-enriched VLDL.<sup>85</sup> Experimental studies show that VLDL increase the production and secretion of PAI-1, by stimulating vascular PAI-1 gene expression and protein synthesis.<sup>86</sup>

Together, these data emphasise the need to increase

**Table 2. Impact of diet quality – key findings from the OmniHeart Study<sup>96</sup>**

Compared a modified carbohydrate-rich diet based on the DASH diet,<sup>97</sup> emphasising fruit, vegetables, high-protein foods (beans, whole grains, nuts, low-fat dairy, fish and poultry) and unsaturated cooking oils vs. a protein-rich diet (about 50% from plant sources) and a diet rich in unsaturated fat (mainly monounsaturated fat). Body weight was kept constant.

- Both protein and unsaturated fat diets reduced blood pressure vs. the carbohydrate-rich diet
- Both protein and unsaturated fat diets significantly reduced TG, total and non-HDL cholesterol vs. the carbohydrate-rich diet
- The unsaturated fat diet raised HDL cholesterol levels vs. other diets
- Partially replacing carbohydrates with protein or mono-unsaturated fat can improve CVD risk

**Key:** CVD = cardiovascular disease; HDL = high-density lipoprotein; TG = triglyceride

awareness of the importance of atherogenic dyslipidaemia to residual vascular risk, as well as to provide insight into effective management of this condition.

### Therapeutic approaches to reducing residual vascular risk

#### Lifestyle modification

##### Diet

Dietary guidelines are moving away from nutrient targets and toward encouraging healthy dietary patterns.<sup>87</sup> Traditional Mediterranean diets as in Greece and Southern Italy are associated with longevity,<sup>88</sup> low CVD mortality,<sup>89</sup> less type 2 diabetes,<sup>90</sup> and a low incidence of a wide range of chronic diseases, including rheumatoid arthritis,<sup>91</sup> Parkinson's disease<sup>92</sup> and Alzheimer's disease.<sup>93</sup> Trichopoulos *et al.*<sup>94</sup> defined a score for the Mediterranean diet which counted vegetables, fruit, fish, whole cereal grains, legumes, unsaturated fats, moderate alcohol intake and limited consumption of red meat. In clinical trials, this diet lowered blood pressure and improved dyslipidaemia.<sup>95</sup> The Mediterranean dietary pattern shares many similarities with the DASH and OmniHeart diets tested in the US, which lowered blood pressure substantially, and lowered LDL cholesterol.<sup>96</sup> Increasing unsaturated fat or protein in the OmniHeart diet improved dietary effects on LDL cholesterol, TG, as well as on blood pressure (table 2).<sup>96</sup> Dietary sodium should also be lowered as much as possible to prevent and treat hypertension.<sup>97</sup>

Polyunsaturated fats, omega-6 and omega-3 fatty acids, improve CVD risk factors and reduce CVD events as proven by randomised controlled trials.<sup>98-102</sup> Linoleic acid, an omega-6 fatty acid found in many vegetable oils including soybean, sunflower, safflower and corn, improves insulin sensitivity, lowers LDL cholesterol and, among the macronutrients, produces the greatest reduction in the LDL to HDL cholesterol ratio.<sup>103</sup> Mono-unsaturated fats, as in olive oil or rapeseed (canola) oil and nuts, improve insulin sensitivity, and reduce the LDL to

**Table 3. Importance of regular physical activity**

- Beneficial effects on insulin sensitivity and glycaemic control
- Beneficial effects on atherogenic dyslipidaemia
- Beneficial effects on weight control
- Improved blood pressure and bone health, reduced atherosclerotic CVD risk, as well as psychological benefits
- Moderate exercise (brisk walking for at least 30 minutes daily) reduces the risk of type 2 diabetes
- Moderate exercise frequency is more important than higher intensity exercise

**Key:** CVD = cardiovascular disease

HDL ratio.<sup>104</sup> Olive oil, especially the virgin type, has other phytochemicals that have beneficial effects on CVD risk factors and related physiological measurements,<sup>105</sup> whereas rapeseed oil has alpha linolenic acid, an omega-3 fatty acid strongly associated with protection against CVD and reduction in coronary events.<sup>106,107</sup> Perhaps liberal use of a variety of natural liquid vegetable oils may be the best dietary means of improving risk of CVD and diabetes.

Clearly, a healthier diet favourably and strongly affects dyslipidaemia and hypertension, even in obese patients who do not lose weight.<sup>96,108</sup> This underappreciated fact should stimulate physicians and their obese patients to improve their diet quality even if they are not able to lose weight.

##### Exercise

Exercise is also a cornerstone in the prevention and treatment of CVD, type 2 diabetes and the metabolic syndrome (table 3). Epidemiological studies suggest that physical activity can reduce the risk for CVD and type 2 diabetes by up to 50%.<sup>109,110</sup> In people with diabetes, increased physical activity was strongly and inversely associated with mortality.<sup>111</sup> In the Women's Health Study in middle-aged and older women, physical activity attenuated but did not eliminate the risk of CHD due to increased body mass index (BMI  $\geq$  25 kg/m<sup>2</sup>).<sup>112</sup>

Regular physical activity improves insulin sensitivity<sup>113</sup> and glycaemic control<sup>114,115</sup> and has broad beneficial effects on the lipoprotein profile, including HDL cholesterol, the total/HDL cholesterol ratio and TG, even in the absence of weight loss.<sup>116,117</sup> Improvements in lipids and lipoproteins due to exercise have been reported in both older adults<sup>118</sup> and children and adolescents.<sup>119</sup> The combination of aerobic and resistance exercise may provide greater benefit in people with atherogenic dyslipidaemia and other components of the metabolic syndrome, due to the combined effects of reduced adiposity, increased muscle mass and improved myocyte function.<sup>120</sup> Furthermore, in addition to these and other physical benefits (table 3),<sup>109,112,121,122</sup> regular physical exercise also improves psychological well-being.<sup>123</sup>

The frequency of exercise is probably more important than its intensity,<sup>115</sup> although some studies suggest that these factors are equally relevant.<sup>124</sup> Moderate intensity exercise, such as brisk walking for 30 minutes or more each day, seems to be preferable for preventing type 2 diabetes<sup>125</sup> or improving the metabolic syndrome.<sup>126</sup>

**Table 4. Effect of fibrate treatment on major coronary and cardiovascular event rates (as defined in the table) in fibrate studies**

<b>A. Primary results based on all patients</b>						
Trial	Patient population	End point	Absolute event rate (%)		Reduction in relative risk (%)	p-value
			Control	Fibrate		
WHO trial <sup>152</sup>	7,194 men without CHD in upper third of cholesterol values, completing five years' treatment	Major CHD events (non-fatal MI + CHD death)	5.8	4.7	20	<0.05
		Non-fatal MI	4.8	3.7	25	<0.05
CDP <sup>151</sup>	3,892 men with CHD (1,103 on clofibrate vs. 2,789 placebo)	Major CHD events	NA	NA	9	0.12
		Mortality	20.9	20.0	4	0.55
HHS <sup>136</sup>	4,081 men without CHD and non HDL-C $\geq$ 200 mg/dL	Fatal + non-fatal MI and CHD death	4.1	2.7	34	<0.02
VA-HIT <sup>137</sup>	2,531 men with CHD and low HDL-C (< 40 mg/dL)	Non-fatal MI + CHD death	21.7	17.3	22	0.006
		Non-fatal MI + CHD death + stroke	26.0	20.4	24	<0.001
BIP <sup>138</sup>	3,090 men and women with previous MI or angina	Fatal or non-fatal MI or sudden death	15.0	13.6	7.3	0.24
FIELD <sup>139</sup>	9,795 men and women with type 2 diabetes	Non-fatal MI + CHD death	5.9	5.2	11.0	0.16
		Total CVD events	13.9	12.5	11.0	0.035

**Key:** p-values are relative to control (placebo); NA = not available

<b>B. Results from post-hoc analyses in patients with diabetes or features of the metabolic syndrome</b>						
Trial	Patient population n (% of total) where reported	End point	Absolute event rate (%)		Reduction in relative risk (%)	p-value
			Control	Fibrate		
HHS <sup>153</sup>	TG $\geq$ 204 mg/dL, HDL-C < 40 mg/dL + BMI > 26 kg/m <sup>2</sup>	Fatal + non-fatal MI and CHD death	NA	NA	78	0.002
VA-HIT <sup>154</sup>	769 (30%) with diabetes 1,185 (47%) with TG $\geq$ 150 mg/dL	Non-fatal MI + CHD death	36.1	24.5	32	<0.001
		+ stroke	27.0	20.0	27	0.01
BIP <sup>155</sup>	459 (15%) with TG > 200 mg/dL 1,470 (48%) with metabolic syndrome <sup>1</sup>	Fatal or non-fatal MI or sudden death	19.7	12.0	39.5	0.02
			18.4	14.1	25.0	0.03
FIELD <sup>156</sup>	Low HDL-C <sup>2</sup> and TG $\geq$ 200 mg/dL	Total CVD events	17.8	13.5	26	0.01

<sup>1</sup> At least three of the following: fasting glucose  $\geq$  110 mg/dL or current use of oral hypoglycaemic treatment, TG  $\geq$  150 mg/dL, HDL-C < 40 mg/dL in men and < 50 mg/dL in women, systolic blood pressure  $\geq$  130 mmHg or diastolic blood pressure  $\geq$  85 mmHg or body mass index  $\geq$  28.0 mg/kg<sup>2</sup>;  
<sup>2</sup> Low HDL-C defined as < 40 mg/dL in men and < 50 mg/dL in women; p-values are relative to control (placebo)

**Key:** CHD = coronary heart disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction; BIP = Bezafibrate Infarction Prevention study; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes study; HHS = Helsinki Heart Study; VA-HIT = Veterans Affairs HDL Intervention Trial; WHO = World Health Organization  
 To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259; To convert triglycerides from mg/dL to mmol/L, multiply by 0.01129

## Alcohol

Cardioprotective effects of light-to-moderate alcohol intake (up to one drink daily for women and one or two drinks daily for men) are recognised. These are predominantly achieved via improvement in insulin sensitivity and HDL cholesterol.<sup>127</sup> It should, however, be noted that excessive consumption is associated with hypertriglyceridaemia,<sup>128,129</sup> mainly due to increased synthesis of TG-enriched VLDL.<sup>129</sup> Moreover, given the lack of randomised outcome data, universal recommendation of

alcohol consumption even for non-drinking individuals is not supported.

Adherence to a healthy lifestyle is associated with lowering the risk of CVD and residual vascular risk in patients already treated with statins or antihypertensive drugs, based on expert consensus of the available clinical evidence. Large prospective studies of lifestyle intervention highlight this issue. In the Health Professionals Follow-up Study<sup>130</sup> in 42,847 men aged 40–75 years without CVD at baseline, 68% of coronary events in statin-treated men would have

been prevented by following a low-risk lifestyle (a healthy diet with regular exercise and moderate alcohol consumption, not smoking and maintaining BMI < 25 kg/m<sup>2</sup>). However, only 2–4% of subjects in this study were able to achieve and maintain this lifestyle. Thus, while lifestyle modification has a role in reducing residual vascular risk, low adherence rates over the longer term suggest that it is most likely to be adjunctive to additional therapeutic intervention.

#### *Pharmacological approaches to reducing vascular risk*

While statins are clearly effective in reducing non-HDL cholesterol and apoB, their effects on raising HDL cholesterol and lowering TG tend to be less impressive and dependent on dose and lipid phenotype. Further reduction of LDL cholesterol can be achieved with inhibitors of cholesterol absorption, such as ezetimibe, or of bile acid reabsorption, such as resins. Treatment with bile acid sequestrants such as cholestyramine resin reduces CVD,<sup>131</sup> and this class of agents has long been established in the armamentarium for management of hyperlipidaemia. The efficacy and safety of ezetimibe, however, await the outcome of large trials. Recently, the combination of simvastatin and ezetimibe was tested in a placebo-controlled trial to treat aortic stenosis.<sup>132</sup> The results showed no reduction in aortic valve replacement, the primary outcome (28.3% vs. 29.9% with placebo, HR 1.00, 95% CI 0.84–1.18,  $p=0.97$ ), but a significant reduction in ischaemic coronary events (HR 0.78, 95% CI 0.63–0.97,  $p=0.02$ ). Since ezetimibe was given in combination with simvastatin and there was no simvastatin monotherapy control group, it cannot be determined whether it exerted additional benefit beyond the well-known effect of a statin. Moreover, cancer deaths were higher in the drug group compared to the placebo group, a finding attributed to chance by the researchers.<sup>132</sup> A subsequent analysis of cancer data from three ezetimibe trials did not indicate evidence of a trend for increase in cancer rates with ezetimibe.<sup>133</sup> Nonetheless, caution has been raised on the use of ezetimibe.<sup>134</sup>

As summarised in this paper, epidemiological data are supportive of associations between low HDL cholesterol or elevated TG and CVD risk. However, it is acknowledged by this group that there are no rigorous outcomes data definitively proving either factor as a target for CVD risk modification. Based on the epidemiological associations, expert consensus indicates a role for treatment of persistently higher TG concentrations and low HDL cholesterol in statin-treated patients. The addition of either a fibrate, niacin or omega-3 fatty acids, in addition to lifestyle modification, may help to achieve non-HDL cholesterol targets in these patients.<sup>7–11</sup> Innovative treatments that target components of atherogenic dyslipidaemia, such as cannabinoid type 1 receptor blockers and cholesteryl ester transfer protein (CETP) inhibitors, are also being developed.

#### *PPAR $\alpha$ agonists*

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors which play an important role in the regulation of lipid metabolism, glucose homeostasis and inflammatory processes. There are three PPAR isotypes:  $\alpha$ ,  $\gamma$  and  $\beta$  (also known as  $\delta$ ). In the presence of a known lig-

and, specific PPAR isotypes form heterodimers with the retinoid X receptor (RXR), another ligand-activated transcription factor. This PPAR-RXR complex then recognises and binds to specific PPAR response elements, leading to modulation of expression of the target genes influencing, for isotype  $\alpha$ , fatty acid oxidation, lipid metabolism, energy balance and inflammation.<sup>135</sup>

#### *Effects on atherogenic dyslipidaemia*

The major effect of all fibrates is a decrease in TG (by about 20–30% in recent major outcomes studies,<sup>136–139</sup> although larger decreases may be evident in patients with above average pre-treatment levels),<sup>140,141</sup> including postprandial TG and remnant lipoprotein particles.<sup>135,140–143</sup> Fibrates also raise HDL cholesterol, typically by 5–10%,<sup>136–139</sup> by stimulation of apoA-I and apoA-II expression.<sup>140,144</sup> Fenofibrate also lowers LDL cholesterol, more so in those with average compared to high baseline TG.<sup>145</sup> Both fenofibrate and gemfibrozil also lower apoCIII levels.<sup>146–149</sup> In addition, PPAR $\alpha$  agonists have anti-inflammatory actions.<sup>140,150</sup>

#### *Impact on macrovascular risk*

Several large randomised outcomes trials with fibrates have been conducted to date and results of these are summarised in table 4.<sup>136–139,151–156</sup> The aggregate results of earlier studies with clofibrate<sup>151,152,157,158</sup> indicated beneficial effects of clofibrate on clinical outcomes, although in the case of the World Health Organization (WHO) trial the significant reduction in non-fatal MI (by 25%,  $p<0.05$ ) was overshadowed by the reported increase in mortality from non-cardiovascular disease, particularly gastrointestinal cancer, with clofibrate.<sup>152</sup> The Coronary Drug Project<sup>151</sup> aimed to evaluate the long-term efficacy and safety of a number of lipid-modifying treatments, although only two – clofibrate and niacin – were continued for the trial duration (see also niacin subsection). However, this trial failed to show a significant benefit on mortality in the overall study population (table 4). The low lipid-modifying efficacy of clofibrate in these trials and concerns about adverse effects of clofibrate in the WHO trial<sup>152</sup> led to the subsequent disappearance of clofibrate from clinical practice. Of the more recent trials, two (the Helsinki Heart Study<sup>136</sup> and the Veterans Affairs HDL Intervention Trial<sup>137</sup>) were positive, whereas the other trials (the Bezafibrate Infarction Prevention (BIP) study<sup>138</sup> and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study<sup>139</sup>) did not show a significant effect on their respective primary study outcome. It should be noted that post-hoc analyses of these trials showed that the relative risk reduction for CVD events was statistically significant in patients with atherogenic dyslipidaemia (high TG, low HDL cholesterol or both), metabolic syndrome or type 2 diabetes, and nominally greater than in those without these conditions,<sup>139,153–156</sup> although formal tests of interaction were not significant.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,<sup>139</sup> the largest fibrate trial so far in about 10,000 patients, illustrates the potential and uncertainties in the evidence based on fibrate therapy. Treatment with fenofibrate did not significantly lower the risk for the

primary end point (non-fatal MI and CHD death) (reduction in RR 11%,  $p=0.16$ ). While risk reductions for the primary end point and secondary end point (total CVD events) were exactly the same, only the latter was significant ( $p=0.035$ ) because of the larger number of cardiovascular events (612 on fenofibrate vs. 683 on placebo) than coronary events (256 vs. 288, respectively). Interpretation of these results is also confounded by non-study use of statins, which was disproportionately higher in the placebo group (17% of placebo group vs. 8%, averaged over the study duration). Various statistical techniques have been used to adjust for this disparity. The method stated in the protocol that used a time-dependent adjustment for drop-ins to other lipid therapy, yielded an estimated risk reduction for CHD events of 9%,<sup>159</sup> which the authors described as counterintuitive, since it is less than the intention-to-treat result of 11%. An alternative method that used a fixed covariate for lipid therapy yielded a 19% reduction.<sup>139</sup> The authors also illustrated a simple way to estimate the effect of unequal statin therapy that assumes that statin use reduced the risk of CHD events by about one third, and this gave a risk reduction in the fenofibrate group in the range of 17–20%.<sup>139</sup>

The R<sup>3</sup>i acknowledge that a pooled analysis of fibrate trials is needed to determine definitively if fibrate treatment truly has additional benefit in atherogenic dyslipidaemia, metabolic syndrome or type 2 diabetes compared to the general population of those at high risk of CVD.

#### Safety considerations

Clinical studies indicate additional lipid-modifying efficacy with the combination of a fibrate and a statin (table 5).<sup>160,161</sup> Together with evidence from the available fibrate monotherapy outcomes trials, there is therefore support for the idea that combination statin-fibrate therapy may provide additional clinical benefit, although this is yet to be proven by outcomes studies with hard clinical end points. Additionally, there are tolerability concerns, especially with respect to the potential for increased skeletal muscle toxicity, given that both statin and fibrate monotherapy are associated with a risk of myopathy.<sup>162,163</sup> Epidemiological studies estimate a 5.5-fold increased risk of myopathy with fibrate monotherapy compared with statin use,<sup>164</sup> although it should be recognised that the absolute risk with either drug class is low. However, there appear to be differences between fibrates in this risk, as highlighted by safety surveillance data from the US Food and Drug Administration's (FDA) Adverse Events Reporting System database (1998–2002). The incidence of case reports of rhabdomyolysis and myopathy (a collective term for myalgia, myositis and myopathy) was 15-fold and 33-fold higher, respectively, with the combination of gemfibrozil and a statin (excluding the discontinued cerivastatin) than fenofibrate plus statin.<sup>165</sup> The reason for this is most likely due to reduced competition between statins and fenofibrate compared to gemfibrozil for specific glucuronidases, major hepatic enzymes for drug metabolism.<sup>166</sup> Additionally, it should be noted that in the FIELD study there were no cases of rhabdomyolysis among the 890 patients who received the combination of fenofibrate plus statin during the study.<sup>139</sup> Recent expert consensus from the National Lipid

**Table 5. Effects of combination lipid-modifying therapy compared with statin monotherapy**

#### Fibrate plus statin

- Further reduction in TG, apoB and non-HDL and VLDL cholesterol
- Further increase in HDL cholesterol
- Rarely, increased risk of myopathy, more so with gemfibrozil than fenofibrate

#### Niacin plus statin

- Further reduction in TG and LDL cholesterol
- Further increase in HDL cholesterol
- Decrease in Lp(a)
- Commonly, skin flushing and rarely, dose-related hepatotoxicity, hyperuricaemia and gout with niacin

#### Omega-3 fatty acids plus statin

- Further reduction in TG and VLDL cholesterol

**Key:** TG = triglycerides; apoB=apolipoprotein B; HDL = high-density lipoprotein; VLDL = very low-density lipoprotein; Lp(a) = lipoprotein (a)

Association in the US<sup>167</sup> indicates that the risk of myopathy with fenofibrate in combination with a statin is low, especially with the statin in its lower dose range. However, the propensity of fenofibrate to increase serum creatinine levels, as shown in the FIELD study, should also be taken into consideration. This effect was reversible within eight weeks of stopping study treatment,<sup>139</sup> indicating that there was no permanent impairment of renal function. Moreover, fenofibrate was associated with reduced progression of albuminuria in this and another trial in type 2 diabetes.<sup>139,168</sup>

Clearly, additional outcomes studies are needed. Results from the ongoing lipid trial protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study<sup>169</sup> will help to address this issue. This blinded trial aims to compare whether the combination of simvastatin plus a fibrate (fenofibrate) is more efficacious in reducing cardiovascular events than a statin plus placebo in a cohort of about 5,000 patients with type 2 diabetes with defined glycaemic control and existing clinical or subclinical CVD or CVD risk factors. Patients are randomised to treatment with either simvastatin (titrated to 40 mg/day if necessary to achieve a target LDL cholesterol level of < 100 mg/dL [2.59 mmol/L]) plus placebo or treated to the same goal LDL cholesterol level with simvastatin plus fenofibrate. This trial will also provide information on the safety of this combination lipid-modifying therapy. Results are expected by the end of 2009.

#### Niacin

Effects on atherogenic dyslipidaemia

Niacin is the most potent agent currently available for raising HDL cholesterol (by about 20–25% with 1.5–2 g daily extended-release [ER] formulation).<sup>170,171</sup> Niacin lowers LDL cholesterol by about 10–15%, TG by about 15–25%, and lipoprotein(a), an independent predictor of CHD,<sup>172–174</sup> by about 15–20%.<sup>170,171,175–177</sup> As well, niacin raises apoA-I by about 10%.<sup>170</sup> The effects of ER niacin on the lipid profile are proportional to the dose in the range 0.5–2.0 g.<sup>170,171,175</sup>

While specific receptors for niacin<sup>178</sup> and an endogenous ligand ( $\beta$ -hydroxybutyrate)<sup>179</sup> have been identified, evidence suggests that these do not mediate the effect of niacin on HDL. The mechanistic studies that are available show that niacin reduces VLDL and LDL production,<sup>180,181</sup> as well as catabolism of apoA-I.<sup>182</sup> Furthermore, studies in animal models show that CETP is essential for the HDL-raising mechanism.<sup>183</sup> Niacin also has a number of anti-atherothrombotic effects that improve endothelial function, reduce inflammation, increase plaque stability and diminish thrombosis.<sup>184</sup> Niacin has additive effects to statins that improve LDL and HDL cholesterol and TG (table 5),<sup>185,186</sup> in line with its effects when used as monotherapy.

#### Impact on macrovascular risk

The Coronary Drug Project remains the only randomised controlled trial of niacin monotherapy for coronary prevention. In 1,119 men with previous MI randomised to niacin treatment (immediate-release formulation), there was significant reduction in coronary death or non-fatal MI by 14% ( $p < 0.05$ ) at five years, when the trial ended.<sup>151</sup> Extended follow-up for mortality showed that the niacin group experienced an 11% reduction in all-cause mortality ( $p = 0.0004$ ), mainly due to a reduction in CHD mortality (by 12%,  $p = 0.005$ ).<sup>187</sup> The benefits of treatment on risk for mortality were also evident across the range of fasting blood glucose values, including values  $\geq 126$  mg/dL (6.93 mmol/L), i.e. in the diabetic range.<sup>188</sup> Angiographic imaging studies also showed that niacin treatment, combined with colestipol as in the Familial Atherosclerosis Treatment Study (FATS)<sup>189</sup> or with a statin in the HDL-Atherosclerosis Treatment Study (HATS),<sup>190</sup> slowed coronary atherosclerosis progression compared with placebo. It is, however, acknowledged that both were small trials and neither study had a statin monotherapy arm for comparison.

#### Safety considerations

Flushing, a common problem, impacts substantially on patient acceptability and adherence, and is a common reason why clinicians may not even consider use of niacin.<sup>191,192</sup> This effect can be ameliorated by aspirin (325 mg twice daily), started the day before the first dose of niacin and continued for the first month or until the full dose of niacin is achieved. Additionally, a recent approach to counter this problem has been to combine ER niacin with laropiprant, an inhibitor of the prostaglandin D<sub>2</sub> receptor, which is implicated in the flushing response.<sup>193</sup> In clinical studies in patients with mixed dyslipidaemia, the combination of laropiprant and ER niacin led to significantly less – and less severe – flushing at treatment initiation and during maintenance therapy.<sup>194</sup> However, the long-term safety of laropiprant combined with niacin has yet to be established. This combination product has been approved for treatment of dyslipidaemia or primary hypercholesterolaemia in Europe, although in the US, the FDA has recently issued a non-approvable letter in response to the new drug application for this product.

Niacin also increases blood glucose by reducing insulin sensitivity, although clinical studies showed that increases in blood glucose observed in individual patients were readily remedied by adjustments of glucose-lowering therapy.<sup>195</sup>

More infrequently, elevated liver function enzymes, increases in uric acid and/or precipitation of gout have been reported with niacin treatment.<sup>192</sup> New-onset diabetes may occur after initiation of niacin therapy in people with metabolic syndrome, particularly if they have impaired glucose tolerance.<sup>196</sup> The risk for such occurrence is unclear at present and will be further evaluated by ongoing studies.

Evidence that combination niacin-statin therapy improves lipids,<sup>186</sup> together with outcomes data from the Coronary Drug Project,<sup>151,187,188</sup> suggest the potential for additional clinical benefit with this combination therapy. Clearly there is a need for outcomes studies, and two ongoing randomised controlled trials with hard clinical end points are addressing this issue. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial is comparing ER niacin combined with simvastatin to simvastatin alone in about 3,300 patients with established vascular disease and atherogenic dyslipidaemia.<sup>197</sup> The other trial, Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) is comparing the combination of ER niacin/laropiprant with placebo in about 20,000 patients with a history of MI, stroke or peripheral arterial disease and whose LDL cholesterol levels are optimised with statin therapy.<sup>198</sup> Results from these two studies are expected in 2011 and 2012, respectively.

#### *Omega-3 fatty acids*

##### Effects on atherogenic dyslipidaemia

Omega-3 fatty acids (containing 20-carbon eicosapentaenoic acid, EPA and 22-carbon docosahexaenoic acid, DHA) lower elevated TG and atherogenic remnant lipoproteins associated with atherogenic dyslipidaemia.<sup>199,200</sup> Clinical trial evidence supportive of their protective effects on CVD has been attributed to a variety of mechanisms, including reduction in TG, mild increases in HDL cholesterol, reduction in blood pressure, changes in the metabolism and expression of adhesion molecules, activation of PPAR $\alpha$ ,<sup>201</sup> reduction in pro-atherogenic cytokines, interference with arachidonic acid metabolism, as well as a direct effect on cardiac myocytes to raise the threshold for ventricular arrhythmia.<sup>202</sup> A prescription formulation (at least 0.9 g of omega-3 fatty acids per 1 g capsule vs. 0.2 to 0.5 g in over-the-counter supplements) is now available in the US for use in patients with markedly elevated TG 5.645 mmol/L ( $\geq 500$  mg/dL). In Europe, the prescription formulation is also indicated as adjuvant treatment for secondary prevention after MI.<sup>203</sup> Lipid-modifying benefits have been observed when added to statin therapy (table 5).<sup>204</sup>

##### Impact on macrovascular risk

Large clinical trials provide support that supplementation with omega-3 fatty acids (EPA/DHA) as part of a Mediterranean diet,<sup>99</sup> or at a dose of 1 g/day,<sup>100,101</sup> has beneficial effects on clinical outcomes, including major cardiac events and sudden cardiac death. These may relate more to effects on cardiac rhythm than to effects on lipids or blood pressure.<sup>205,206</sup> The Japan EPA lipid intervention study (JELIS)<sup>207</sup> is supportive of the premise that the combination of

omega-3 fatty acids and a statin may improve lipids and may provide additional clinical benefit. EPA supplementation (1,800 mg daily) combined with low-dose statin therapy (pravastatin 10 mg or simvastatin 5 mg daily) compared with statin monotherapy reduced major coronary events without altering rates of sudden cardiac death. Although TG levels decreased by 9% in the EPA group (vs. 4% in controls), there were no effects on total, LDL or HDL cholesterol in either group. Clearly, there is a need for further outcomes studies. Furthermore, it should be noted that the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) study<sup>208</sup> has recently reported that supplementation with omega-3 fatty acids (1 g daily) can provide a small but significant beneficial prognostic advantage (vs. placebo) in terms of mortality (adjusted HR 0.91, 95.5% CI 0.833–0.998,  $p=0.041$ ) and admission to hospital for cardiovascular reasons (adjusted HR 0.92, 99% CI 0.849–0.999,  $p=0.009$ ) in patients with heart failure.

Established diabetes treatments, including the thiazolidinediones rosiglitazone and pioglitazone (both of which are PPAR $\gamma$  agonists) and metformin, have varying effects on lipids and lipoproteins. While pioglitazone and rosiglitazone have similar effects on insulin sensitivity and inflammation, they differ in their effects on lipids. Pioglitazone lowers TG by about 15–20%, raises HDL cholesterol by 10–13% and has a negligible effect on LDL cholesterol (either no change or an increase by 5%), whereas rosiglitazone may raise TG by 10–20%, and raise HDL cholesterol by 5–7% and LDL cholesterol by 5–20%.<sup>209</sup> Meta-analyses of clinical trials indicate that metformin treatment results in a decrease in LDL cholesterol and TG, each of about 10 mg/dL, compared with second generation sulphonylureas, with minimal or no effect on HDL cholesterol.<sup>210</sup>

While pioglitazone treatment has been associated with reduction in hard clinical end points in high-risk patients with type 2 diabetes,<sup>211,212</sup> considerable uncertainty remains regarding the aggregate CVD effects of the PPAR $\gamma$  agonists, and data are awaited from further prospective trials. Similarly, several dual PPAR $\alpha/\gamma$  agonists have been discontinued in mid-to-late clinical development because of an excess of heart failure and other CVD events attributed to the PPAR $\gamma$  component.

### Innovative therapy

PPAR $\beta/\delta$  agonists may be of interest in the treatment of the metabolic syndrome, given their effects on lipoprotein metabolism (raising HDL cholesterol and lowering LDL cholesterol and VLDL-TG), and in reducing vascular inflammation and regulating glucose homeostasis in different animal models.<sup>140</sup> Future approaches are aimed at the development of selective PPAR modulators (SPPARMs) with tissue- and target gene-selective activities, with a focus on the development of dual PPAR $\alpha/\gamma$  and PPAR $\alpha/\delta$  agonists as these may offer potential for management of cardiometabolic risk.

Inhibitors of CETP, which promotes the transfer of cholesterol in the plasma from the HDL lipoprotein fraction to the pro-atherogenic LDL lipoprotein fraction, as well as the transfer of TG from the latter to the HDL lipoproteins, have been investigated in the clinical setting. Torcetrapib, the first

of these, was terminated due to significant excess of mortality (HR 1.58, 95% CI 1.14 to 2.19,  $p=0.0006$ ) and cardiovascular events (HR 1.25; 95% CI 1.09 to 1.44,  $p=0.001$ ) in patients treated with torcetrapib plus atorvastatin (vs. atorvastatin alone) in the Investigation of Lipid Level Management to Understand its Impact on Atherosclerotic Events (ILLUMINATE) trial.<sup>213</sup> This was despite substantial elevation in HDL cholesterol levels (by 72%). Whether the problem stemmed from an idiosyncratic effect on the renin-angiotensin aldosterone system<sup>213</sup> or from CETP inhibition itself remains unclear. Ongoing clinical development with other CETP inhibitors is continuing, although clinical outcomes data are not expected until 2011 or beyond.

Selective endocannabinoid type 1 receptor blockers (reverse agonists) raise HDL cholesterol levels, lower TG and reduce body weight, as well as improving insulin sensitivity and HbA $_{1C}$ <sup>214-216</sup> to a modest degree. The first of this class, rimonabant, was investigated for effects on coronary atherosclerosis progression in STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant – The Intravascular Ultrasound Study). At 18 months, rimonabant treatment failed to impact on the primary end point (increase in percent atheroma volume by 0.25% vs. 0.51% on placebo,  $p=0.22$ ), although a secondary angiographic outcome (change in total atheroma volume) was significantly improved ( $p=0.03$ ).<sup>217</sup> Concerns have been raised about the increased risk of neurological and psychiatric adverse events with rimonabant,<sup>218</sup> which prevented its approval in the US. In Europe, rimonabant is available for use in obese patients (BMI  $\geq 30$  kg/m<sup>2</sup>) or in those who are overweight (BMI  $\geq 27$  kg/m<sup>2</sup>) with other cardiovascular risk factors. Treatment is contraindicated in patients with ongoing major depression or those taking antidepressants, and should be stopped if depression develops. These data highlight the need for more extensive long-term safety evaluation of agents in this class.

### Reducing residual microvascular risk – does lipid-modifying therapy have a role?

Lifestyle intervention, a healthy diet, weight loss and increased physical activity are integral to type 2 diabetes management in order to improve glycaemia, dyslipidaemia and blood pressure.<sup>219</sup> Despite this, patients remain at risk of microvascular complications. The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial<sup>220</sup> showed that intensive glycaemic control (6.5% vs. 7.3% with conventional control) did reduce the incidence of combined microvascular and major macrovascular events by 10%. This was predominantly due to a significant reduction in the development of microalbuminuria (19.6% vs. 23.6% with conventional control, reduction in RR 21%, 95% CI 14–27%,  $p<0.0001$ ). However, there was no significant benefit on retinopathy. Intensive blood-pressure lowering did not reduce the overall risk of microvascular events (relative risk reduction 9%,  $p=0.16$ ).<sup>221</sup> Added to this, interim analysis of the ACCORD study reported increased mortality (increase in risk by 22%,  $p=0.04$ ) associated with intensive glycaemic control (lowering HbA $_{1C}$  to a median of 6.4% vs. 7.5% with

**Table 6. Summary of key effects of fenofibrate on retinopathy in the FIELD study<sup>231</sup>****Main study (n=9,795)**

- ↓ First laser treatment (tertiary end point)
  - Overall by 31% (4.9% with placebo vs. 3.4% with fenofibrate, ARR 1.5%, p=0.0002)
  - For macular oedema, by 31% (3.4% vs. 2.4%, ARR 1.0%, p=0.002)
  - For proliferative retinopathy, by 30% (2.2% vs. 1.5%, ARR 0.7%, p=0.015)
  - Greater benefit (↓ by 39%) in patients without pre-existing retinopathy (2.8% vs. 1.7%, ARR 1.1%, p=0.0008)

**Ophthalmology substudy (n=1,012)**

2-step progression of retinopathy on ETDRS scale (primary end point)

- ↓ by 22% (12.3% vs. 9.6%, ARR 2.7%, p=0.19) in all patients
- ↓ by 79% (14.6% vs. 3.1%, ARR 11.5%, p=0.004) in patients with pre-existing retinopathy

**Composite outcome\***

- ↓ by 31% (16.1% vs. 11.1%, ARR 5.0%, p=0.022) in all patients

**Key:** \* Composite outcome defined as any of 2-step progression of retinopathy grade, macular oedema or laser treatment (either eye); ETDRS = Early Treatment Diabetic Retinopathy Study criteria  
Data are given as relative risk reduction (event rate and absolute risk reduction, ARR).

conventional control), leading to early termination of this treatment arm after a mean of 3.5 years' follow-up. ACCORD also showed no significant benefit on the primary outcome (non-fatal MI, non-fatal stroke or death due to cardiovascular causes, RR 10%, p=0.16) in this high-risk patient population.<sup>222</sup> Attention has therefore increasingly focused on the possible role of other pharmacological interventions, including lipid-modifying therapy, to reduce this residual risk of microvascular complications.

**Diabetic nephropathy**

A large body of evidence supports the benefits of statin therapy in reducing the rate of decline in renal function,<sup>223-225</sup> and improving albuminuria in people with baseline excretion > 30 mg/day.<sup>226</sup> Statin-related improvement in estimated glomerular filtration rate was significantly greater in patients treated with atorvastatin 80 mg than 10 mg daily.<sup>227</sup> As well, treatment with gemfibrozil or fenofibrate has been shown to reduce the progression of microalbuminuria.<sup>139,168,228</sup> In the FIELD study, fenofibrate treatment led to reduction in the progression of albuminuria (14% less progression and 15% more regression of albuminuria compared with placebo, p=0.002); however, fenofibrate was also associated with a significant, although reversible, increase in serum creatinine (see previous discussion).<sup>139</sup>

**Diabetic retinopathy**

Evaluation of the effect of statin therapy on diabetic

retinopathy has so far proved inconclusive. The Collaborative Atorvastatin Diabetes Study (CARDS), a primary prevention study in patients with type 2 diabetes, showed no evidence of significant benefit on the progression of diabetic retinopathy with atorvastatin.<sup>229</sup> Several small studies have indicated regression and reduction in the severity of macular exudates associated with statin therapy.<sup>63,230</sup>

The FIELD study showed that fenofibrate had significant preventive effects on the development of diabetic retinopathy, reducing laser treatment (a pre-defined tertiary end point) by 31% (p=0.0003).<sup>139</sup> These data were analysed further following independent confirmation of the requirement for laser therapy and showed significant benefits in both macular oedema and proliferative retinopathy (table 6).<sup>231</sup> As well, the FIELD ophthalmology substudy (n=1,012), in which retinal photographs were assessed using ETDRS grading criteria, provided some information on the effects of fenofibrate on retinopathy progression (table 6).<sup>231</sup> The mechanism(s) of these effects do not seem related to lipid levels, as there were no differences in baseline lipid values between the group of patients who underwent laser therapy and the group who did not.<sup>231</sup> While there were a number of limitations to these findings,<sup>232</sup> notably the absence of retinal photography at baseline in the main study to establish the extent of pre-existing retinopathy, the small numbers of events in both main and substudy, and lack of an established biological mechanism, the weight of evidence supports a beneficial role for fenofibrate treatment, especially at the very early, often asymptomatic stages of this complication.<sup>233</sup> Findings are awaited from the ACCORD-EYE substudy, which is evaluating the effects of intensive glycaemic control, intensive blood pressure lowering and the combination of fenofibrate plus simvastatin on the prevention and progression of diabetic retinopathy, to confirm these findings.<sup>234</sup>

**Diabetic neuropathy and amputation**

Studies suggest that lipid-modifying treatment may have beneficial effects on neurovascular function and diabetic neuropathy.<sup>235-238</sup> Preliminary observational data based on a longitudinal subgroup of 531 subjects with type 2 diabetes in the Fremantle Diabetes Study showed that statin use (HR 0.65, 95% CI 0.46-0.93) or fibrate use (HR 0.52, 95% CI 0.27-0.98) were significant inverse determinants of incident diabetic neuropathy (p<0.05).<sup>239</sup> However, the STENO-2 study showed that intensive multifactorial intervention (including widespread use of statin therapy) failed to prevent the development or progression of peripheral neuropathy.<sup>13</sup> On the whole, clinical data are limited. Treatment with omega-3 supplements (EPA 1,800 mg/day for 48 weeks) had beneficial effects on diabetic peripheral neuropathy, assessed clinically and by vibration perception threshold sense of the lower extremities.<sup>240</sup> The FIELD study also showed that fenofibrate reduced the number of lower-extremity non-traumatic amputations (a pre-specified tertiary outcome) compared with placebo (38%, p=0.011).<sup>241</sup>

**Addressing the problem: a call to action to reduce residual vascular risk**

This position paper highlights atherogenic dyslipidaemia as a

**Table 7. Recommendations of the R<sup>3</sup>i to improve management of residual vascular risk**

- Initiate lifestyle modification as a first step
- Improve achievement of lipid goals if needed. Addition of a fibrate, niacin or omega-3 fatty acids to statin therapy may be useful. However, outcomes studies are still needed for these combinations compared with statin alone
- Normalise glycosylated haemoglobin (HbA<sub>1c</sub>) and blood pressure
- Intervene earlier in the disease process with lifestyle modification and drug therapy

key factor associated with residual macrovascular risk in dyslipidaemic patients, including those receiving therapy for high LDL cholesterol and for diabetes in accordance with current standards of care. Atherogenic dyslipidaemia is also implicated in the pathogenesis of microvascular residual risk in diabetes patients.

To address the challenge posed by the global epidemics of obesity, metabolic syndrome, and type 2 diabetes, the R<sup>3</sup>i emphasises the need for education and communication to increase awareness of the extent and importance of atherogenic dyslipidaemia to residual vascular risk. Lifestyle modification is an important, effective and underutilised first step in reducing this risk. Intervention with pharmacotherapy aimed at achievement of all lipid targets is also likely to be required (table 7). Three major studies, ACCORD, AIM-HIGH and HPS2-THRIVE, will provide crucial information regarding the use of combination lipid-altering treatments.

#### Conflict of interest statements

J-CF has received advisory board honoraria from Solvay. Honoraria as a member of the speakers' bureau/consultant for Solvay, AstraZeneca, Sanofi-Aventis, Kowa Company Ltd. Cofounder and President of the supervisory Board of Genfit.

FMS has received research support from ISIS, and honoraria for consultancy to Abbott, Aegerion, AstraZeneca, Genzyme, ISIS, Lilly, Lipid Sciences, Merck, and Solvay. He has received honoraria for lectures from WebMD, Abbott and Solvay. He is a shareholder of Lipid Science.

MPH has served on an advisory panel and/or received honoraria and/or scientific or travel grants from AstraZeneca, Bayer, Covance, Danone, Fournier, E Lilly, Solvay Pharma, GSK, LifeScan, Lipha, Medtronic-Minimed, Menarini, MSD, MSH, NovoNordisk, Nycomed, Pfizer, Roche, Sanofi-Aventis, Servier and Solvay.

GA has received advisory board honoraria from Solvay.

WVB has received research grants from AstraZeneca, Abbott and Lilly, and honoraria for speaking or consulting from AstraZeneca, Abbott, Amgen, Glaxo SmithKline, Lilly, Merck, Merck-Schering Plough, Pfizer, Sanofi-Aventis and Solvay.

MJC has received research funding from Merck, Pfizer and AstraZeneca, and has received sponsorship for presentation of educational conferences from these same companies.

PMD has received honoraria for advisory board mem-

bership from Pfizer, AstraZeneca, Takeda and Solvay, and research grants from Eli Lilly.

HNG has received honoraria for speaking or consulting from Merck, Schering Plough, Astra Zeneca, Pfizer, Takeda, Reliant, Glaxo SmithKline, ISIS, Sanofi-Aventis, and research support from ISIS, Takeda, Sanofi-Aventis and Reliant.

J-ML has received honoraria from AstraZeneca, MSD Schering Plough, Novartis, Pfizer and Solvay.

NM has received research grants from Glaxo SmithKline, Takeda, Boehringer Ingelheim, Novartis, MSD, and honoraria for advisory board membership from Glaxo SmithKline, Boehringer Ingelheim, NovoNordisk, MSD, Sankyo, and for speaking from Glaxo SmithKline, Takeda, Boehringer Ingelheim, BerlinChemie and MSD.

JP has received honoraria for consultancy from Dainippon Sumitomo America, Inc., Glaxo SmithKline, NovoNordisk, ONO Pharmaceuticals, Sanofi-Aventis and Takeda, and for speaking from Takeda.

ZR has received honoraria from MSD, Merck, Schering-Plough, GSK, Pfizer, Novartis, Solvay, Krka and Menarini.

RSR has received funding from Abbott Laboratories Inc., Anthera, Inc. and AstraZeneca Inc.(research grant) and he serves on the speaker's bureau and receives honoraria payments from Abbott and AstraZeneca, Inc. He has ownership interest and serves as a consultant/advisory board for LipoScience.

BS has received honoraria for lectures from Solvay.

RS has received research grants from Fournier Philippines, Pfizer Philippines and Takeda Philippines and honoraria for speaking from MSD, Novartis, Pfizer, Therapharma, Sanofi-Aventis and Solvay.

AZ has received honoraria for speaking from Solvay and AstraZeneca.

PZ has received honoraria from Bayer, Bristol-Myers Squibb, Glaxo SmithKline, Sanofi-Aventis, Solvay, Fournier, Novartis, Lilly and Merck Serono.

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