

Residual vascular risk: A major challenge for healthcare in the 21st century

Why is residual vascular risk important?

In the last 20 years, research has identified dyslipidemia, high blood pressure and, in people with diabetes, raised blood sugar (hyperglycemia) as the major modifiable risk factors associated with cardiovascular disease (CVD). Dyslipidemia alone is responsible for 54% of population-attributable risk for heart attack, as shown in the INTERHEART study.¹ Reducing dyslipidemia-related CV risk is therefore an important treatment goal.

Current treatment guidelines for dyslipidemia focus on reducing low-density lipoprotein cholesterol (LDL-C), with high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) considered secondary targets. However, a growing body of evidence suggests that LDL-C-based treatment does not sufficiently address the residual risk (both macro- and micro-vascular), that remains despite optimal LDL-C treatment in accordance with current standards of care.

What causes macrovascular residual risk?

LDL-C, an important component of macrovascular risk, is markedly and consistently reduced by statins, leading to a significant reduction in the risk of major vascular events. However, data from large prospective, well-controlled, clinical trials show that statins, even at high doses, only reduce the risk of heart attack by about one-third.² A meta-analysis of 14 statin trials made up of 90,056 patients found that despite statin treatment, there was still a 77% residual risk of cardiovascular events.³ Further lowering of LDL-C with maximal statin doses reduced but did not eliminate residual vascular risk (Figure 1).⁴

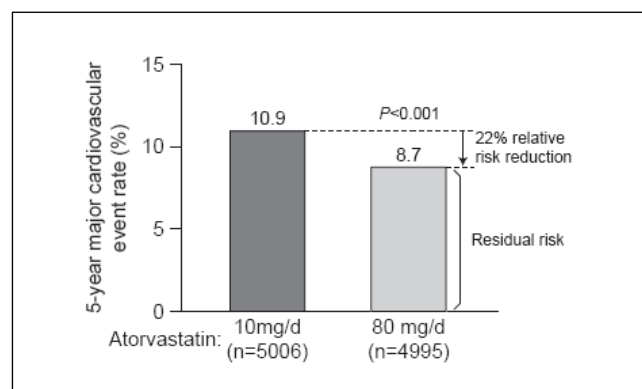


Figure 1. Cardiovascular residual risk persists even with maximum-dose atorvastatin (80 mg). Data from the TNT study⁴.

Atherogenic dyslipidemia, characterized by elevated TG and a low plasma concentration of HDL-C is prevalent in patients with type 2 diabetes, metabolic syndrome and/or established cardiovascular disease (CVD).^{5,6} Atherogenic dyslipidemia increases the risk of macro- and microvascular events. In the German PROspective Cardiovascular Münster (PROCAM) study, one in seven patients with atherogenic dyslipidemia experienced myocardial infarction (MI) (Table 1).⁷

	Incidence of MI in patients with TC/HDL-C >5.0 (%)
HDL-C ≥ 35 mg/dL + TG <150 mg/dL	8.3
HDL-C < 35 mg/dL + TG <150 mg/dL	10.0
HDL-C ≥ 35 mg/dL + TG ≥ 200 mg/dL	9.6
HDL-C < 35 mg/dL + TG ≥ 200 mg/dL	15.0

Table 1. The combination of low HDL-C and TG increases the risk of myocardial infarction. Data from the PROCAM study⁷.

Low HDL-C and elevated TG are each associated with increased cardiovascular risk independently of LDL-C. Because statins primarily address LDL-C, they do not sufficiently address TG and HDL-C, leaving patients at residual vascular risk.⁸⁻¹¹

Even in patients with very low LDL-C (less than 70 mg/dL) on high-dose statin, HDL-C remains an important determinant of cardiovascular risk. In the TNT trial, subjects with the highest levels of HDL-C had a 39% lower risk of incident CVD compared to those with the lowest levels (Figure 2).⁴ There is therefore an HDL-C associated residual vascular risk that is not adequately addressed by statin treatment.

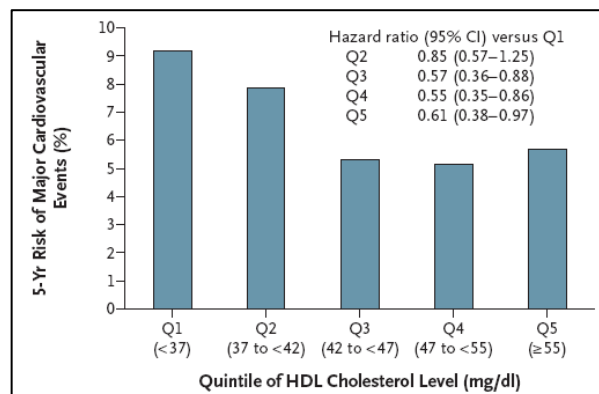


Figure 2. Low HDL-C increases the risk of major cardiovascular events in patients with LDL-C <70 mg/dL. Data from the TNT study⁴.

Additionally, reduced TG levels are independently associated with a lower risk of recurrent coronary heart disease events following acute coronary syndrome (ACS). Even in statin-treated patients with very low LDL-C levels (<70 mg/dL), elevated TG (>200 mg/dL) significantly increased the risk of death, MI or further ACS by 56%.¹²

What causes microvascular residual risk?

Although not typically life-threatening, microvascular complications can have devastating effects on patients' health and well-being. Diabetic retinopathy (diabetic eye disease) is the number one cause of blindness in working-age adults, diabetic nephropathy is the primary cause of end-stage renal disease and diabetic neuropathy can lead to lower-limb amputation.¹³

Despite the impact of microvascular consequences on patients' lives, the mechanism remains unclear, although low HDL-C and high TG appear to contribute.^{5,14,15}

No clear effect of statin treatment on retinopathy has been shown and the evidence for reduction of neuropathy is limited.¹⁶⁻¹⁸ Statin therapy has been shown to reduce the rate of decline in renal function, and improve albuminuria in people with baseline excretion >30 mg/day, with greater benefits conferred by higher doses.^{17, 19-22}

Blood pressure and glycemic control have both been implicated in the development of microvascular complications although results are not consistent. In the United Kingdom Prospective Diabetes Study (UKPDS), a large prospective study in patients with newly-diagnosed type 2 diabetes, tight blood pressure control (<150/85 mmHg) resulted in a 47% reduction in loss of visual acuity (p=0.0004), with no difference in the risk of neuropathy or renal disease.²³ However, the recent Action in Diabetes and Vascular Disease (ADVANCE) study did not confirm these results: aggressive blood pressure reduction had no significant effect on the risk of microvascular events.²⁴ Even more recently, DIRECT-Protect 2 showed that blockade of the renin-angiotensin system (RAS) with candesartan did not significantly reduce progression of diabetic retinopathy in patients with type 2 diabetes.²⁵

In UKPDS, each 1% reduction in HbA_{1c} (a validated marker of recent glycemic exposure) was associated with a 37% reduction in microvascular endpoints (retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or non-fatal renal failure).²⁶ By contrast, the ADVANCE study showed a 21% reduction in nephropathy but no significant effect on retinopathy in intensive glycemic-control patients (HbA_{1c} <6.5%).²⁴

Even intensified, target-driven therapy involving a combination of medications and focused behavior modification did not significantly prevent the progression of microvascular disease in a majority of patients.^{27, 28} The STENO-2 study showed that despite almost 8 years of intensive multifactorial treatment, retinopathy developed or

progressed in almost half of patients (Figure 3).³ This and other microvascular complications continued to worsen over time.^{27, 28}

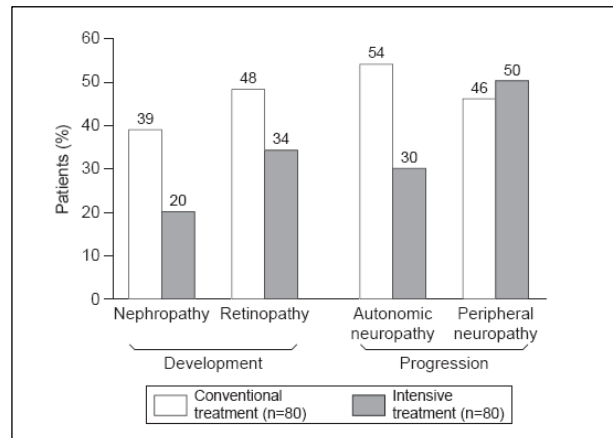


Figure 3. The STENO-2 trial 8-year follow-up³

These studies indicate that additional intervention beyond LDL-C reduction and control of blood pressure and glycemia is still needed to reduce residual vascular risk.

What can be done to address residual vascular risk?

Although great strides have been made in the management of macro- and microvascular risk factors, the current unidirectional focus on LDL-C lowering does not go far enough. Atherogenic dyslipidemia cannot efficiently be treated with statins and so there remains a substantial risk of cardiovascular events. Indeed, up to 50% of adults with CVD, diabetes or the metabolic syndrome have elevated TG or low HDL-C.²⁹

Large ongoing studies are evaluating whether a combination of lipid-modifying treatments that addresses all three lipid parameters (LDL-C, HDL-C and TG) can reduce residual vascular risk compared to statin monotherapy.³⁰⁻³²

The Residual Risk Reduction initiative (R³i) seeks to draw attention to unaddressed lipid-related residual vascular risk and to encourage the development of improved treatment strategies.

Further information on residual vascular risk can be obtained from the R³i website, www.r3i.org.

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