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AMPATHCHAT

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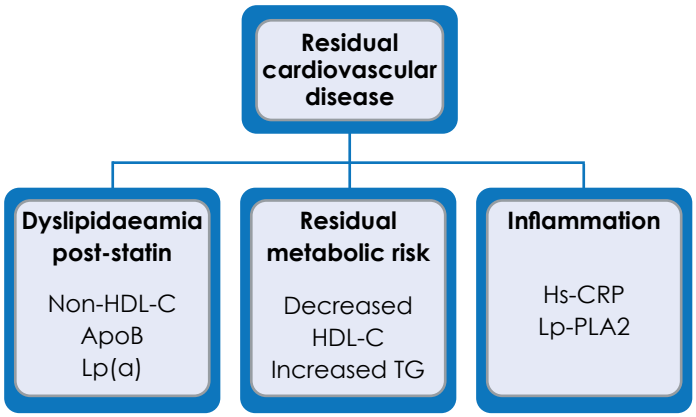
Residual cardiovascular risk factors

The management of cardiovascular disease has seen unprecedented progress in previous decades. Critical advancements have been made in the recognition and treatment of major traditional risk factors, including dyslipidaemia, high blood pressure, hyperglycaemia, inflammation and unhealthy lifestyle for atherosclerotic cardiovascular disease (ASCVD); among them, elevated low-density lipoprotein-cholesterol (LDL-C) levels, one of the principal drivers of atherosclerosis. An LDL-centric approach to risk reduction, namely with statins, has served as the foundation for primary and secondary prevention for decades and has led to a significant improvement in cardiovascular outcomes. Despite clear guidelines, many patients on statins fail to attain the therapeutic target levels, leading to the concept of "residual cardiovascular risk"[1].

Residual cardiovascular risk (RCVR) is defined as the residual risk of incident vascular damage events or the progression of established vascular damage that persists in patients treated with the current evidenced-based recommended care[2]. Although lowering of LDL-C levels is the cornerstone of cardiovascular risk reduction, there are a myriad of other drivers of residual risk that are not directly addressed through current management strategies (Figure 1).

Figure 1: Residual cardiovascular disease causes



Dyslipidaemia post-statin treatment

Patients on statins have relative cardiovascular (CV) risk reduction of approximately 25–35%, depending on the baseline level of risk. The addition of further drugs or the use of high-dose statin therapy allows further CV risk reduction, but leaves out considerable lipid-related RCVR due to abnormal non-LDL-C constituents, which do not respond to, or are only slightly improved by, statins[2].

Atherogenic markers

Non-high-density lipoprotein and apolipoprotein B (ApoB)

Non-HDL cholesterol (non-HDL-C) is total cholesterol (TC) less HDL-C. It provides an estimation of the total number of atherogenic particles in plasma, including ApoB-containing lipoproteins such as LDL, very low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and lipoprotein(a)[3]. ApoB is a major structural protein on the surface of a heterogeneous pool of atherogenic lipoproteins with varying content of cholesterol and triglycerides (TG) and relates to non-HDL-C with the concentration of atherogenic lipoproteins[3].

A study by Johannesen et al. demonstrated that elevated ApoB and non-HDL-C, but not LDL-C, are associated with residual risk of all-cause mortality and myocardial infarction in patients on statin treatment[4]. The postulated mechanism is that cholesterol within every ApoB particle is atherogenic and that assessing only LDL-C overlooks the atherogenic potential of the remaining ApoB particles[4]. The study also demonstrated that ApoB is a more accurate marker of all-cause mortality risk in statin-treated patients than LDL-C or non-HDL-C, and, additionally, that ApoB is a more accurate marker of risk of myocardial infarction than LDL-C[4].

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Lipoprotein(a)

Lipoprotein(a) (Lp(a)) is a LDL-like molecule consisting of an apolipoprotein B-100 (apo B-100) particle attached by a disulphide bridge to apolipoprotein(a). Increased levels of Lp(a) confer an increased risk for cardiovascular disease (CVD) via prothrombotic/anti-fibrinolytic effects as apolipoprotein(a) possesses structural homology with plasminogen and plasmin, but has no fibrinolytic activity; or via accelerated atherogenesis as a result of intimal deposition of Lp(a) cholesterol[5].

A sub-analysis from *Justification for the Use of statin in Prevention: An Intervention Trial Evaluating Rosuvastatin* (JUPITER) demonstrated that Lp(a) was a strong predictor of residual risk in patients already on a statin (adjusted HR 1.27; 95% CI 1.01–1.59, p = 0.04), independent of LDL-C and other risk factors. Lp(a) measurement should be considered once in adult lifetime as per the European Society of Cardiology / European Atherosclerosis Society (ESC/EAS) lipid treatment guidelines for the management of dyslipidaemias[5].

Residual metabolic risk

Atherogenic dyslipidaemia (AD) is the prevalent form of non-LDL-C dyslipidaemia characterised by the presence of decreased HDL-C and high-fasting TG levels commonly noted in patients with diabetes mellitus or metabolic syndrome[2,6]. The *REsiduAl risk, LIpids and Standard Therapies* (REALIST) macrovascular study has demonstrated that the combination of elevated TG (≥ 2.15 mmol/l) and low HDL-C (< 0.77 mmol/l) contributed synergistically to increased cardiovascular risk even at LDL-C levels < 3.37 mmol/l[7]. The *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) lipid study noted that patients with Type 2 diabetes and optimally treated LDL-C levels had a 70% higher risk of developing an incident cardiovascular event when AD was present at baseline compared with those without this dyslipidaemia[8].

Inflammation

Recent studies have established a fundamental role for low-degree chronic inflammation in mediating all stages of atherosclerosis. Observational evidence has linked high sensitivity C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A2 as inflammatory biomarkers associated with risk of future vascular events[9].

High-sensitivity C-reactive protein

The hs-CRP detects small elevations of C-reactive protein (CRP) and, in addition to lipid evaluation and global risk scoring systems, helps in the evaluation of cardiovascular disease risk in an individual [9]. The levels of hs-CRP < 1, 1 to 3, and > 3 mg/l are associated with low, moderate and high cardiovascular risks, respectively[9,10].

Studies by Dai and Guedeney et al. demonstrated that baseline hs-CRP level was an independent predictor of residual risk of cardiovascular events in patients with stable CAD having achieved the therapeutic goal for LDL-C (<1.8 mmol/l) after three months of optimal medical treatment[11,12].

Lipoprotein-associated phospholipase A_2

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is an enzyme that is produced by inflammatory cells and co-travels with circulating low-density lipoprotein (LDL). Its enzyme activity is concentrated within the atherogenic small, dense LDL particle. Evidence demonstrates that its contribution to atherogenesis is by producing pro-inflammatory and pro-apoptotic mediators within atherosclerotic plaques. Lp-PLA_2 reflects the presence of rupture-prone plaques, which makes it more specific for the vascular inflammation associated with CVD[13].

The Lp-PLA_2 measurement has been advocated to be an adjunct marker to other traditional markers for cardiovascular risk stratification by the consensus expert panel[14]. The panel also recommends that Lp-PLA_2 testing be performed in patients who are at moderate and high risk, and who will benefit from more aggressive lifestyle changes and lipid-modifying therapies.

Lp-PLA_2 values < 200 ng/ml requires no risk adjustment, whereas with values > 200 ng/ml, a patient's risk status is adjusted to high risk or very high risk, with LDL-C targets being adjusted to 2.5 mmol/l and 1.8 mmol/l respectively[15]. Identification and treatment of residual cardiovascular risk is critical to optimise patient outcomes, particularly in those at risk for recurrent events despite optimal treatment of traditional risk factors.

Apolipoprotein B (APOB), lipoprotein(a) (APOA) and hs-CRP (HSCRP) testing are all available at Ampath. We plan to offer Lp-PLA_2 in the near future.

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