COMMENTARY

Commentary on High-density Lipoprotein *Versus* Low-density Lipoprotein Therapy and Cardiovascular Outcomes in Patients with Acute Coronary Syndromes by Nikolaos Papageorgiou *et al.*

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COMMENT

Understanding atherosclerosis and its prevention remain high on the agenda of those interested in population health and those with the disease [1]. We know that the atherosclerosis plaque has at its core cholesterol deposits and that high serum cholesterol as found in Familial hypercholesterolaemia results in devastating early atherosclerosis and resultant myocardial infarction [2]. Separation of lipoproteins into various densities made it possible to investigate particle composition and the atherogenicity of the various particles. The lipoproteins apo B48 and B100 define the pro-atherogenic particles and apo A1 /A2 define the athero-protective lipoproteins. Excess dietary cholesterol was thought to be an important player in atherosclerosis and many important societies made recommendations to limit weekly intake to the detriment of the hen and seafood industries. Many years ago, an elderly man who had almost normal serum cholesterol levels was described because he remained well in spite of eating 20 plus eggs a day [3]. Now even the learned societies suggest that cholesterol in the diet should not be limited [4, 5]. In a similar vein, HDL cholesterol may no longer be described as the good cholesterol and raising HDL cholesterol may not be a goal in order to defeat atherosclerosis [6]. The art of Medicine is alive and well and the physician still has the duty and right to analyse 'Consensus statements' from learned societies!

The excellent article in this journal by Nikolaos Papageorgiou *et al.* [7] well describes the present state of play in the knowledge we have about the good, the bad and the very bad lipoproteins and their treatment.

The lipoprotein particle cascade starts with the absorption of intestinally derived dietary cholesterol. The ensuing particle, the chylomicron, is defined by the solubilising lipoprotein Apo B48. It is a triglyceride-rich large particle. Apo E attaches itself to the particle. Clearance of the particle depends on the Apo E isoform. There is good evidence that these particles are atherogenic and can enter the endothelial

space to deposit cholesterol [8]. High fat intake will increase the size and number of chylomicrons. Lipoprotein lipase defects will also delay the delipidation of the particle and its clearance. The cholesterol content per particle is low compared to LDL but it has to be remembered that the circulation time for LDL is in days and chylomicron is minutes hence the cholesterol carrying capacity is similar to LDL yet the atherogenicity of the chylomicron undervalued in our opinion [9]. Apo A1 attaches itself to the chylomicron and is only released when the chylomicron is taken up through the ApoB and B/E receptors. Hence there is an inverse relationship between HDL and the Chylomicron [10, 11].

VLDL is the triglyceride-rich particle synthesised in the liver designed to transport fatty acids in the form of triglyceride to fat stores. VLDL is also a cholesterol-carrying particle which when delipidated sheds ApoE and becomes LDL. The recognition that the triglyceride-rich lipoproteins are atherogenic has resulted in the preference for using Apo B or non HDL cholesterol rather than LDL as the better marker of atherogenic risk [12]. Statins inhibit *de novo* cholesterol synthesis and will reduce serum cholesterol but through the feedback mechanism will, and do, increase cholesterol absorption [13]. Hence, the value of ezetimibe, the drug that inhibits cholesterol absorption, as an add-on therapy to a statin particularly in those patients who are high cholesterol absorbers [14].

The article by Papageorgiou *et al.* [7] describes in detail the drugs that affect triglycerides, cholesterol synthesis and absorption.

High triglycerides are usually, but not always, associated with low HDL. Some of the reasons have been given above. The difficulty in assessing individual risk of triglycerides, chylomicron and HDL is because of the interrelationship. Treatment of triglycerides will affect HDL. Indeed it would be hard to imagine how one could tease out whether the major benefit of a treatment to reduce triglyceride was due to lowering triglyceride or raising HDL. Fortunately, much help has been gained through genetic randomisation studies which define the relationship between triglycerides, HDL and atherosclerosis. For example, using this technique, Voigt *et al.* [15] examined 14 common Single Nucleotide Polymorphisms (SNP) that exclusively associate with HDL

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cholesterol and one SNP in the endothelial lipase gene. They found that some genetic mechanisms that raise HDL cholesterol do not seem to lower risk of myocardial infarction [16].

High HDL has been shown in many studies to protect subjects from cardiovascular events [17, 18]. It was logical to expect that increasing HDL by inhibiting Cholesterol Ester Transport Peptide (CETP), the protein that transfers cholesterol from HDL to LDL in exchange for triglyceride would be successful in reducing myocardial ischaemic events. The inhibitors have been alas unsuccessful in preventing cardiovascular events even though they raise HDL. The last to be disbanded was anacetrapib [17]. It did show some reduction in events but was withdrawn, presumably the manufacturers felt that the effect was too small and therefore not economical. HDL has many functions. Cholesterol transport from the macrophage in the periphery to the Liver is a major function. Raising HDL may not increase this function [19].

CONCLUSION

In conclusion, the article by Papageorgiou reviews in depth the studies that have made the treatment of dyslipidaemia such a success. There is still a long way to go. The article points the way forward in a fast moving exciting arena.

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