Exciting advances have recently been made in our understanding of the relationship between the atheroprotective activities of high density lipoprotein (HDL) and heterogeneity of HDL particles. HDL is highly heterogeneous not only in structure but also in intravascular metabolism and anti-atherogenic activity. Small dense HDL include discoid HDL but equally mature spherical HDL3 particles (hydrated density 1.125-1.21 g/ml). HDL3 are lipid-poor (<55% of total mass) and protein-rich (up to 65%). Recent evidence indicates that small dense HDL possess potent antioxidative activity which is however compromised under conditions of atherogenic dyslipidemia. Such functional HDL deficiency frequently coincides with low circulating levels of HDL cholesterol (HDL-C) and is intimately associated with alterations in HDL metabolism and structure. Formation of small, dense HDL particles with attenuated anti-atherogenic activity can be mechanistically related to HDL enrichment in triglycerides and in serum amyloid A, depletion of cholesteryl esters, covalent modification of HDL apolipoproteins and attenuated anti-atherogenic function of apolipoprotein A-I. Low circulating levels of HDL-C may therefore be associated with the defective functionality of small HDL particles of abnormal structure and composition. Deficiency of HDL particle number and function may favour accelerated atherosclerosis. Therapeutic normalisation of the quantity, quality and biological activities of HDL particles therefore represents a novel approach to attenuate atherosclerosis in dyslipidemic subjects with metabolic disease; such normalisation may potentially be achieved by efficacious raising of HDL-C levels involving use of inhibitors of cholesteryl ester transfer protein, niacin, reconstituted HDL and other agents. Induction of selective increase in the circulating concentrations of small, dense HDL3 particles possessing elevated anti-atherogenic activity may be especially promising; small, dense HDL3 particles therefore constitute a new therapeutic target in atherogenic dyslipidemia.