



## **Cardiovascular Risk Starts Before Diabetes – *New Approaches to the Problem***

People with diabetes have an elevated risk of developing and dying from cardiovascular disease and their prognosis is worse than that for cardiovascular disease alone in people without diabetes. With diabetes, people develop more severe multivessel coronary artery disease at a younger age, and they have a greater risk of heart failure after myocardial infarction, often as a consequence of previously undetected diabetic cardiomyopathy. Not all the risk can be ascribed to hyperglycaemia. Macrovascular complications remain even after long term intensive control of blood glucose though a recent paper showed that intensively treated Type 1 patients in the DCCT trial had significantly less progression of intima media thickness than the less intensively treated group.

The prevalence of the conventional major risk factors is also higher in patients with diabetes. LDL cholesterol, as expected, is a strong predictor and the value of treating patients with **low** LDL cholesterol levels with simvastatin was seen only in people with diabetes and not in those without diabetes in the Heart Protection Study. But non LDL cholesterol risk factors are also important. These include HDL cholesterol (x0.55), systolic blood pressure (x1.82), smoking (x1.4), fibrinogen (x1.75), von Willebrand factor (x1.7), Factor VIII activity (x1.58) and the leucocyte count (x1.9).

However, even with good attention to lifestyle measures, blood pressure and glycaemic control, there appears to be an increasing burden of cardiovascular disease in diabetes (13% men, 23% women) while cardiovascular disease mortality and coronary artery disease related deaths have declined in those without diabetes in developed countries. Why is this so?

**What other risk factors need to be targeted?** There are additional risk factors which will help to better define risk. The current Risk Factor Profile at The London Diabetes & Lipid Centre includes a full lipid profile and lipoproteins, fasting insulin and PA1, lipoprotein (a), hs CRP (high sensitivity C reactive protein), fibrinogen and fasting serum homocysteine.

### **Scanning for non invasive markers of atherosclerosis:**

**Carotid ultrasound:** We have been using the intima media thickness of the common carotid arteries as a surrogate marker of early atherosclerosis for over 10 years now. There is now an extensive literature on its use and it is a fully validated and accepted measure of progression and regression of atherosclerosis.

**Echocardiography:** Left ventricular hypertrophy and left ventricular dysfunction, found in between 20-30% of patients with Type 2 diabetes independent of blood pressure or use of ACE inhibitors, now appear to be more important and relevant than conventional risk factors, particularly with regard to their effects on mortality and morbidity. They identify a group of patients, often symptomless, who are at particularly high risk, as they are both adverse prognostic indicators. Documenting

blood pressure reduction is not a surrogate marker for hypertrophy regression which can only be confirmed using echocardiography.

**Coronary Calcification Score by Electron Beam CT Scanning:** Coronary calcification scores are a reliable non invasive measure of cardiovascular risk being used in high risk populations as a surrogate marker for atherosclerosis risk. The test is fast and accurate, allowing images that have great clarity and reproducibility. The calcium scores, which quantify calcium deposition in individual coronary arteries, are rated against age matched values. The only Electron Beam scanners in London are in Harley Street and Canary Wharf (European Scanning 08000 328888)

**New non-invasive techniques being developed** Plaques seen on ultrasound and calcium deposited in coronary arteries do not identify the vulnerable plaque (the one with lipid filled foam cells that is inflamed and that is likely to lead to coronary thrombosis). Two studies recently found that magnetic direct thrombus imaging (MRDTI), which uses the ability of MRI to detect deoxygenated haemoglobin paramagnetically, could identify "complicated" plaque (the vulnerable plaque containing more fatty foamy cells) in the carotid arteries of patients with cerebral ischaemia with a sensitivity of 84% and a specificity of 84%. Complicated plaque is recognised as having haemorrhaged, and has associated thrombus and surface disruption.

**Find the at risk patient earlier.** Cardiovascular risk can be identified before diabetes is diagnosed. Impaired glucose tolerance is known to be associated with an increased risk of cardiovascular disease and vascular dysfunction is already present at the time of diagnosis of diabetes. Furthermore, there is evidence for atherogenic risk factors being present before the diagnosis of diabetes. Also symptomless coronary artery disease is common in patients with type 2 diabetes and often goes undetected.

**Managing the risk early.** Delaying the onset of diabetes with lifestyle interventions and metformin have both been shown to be effective and relevant now (particularly if we follow the trend in the USA where there are 2.5% of obese children with impaired glucose tolerance). Identifying patients with established diabetes (it is estimated that 35% of patients remain undiagnosed in the community) with screening programmes in the 'at risk' population is essential. Specifically targeting the insulin resistance syndrome (detected with surrogate markers such as fasting insulin, raised triglycerides, low HDL and a high waist:hip ratio and hypertension), even in non diabetic individuals, is likely to be a major target for reducing cardiovascular disease.

Once identified, the patient at risk of early cardiovascular disease can be offered more intense management of lifestyle with lifelong follow up of abnormal metabolic variables and non invasive imaging, therapy with statins, ACE inhibitors and aggressive hypotensive management with regular monitoring to achieve regression of intima media thickening, regression of any left ventricular enlargement and reduced rate of coronary calcification score increase with time. Some but not all of these, are associated with a reduction in cardiovascular event rate.

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