EDITORIAL

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Guest editorial
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Dyslipidaemia, diet and drugs

When considering dyslipidaemia, the cardiologist's predominant concern is the relationship between serum low density lipoprotein cholesterol (LDLc) and the development of atherosclerotic cardiovascular disease (ASCVD). However, ASCVD is a multifactorial condition with its roots in our physical environment, the lifestyle we choose, our exposure to tobacco smoke, the diet to which we have become accustomed from a young age, the presence of specific morbidities: hypertension, diabetes, adiposity and elevated cholesterol levels, male sex and individual genetic propensities. Frequently these risk factors are found clustering in susceptible individuals. They ultimately find their expression as ASCVD and its complications as we age. Accepting the complexity of its origins, it is unsurprising that a multifaceted approach to the prevention of ASCVD, or its containment once it has emerged, is mandatory.

The first signs of ASCVD may be detected in the arterial walls of children and youths. This process progresses over subsequent decades, eventually resulting in myocardial infarction (MI) and stroke from around the 6th decade of life. Flowing from this concept of continuous evolution, there can be no true separation between the "primary" and "secondary" prevention of ASCVD. The 59-year-old male smoker with hypertension who is receiving effective treatment and achieving "primary" prevention goals, requires "secondary" prevention and the attainment of even more stringent treatment goals from the first day that he has his MI. None the less, the risk of a future cardiovascular event is much higher in the patient who has already experienced a cardiovascular event than in the subject who has not (yet) done so.

To complicate matters, the ideal treatment goals mandated by guidelines for various risk factors, viz. blood pressure, glycosylated haemoglobin (HbA1c) and LDLc, are uncertain. Whereas the recommended blood pressure and glycaemic goals may have been set too low until recently, successive trials of lipid-lowering agents indicate that "lower is better" and that the ideal treatment target for LDLc may lie closer to 1mmol/L than to the 1.8mmol/L currently recommended by European and South African guidelines.

While a wide variety of conditions resort under the term dyslipidaemia, in the context of ASCVD it is only LDLc which is of clinical concern. Total cholesterol, high density lipoprotein cholesterol (HDLc), the ratio of HDLc to total cholesterol, small dense LDLc, triglycerides and apolipoproteins A, B and (a) have all figured amongst others in risk factor calculations and, in certain instances, have been shown to be more highly predictive of the development of

ASCVD than LDLc. However, none of these have been shown to beneficially influence clinical outcome when altered by therapy. LDLc responds to treatment with 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) reductase inhibitors or "statins" with a near linear relationship between the extent of reduction in LDLc and the subsequent reduction in heart attack and stroke. The data from randomised clinical trials indicate that this relationship is particularly strong in patients with established ASCVD but with a lesser effect mmol for mmol change in LDLc in pre-symptomatic ("primary prevention") individuals.[1]

MANAGEMENT OF THE PATIENT WITH RISK FACTORS

Despite the greatly reduced cost of effective statin treatment which followed the release of generic brands and the demonstrated cost-effectiveness of treatment in the pre-symptomatic subject, the widespread use of statin therapy in this group is not accorded a strong recommendation. Several lifestyle changes, especially when made in conjunction with one another, may exert a potent negative effect on the development of ASCVD.[2] The correct diet, regular exercise, control of body weight, avoiding smoking and moderation of alcohol consumption should all be advised in the subject with a modest elevation in LDLc unassociated with other risk factors. Statin therapy should be prescribed to those individuals with multiple risk factors or an isolated, but more marked, elevation in LDLc. Many subjects in the pre-symptomatic group fall between these extremes and deserve meticulous assessment and careful explanation of the risks and benefits of statin treatment. In such cases the demonstration of subclinical atherosclerosis on carotid ultrasound, a high coronary artery calcium score on CT or the presence of ancillary risk factors such as high-sensitivity C-reactive protein (hs-CRP) or apolipoprotein (a) may sway the decision towards commencing treatment.

Of late, much has been made of the purported benefits of certain diets. It is very important to recognise that there is significant difficulty in conducting randomised controlled trials of food intake over a prolonged period. Such trials are plagued by poor adherence to the prescribed dietary regimen, dropout and crossover. In consequence, the scientific evidence supporting any one diet is insubstantial. The scientific basis of the current dietary guidelines recommending adherence to a low saturated fat diet have recently been criticised.[3] However, lack of convincing proof does not negate observations linking a high saturated fat diet to a higher prevalence of ASCVD and the reduction in LDLc recorded when saturated fat is reduced in the diet. The best evidence relating diet to cardiovascular outcome comes from the PREDIMED diet study[4] which found that the Mediterranean diet reduced MI, stroke and

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death from cardiovascular causes. This diet is higher in fruits, vegetables, whole grains and fatty fish and lower in red meat. Low fat or fat-free dairy products and nuts, oils or rapeseed/flaxseed margarine blends replace butter and other fats. Contrast this diet, which is largely similar to the recommendations of the American College of Cardiology/American Heart Association, with that recommended by Noakes and his associates.[5] They contend that "high fat diets have the unique ability to reverse all known coronary risk factors" and advocate the virtual elimination of carbohydrate from the diet and its substitution with saturated fat in substantial quantities. To date, there are numerous cases on record in which a marked rise in serum cholesterol has been observed, particularly in devotees of the diet who simultaneously discontinue statin treatment. Such extreme aberrations in dietary pattern are imprudent and should be discouraged, in favour of one recommended by a professional society, e.g. the MED or DASH diet.[6]

MANAGEMENT OF THE VERY HIGH RISK PATIENTS AND THOSE WITH ESTABLISHED ASCVD

A radically different approach should be adopted when dealing with very high risk patients and those with established ASCVD. Patients with type 2 diabetes, with chronic kidney injury, those who have had an MI or stroke or have peripheral vascular disease, and those with severe elevation in serum cholesterol (generally arising from a genetic tendency) each deserve to receive intensive statin therapy. In this aspect, there are transatlantic differences in guidelines' recommendations. Whereas South African[7] and European[8] guidelines advocate "treating-to-target", aiming to administer sufficiently potent statins to reduce LDLc below 1.8mmol/L, recent North American guidelines[9] recommend a "fire and forget" regimen, immediately using the highest doses of the most potent statins (atorvastatin 40 or 80mg or rosuvastatin 20 or 40mg daily) in all but the elderly without monitoring the effect on LDLc. The authors of the latter recommendation base their advice on the fact that all randomised controlled clinical trials adopted this approach without subsequent dose titration to reach a given target. This guideline has attracted much negative criticism from a number of authorities on the subject.

Unfortunately, although the use of potent statin therapy in "secondary" prevention and very high risk cases is supported by a number of randomised trial results and advocated by national and international guidelines, experience has shown that no more than half of all patients receive potent statins in the highest doses. Similarly, no more than half attain the treatment target. While the failure of effective secondary prevention with statins is in part ascribable to physician laxity, patient resistance to "high" doses and statin intolerance, certain patients are unable to reach the treatment target despite adhering to a regimen of high dose, potent statin therapy. In such cases the addition of ezetimibe could be considered. In future, it is conceivable that even more substantial reductions in LDLc may be easily achieved in the majority of patients when (and if) the proprotein convertase subtilin/kexin type 9 (PCSK9) inhibitors are approved for general use, alone or in combination with a statin.[10]

The following summarises the decision process when managing a patient with an elevated LDLc:

- Lifestyle changes should be strongly encouraged in all.
- If the patient's problem is that of the presence of risk factors alone, an initial conservative approach should be adopted, considering the introduction of small to moderate doses of statin therapy more readily in those patients with multiple risk factors.

- Although there is a lack of outcome trials to provide guidance, pre-symptomatic patients with evidence of arterial atherosclerosis probably should be treated with statins in a dose titrated upwards to achieve an LDLc below 1.8mmol/L.
- In patients with extreme elevations in LDLc, or at very high risk of a cardiovascular event (type 2 diabetes, type 1 diabetes with proteinuria or chronic kidney injury) or those who have had a cardiovascular event (whether MI, stroke or peripheral vascular disease) high-dose potent statin treatment must be initiated immediately, aiming to reduce the LDLc to below 1.8mmol/L.

The willy-nilly prescription of statins cannot be supported but when they are given to appropriate patients in appropriate doses, they contribute to curbing the major source of cardiovascular morbidity and mortality, without producing significant side-effects.

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