

The management of special patient populations

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It is now possible to modify dramatically risk factors that contribute to atherogenesis as well as morbidity and mortality. This has raised a number of crucial questions, such as how early should risk factor modification be started both before and after clinical presentation of atherosclerosis, and how low should risk factor targets be to obtain the best event reduction. Recent and ongoing clinical studies are starting to provide answers to these questions. Risk factors are known to interact to affect cardiovascular outcome, and recent data in high-risk populations have shown the importance of targeting blood pressure and low-density lipoprotein cholesterol, with increased benefit from lowering levels to below the targets that are currently accepted. In addition to more active treatment of high-risk groups, attention should be directed at the impact of risk factors on atherogenesis and eventual clinical complications in the pre-clinical population. This ‘investment’

component of risk factor modification is largely ignored in current risk reduction strategies. In the individual at average risk, optimal life prolongation without clinical events may require initiation of therapy in middle age (40–45 years) rather than waiting for high absolute risk in older patients. In order to optimize coronary event reduction, a rational approach to risk factor modification must be introduced, which evaluates overall lifetime risks. The best results are obtained by both treatment of high-risk individuals and early treatment of pre-clinical patients in order to modify the evolution of atherosclerosis to clinical disease.

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Introduction

There is now great awareness of the multiple influences that predispose to the development of atherosclerosis over many years in the coronary, cerebral and peripheral circulations. Significant progress has been made, particularly over the past decade, in our ability to modify these risk influences, and this has resulted in a dramatic and positive impact on clinical morbidity and mortality from atherosclerotic disease. For example, during the past few years a number of landmark trials have demonstrated the ability of statins to reduce mortality across a broad range of individuals, both with manifest clinical disease and with risk factors for atherosclerosis^[1–4]. The benefits of statin therapy shown by those studies may represent the most important medical advance, in terms of risk reduction in the population, since the introduction of antibiotics.

However, these statin trials have raised a number of very important issues that now need to be addressed, in terms of

the practical management of patients at risk. For example, how do we extrapolate these data to the treatment of patients in our clinics? Whom should we treat? How early should we begin treatment in patients with coronary disease, particularly in those with acute coronary syndromes? How low should we target the various risk factors in different risk factor populations in order to achieve the optimal event reduction? Finally, when should we start treatments in order to gain the maximum benefit in terms of event reduction over the lives of our patients?

This paper reviews data from some of the recently completed trials and provides a preview of ongoing trials that are attempting to answer these questions.

Secondary prevention

In individuals with established coronary disease, it is not difficult to draw conclusions regarding the benefits of risk factor management in different populations. This is because all of the subgroup studies to date show benefit from aggressive risk factor reduction, and cholesterol lowering in particular. For instance, in the Scandinavian Simvastatin

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Survival Study (4S) study, equal benefit was seen when men versus women, younger versus older patients, and diabetic versus non-diabetic patients were compared^[5,6]. Similar findings have been reported in the population evaluated in the Cholesterol And Recurrent Events (CARE) study^[7,8].

Although these subpopulations benefited equally well from cholesterol lowering with a statin, therapy in those trials was not initiated until 3–6 months after the event and the clinical benefits took several months to appear. More recently, however, data from studies that assess our ability to modify the biology of atherosclerosis and vascular disease indicate that a reduction in coronary events may be achieved by risk factor intervention at a more acute stage. For example, Tamai *et al.*^[9] demonstrated a dramatic improvement in vascular endothelial function, measured as forearm blood flow in response to acetylcholine, following low-density lipoprotein (LDL) apheresis^[9]. More recently, Tsunekawa *et al.*^[10] showed that almost all of the improvement in endothelial dysfunction after starting a statin therapy could be detected within 3 days of treatment. Similarly, in the Reduction of Cholesterol in Ischemia and Function of the Endothelium (RECIFE) study, Dupuis *et al.*^[11] showed that administration of a statin for just 6 weeks to patients with acute coronary syndromes led to a significant recovery in endothelial function.

Such findings suggest that early intervention with risk factor reduction may play a role in restabilizing the atherosclerotic process. The first major, prospective clinical trial to address this was the recently reported Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial^[12]. MIRACL filled a ‘gap’ in terms of our knowledge of statin therapy in clinical trials, because treatment (in this case either atorvastatin 80 mg · day⁻¹ or placebo plus usual care) was initiated within 24–96 h of hospitalization for an acute coronary syndrome event, and outcomes were followed up for 16 weeks.

In MIRACL, the primary end-point (time from randomization to the first occurrence of death [any cause], non-fatal myocardial infarction [MI], resuscitated cardiac arrest, or worsening angina pectoris with new objective evidence of myocardial ischaemia requiring urgent rehospitalization) was significantly ($P = 0.048$) lower in the statin group than in the placebo group^[13]. It was the ischaemic manifestations of coronary disease that appeared to be most impressively reduced by early introduction of the statin (relative risk reduction 26%; $P = 0.02$).

The idea that early intervention, counterintuitive to our traditional ideas, may be beneficial is supported by registry data recently reported from Sweden^[14]. That study examined the prescription of statins, following acute MI, at the time of discharge from hospital, and then recorded clinical outcomes in those individuals at 1 year. In patients who were prescribed statin therapy on discharge from hospital there was an approximate 30% reduction in clinical events, as compared with patients who did not receive early statin therapy after hospitalization. The results of that study lend further support to the concept that coronary disease can be ‘restabilized’, thereby favourably influencing morbidity and mortality, by early introduction of risk factor modification.

Despite these positive findings, early and aggressive risk factor modification in patients following a coronary event has not yet gained wide acceptance in clinical practice. Recent data from the U.S. National Registry, which is examining the number of patients who are prescribed lipid-lowering medication after acute MI, showed that over 40% of patients younger than 55 years were discharged from hospital with lipid-lowering therapy, but this percentage decreased with increasing age^[15]. Furthermore, men were more likely than women to receive lipid-lowering treatment after discharge.

There are a number of ongoing prospective clinical trials that are examining this question, and will supplement the data from MIRACL. The Aggrastat to Zocor (AtoZ) trial^[16], the PRavastatin Or atorVastatin Evaluation and Infection Trial (PROVE IT)^[17] and the Pravastatin in Acute Coronary syndromes Trial (PACT)^[18] will all examine the impact of early lipid management in acute coronary syndromes.

Primary prevention

Patients with established CHD are at the highest risk for coronary events, and therefore require prompt and aggressive reduction in risk factors. However, attention must also be paid to individuals with risk factors for coronary disease but without clinical disease, particularly because the first presentation of coronary disease is very often an acute MI or sudden death.

It is much more difficult to demonstrate a benefit of risk factor modification in a primary prevention population than it is in patients with established disease, although studies such as the West Of Scotland Coronary Prevention Study (WOSCOPS) have shown such a benefit with statin therapy^[2]. A number of ongoing clinical trials are examining the benefits of lipid modification for primary prevention in specific groups of individuals, such as patients with diabetes, the elderly and women^[19–22]. Diabetes represents a very important example of how risk factors interact to predispose to coronary morbidity and mortality. In primary prevention therapy in patients with diabetes, it makes sense to be aggressive in terms of lipid lowering. Haffner *et al.*^[23], examined cardiovascular risk in people with type 2 diabetes with and without previous MI. Those investigators showed that risk for cardiovascular complications over 7 years in a diabetic individual without coronary disease was the same as that in patients with documented coronary disease but no diabetes. Diabetes is thus a ‘coronary equivalent’ in terms of predicting outcome.

Worryingly, type 2 diabetes is becoming a disease of epidemic proportions, not just in the developing countries but also in developed countries. World Health Organization predictions indicate that, by 2025, in the Americas alone, there will be almost 70 million people with type 2 diabetes^[24]. Because type 2 diabetes is associated with a substantially elevated risk for cardiovascular morbidity and mortality, the prospect exists of a new ‘epidemic’ of coronary heart disease (CHD) over the next two decades, with a growing number of individuals eligible for primary prevention therapy^[25].

The interaction of diabetes with other major cardiovascular risk factors has been documented in a recent study by Jamerson^[26]. The more cardiovascular risk factors an individual had, the greater the risk of death, but diabetes amplified the relationship between multiple risk factors and cardiovascular clinical events.

Because diabetes substantially increases risk for cardiovascular events, even from an early 'pre-clinical stage', the cost implications of intervention are becoming an important issue. Recent cost-effectiveness data from Grover *et al.*^[27] revealed that, in men aged 40–60 years, it is more cost effective to treat risk factors in diabetic patients without coronary artery disease than it is in non-diabetic patients with coronary artery disease – a group for which indications and effectiveness of aggressive intervention are clear.

A number of ongoing trials are addressing the level of benefit that can be achieved by lipid-lowering interventions in patients with type 2 diabetes mellitus without CHD. These include the Atorvastatin Study for the Prevention of coronary heart disease Endpoints in NIDDM (ASPEN), Collaborative Atorvastatin Diabetes Study (CARDS), Lipids in Diabetes Study (LDS) and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)^[28–30].

How low should risk factor targets go?

Having established the importance of early and aggressive risk factor modification in high-risk individuals, even in pre-clinical populations, another issue needs to be addressed – how low should risk factor targets be in order to gain maximum benefit? In population studies, the relationship between plasma cholesterol levels and cardiovascular outcome still holds true even at low levels, such as those found in the Chinese population^[31]. In the Bogalusa Heart Study, conducted in the U.S.A., there was a linear relationship between LDL-cholesterol levels and early atherosclerosis in children, down to levels as low as 1.0 mmol . l⁻¹ (40 mg . dl⁻¹)^[32].

The interaction between risk factors and the vessel wall at this early pre-clinical stage results in vascular damage, which is the precursor of clinically relevant atherosclerosis decades later. Stamler *et al.*^[33], in an analysis of more than 11,000 men, demonstrated that cholesterol levels in the young tracked closely with cardiovascular events over a 25-year period. Meta-analysis of primary and secondary prevention trials of statins show linear relationships between event rates and the LDL-cholesterol levels achieved with treatment^[34]. There is no evidence of a threshold for LDL-cholesterol reduction below which no further clinical benefits can be achieved, and reducing LDL-cholesterol levels to below the currently recommended targets may achieve further clinical benefit. Ongoing trials examining this issue include the Treating to New Targets (TNT) trial^[35], the Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine (SEARCH)^[36] and the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial^[28].

The findings of the recent Heart Protection Study (HPS) have been provocative and will alter the approach to risk factors assessment and management^[19]. Twenty thousand individuals who were perceived to be at a high risk for coronary artery disease were randomly assigned to an antioxidant supplementation regimen, a statin regimen or a combination of the two. The population was much broader than in previous statin trials, including many women, diabetic persons and patients with peripheral vascular disease, with a wide age range and wide levels of various risk factors. More than half of them had LDL-cholesterol levels at or below currently recommended levels at entry into the trial. There was no benefit from antioxidant therapy, but there was a significant reduction in all adverse outcomes in those who received statins. Of note, the benefit of statins was not related to the entry LDL-cholesterol level. This emphasizes the value of aggressive targeting of modifiable risk factors in individuals with high global cardiovascular risk profiles.

How early should intervention begin?

Treatment of atherosclerosis is aimed at reducing risk in established disease, and at impacting positively on disease progression. However, it is important to consider not only the absolute risk for events, as can be demonstrated in clinical trials over a relatively short period (3–5 years), but also the 'investment' component of intervention on lifetime risk for cardiovascular events (10–30 years).

It is now well established that atherosclerosis has a long pre-clinical window. Autopsy studies of Korean War casualties, for example, revealed that over three-quarters of apparently fit American soldiers, at an average age of 22 years, already had evidence of atherosclerosis^[37]. This alarming finding has been confirmed in numerous subsequent autopsy reports and more recently in studies using intra-vascular ultrasound. Tuzcu *et al.*^[38], examining coronary arteries of donor hearts in a transplantation programme, showed that atherosclerosis was present in almost one-fifth of teenagers and in 85% of those aged 50 years or older.

Current guidelines for intervention are based on evaluation of 'absolute risk'. However, this absolute risk based approach may promote treatment in a suboptimal manner for lifetime risk benefit. For moderate risk cohorts, current interventional thresholds indicate that initiation of therapy at around age 55–60 years is appropriate. Our own computer-based programme for risk assessment (Cardiorisk), which is used in a risk factor clinic, not only enables individual risk to be predicted, but also indicates the optimal age of treatment for prolongation of event-free life^[39]. Using this programme, it appears that, for an individual at moderate risk, optimal life prolongation without clinical events may require initiation of therapy in middle age (40–45 years), rather than waiting for high absolute risk at 55–60 years. Not only is early therapy associated with longer predicted event-free survival, but also the benefits from therapy manifest at an earlier stage in the patient's life.

Conclusion

In conclusion, there are now very exciting epidemiological and clinical trial data that should be incorporated into clinical practice. The introduction of statins has revolutionized lipid management and had a huge impact on cardiovascular morbidity and mortality. However, the focus must now be on risk reduction using a multiple risk factor approach, rather than targeting a single risk factor. Ongoing studies in primary prevention are addressing specific populations, such as the elderly, diabetic persons and women. Although such studies concentrate on the individuals who are at the highest risk, it should be realized that earlier intervention has the potential to produce huge cumulative long-term benefits in event-free survival, even in individuals with moderate risk factor levels.

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