Review article

Diet, hyperlipidaemia and cardiovascular disease

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Reviewed here are results of intervention studies examining relationships between diet and hyperlipidaemia, or diet and cardiovascular disease (CVD). A reduction in the intake of saturated fatty acids (SFAs) and trans-fatty acids (TFAs), and an increase in the intake of polyunsaturated fatty acids (PUFAs), are favourable to lipoprotein status. Where a reduction in total fat intake is achieved by a reduction in dietary SFAs, there would appear to be a favourable effect on CVD events and mortality, although the evidence for this from intervention studies is not strong. Adequate dietary PUFA intake, both ω6 and ω3, may be associated with reduced risk for CVD events more via pathways other than those which operate through lipoproteins. Other macronutrients including carbohydrates, proteins and alcohol can have significant effects on lipoproteins, although the effects of dietary intervention with these nutrients on coronary and total mortality are virtually unknown. Non-nutrient components of foods with small lipid lowering properties may be cumulatively important in an overall diet. In relation to food, results of secondary intervention studies provide support for a beneficial role of plant food and fish in reducing coronary and total mortality. Therefore as far as both hyperlipidaemia and CVD are concerned, the total dietary approach may be more important than the single nutrient approach.

Introduction

Dietary modification of serum lipoproteins is usually intended to reduce cardiovascular and total mortality. Available studies deal with the way diet changes serum lipoproteins, as well as atherosclerosis, coronary artery disease (CAD), myocardial infarction (MI), and mortality. Dietary management of hyperlipidaemia therefore concerns not only the modification of serum lipoproteins, but more importantly the prevention of cardiovascular disease (CVD) and mortality.

The majority of studies which have examined relationships between diet and CVD or CVD risk factors have emphasised the fat component of the diet. Other dietary components, including protein, carbohydrate, vitamins, minerals and non-nutrient components of food may affect serum lipoproteins and CVD risk. However, in most populations the quantity and quality of fat in the diet is believed to be a powerful dietary indicator of CVD risk.

The evidence reviewed here includes intervention studies which have examined the relationship between diet and serum lipids and lipoproteins, as well as CVD end points. Where information from intervention studies is limited, evidence from prospective, cross-sectional and case-control studies is examined.

Diet and cardiovascular disease: an introduction

The "diet-heart" hypothesis was proposed to explain the relationship between diet, fatty acids in particular, and CVD. According to this hypothesis, a high intake of saturated fatty acids (SFAs) and cholesterol and a low intake of polyunsaturated fatty acids (PUFAs) increases serum cholesterol, which leads to the development of atheromatous plaques in the coronary arteries. Accumulation of these plaques leads to narrowing of the coronary arteries, reduced blood flow to the heart muscle, and finally to the occurrence of MI[1]. This hypothesis is supported by two lines of evidence: studies which have associated dietary fatty acids with serum cholesterol concentrations, and studies which have found a positive association between serum cholesterol concentration and CVD. Various other dyslipidaemias, including low high-density lipoprotein (HDL) cholesterol concentration, raised serum triglyceride concentration, increased serum concentration of small dense low-density lipoprotein (LDL) particles, and poor chylomicron remnant clearance, have now been associated with increased risk of CVD. Dietary fatty acids have also been related to CVD risk through these other dyslipidaemias. These developments have altered the hypothesis to include many other aspects of lipid and lipoprotein metabolism.

The key role which thrombosis plays in CVD was not included in the "diet-heart" hypothesis, and until recently thrombosis was regarded separately to the process of atherosclerosis. The development of coronary thrombosis as a result of fissuring of an atherosclerotic plaque is the major determinant of progression of stable atherosclerotic lesions to MI[2]. Thrombosis may also be involved in atherosclerotic plaque development. Atherosclerotic plaques may increase in size after rupturing and thrombus formation[3]. Furthermore, lipoproteins might influence thrombosis via effects on coagulation, in addition to their role in atherosclerosis[4]. Dietary fatty acids have also been linked to thrombosis[3]. Omega-3 fatty acids in particular have been shown to be antithrombotic. However, there is no clearly established prothrombotic effect of saturated

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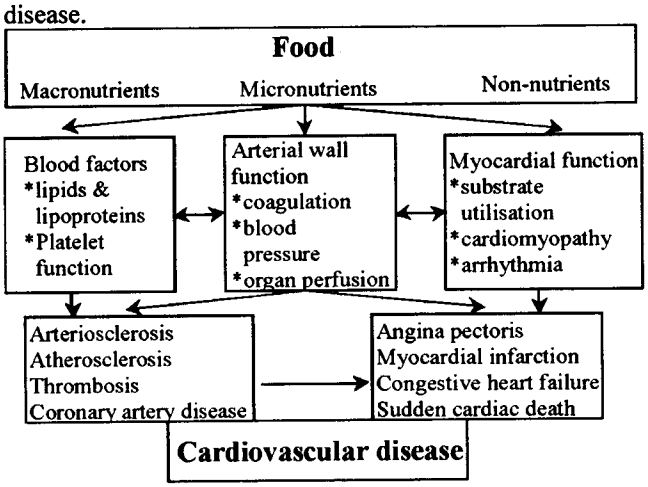
fatty acids, although this has not been ruled out[5].

The role of diet in CVD has been summarised briefly in Figure 1. Blood factors, including lipoproteins and platelet function, and arterial wall function, with its effects on coagulation, blood pressure, and organ perfusion influence the processes of arteriosclerosis, atherosclerosis and thrombosis, which can lead to CAD. Coronary artery disease, along with these other processes may result in angina, MI or death. Diet may also influence CVD through pathways other than atherosclerosis and thrombosis[6]. For example CVD may result from poor myocardial function. Particular micronutrients, including selenium deficiency[7] and cobalt toxicity[8] may lead to cardiomyopathy, impaired myocardial function, and congestive heart failure. There is also evidence that myocardial function can be influenced by dietary fat[9,10], and alcohol[11].

Figure 1. Potential pathways linking diet to cardiovascular disease.



In relation to CVD, most intervention studies have investigated links between diet and hyperlipidaemia, hyperlipidaemia and CVD end points, or diet and CVD end points presumed to be operating through hyperlipidaemias. Outlined in Figure 1 are several other pathways through which diet might influence CVD. The importance of these pathways to CVD is recognised, and it is recognised that many of the changes in CVD produced by dietary intervention may relate to pathways other than those which operate through serum lipids and lipoproteins. The main focus in this review, however, is the diet-hyperlipidaemia-CVD pathway.

The nature of diet

Diet or food intake may be described, or changed, in terms of foods or nutrients. Most dietary intervention studies have examined one particular nutrient, namely fat, but other dietary components including protein, carbohydrates, dietary fibre and alcohol have also been studied. Few studies have used foods such as plant-derived or fish as the dietary intervention. Even here, the assumption in studies of food intervention is that specific nutrient effects are usually in question. However, foods contain more than one nutrient, and indeed many non-nutrients of biological importance. Some of the effects observed may therefore be due to other factors in food, although the evidence for certain nutrient relationships is quite strong. Secondary dietary changes resulting from the desired intervention should also be taken into account. For example, a reduction in the total fat intake will usually result in changes in carbohydrate and/ or protein intake.

Predicting dietary responsiveness

Not all individuals will respond to the same dietary change with the same change in serum lipoprotein status, let alone in cardiovascular event or total mortality end points. There are several reasons for these differences which need to be taken into account in the evaluation of intervention studies. The background diet of the study community or individual is one of the most important considerations. In addition, there are genetic determinants of hyperlipidaemia or atherosclerosis susceptibility. These include familial hypercholesterolaemia which is usually poorly responsive to diet, although ordinarily LDL receptors are responsive to dietary change[12]. Apo E status is indicative of responsiveness of serum lipids to dietary fat change, with apo E_4 being more responsive than apo E_3[13,14]. There are also non-dietary lifestyle factors such as physical inactivity and cigarette smoking which may influence dietary responsiveness.

Energy balance and hyperlipidaemia

Increased body fatness represents positive energy balance, whether for reasons of excessive intake or under-expenditure. Over fatness and an abdominal distribution of fatness are the most potent factors in increasing VLDL triglyceride and LDL cholesterol and decreasing HDL cholesterol[15]. An increasing prevalence of obesity (body mass index >30 kg/ m_2) in the Australian population during the 1980s is therefore of considerable importance[16].

Dietary fat and hyperlipidaemia

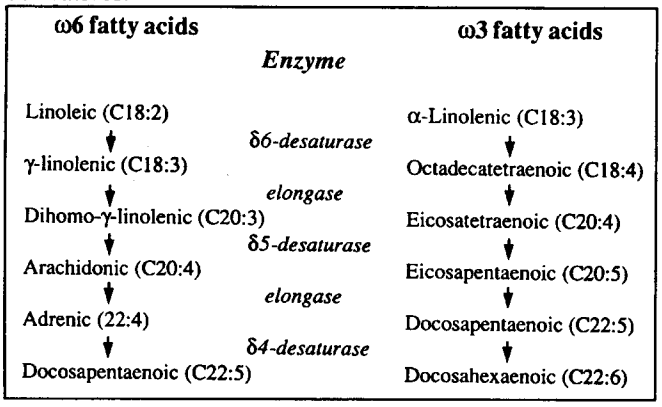
Introduction

Dietary fat may be derived from animal or plant sources. The most abundant type of dietary fat is triglyceride, which may provide SFA, monounsaturated fatty acids (MUFA), and PUFA. Most PUFAs in the diet are essential fatty acids (EFA) or EFA derivatives. There are two classes of EFAs, omega-6 (ω6) and omega-3 (ω3). Linoleic acid (18:2ω6) and α-linolenic acid (18:3ω3) are the precursor or parent ω6 and ω3 EFAs, from which longer chain EFAs are derived by enzyme desaturation and elongation. The same group of enzymes are shared between fatty acid classes (Fig. 2). SFAs and MUFAs are not essential, because humans possess the ability to derive these from protein and carbohydrate if necessary. Although *trans*-fatty acids (TFA) can be classed as either MUFA or PUFA, they are often classified as a separate group because most unsaturated fat, both dietary and *in vivo* derived, in humans is in the *cis* configuration. The fatty acid classes can also be described in terms of individual fatty acids. This is useful when different fatty acids within one class have different metabolic effects. Cholesterol and phospholipids are also important dietary fats.

Hyperlipidaemia has been classified as type IIA (raised LDL cholesterol), type IIB (raised LDL cholesterol and raised VLDL, characterised by an elevated fasting serum

triglyceride measurement), or type IV (raised VLDL only). More recently, the term dyslipidaemia has been used to describe hyperlipidaemias as well as low HDL cholesterol concentration, raised serum triglyceride concentration, increased serum concentration of small dense LDL particles in serum, and poor chylomicron remnant clearance.

Figure 2. Metabolic pathways for the conversion of ω6 and ω3 essential fatty acids to essential fatty acid derivatives.



Fatty acid classes

In one of the earliest studies on dietary fat and serum cholesterol, Kinsell et al[17] found that diets high in vegetable fat lowered serum cholesterol concentrations, findings that were confirmed in the same decade[18-23]. These studies established that serum cholesterol concentrations were more upwardly responsive to dietary saturated fat than to total fat or cholesterol in the diet. After comparisons of different fats and oils in these studies, it was proposed that SFAs were responsible for a hypercholesterolaemic effect, and that PUFAs were responsible for a hypocholesterolaemic effect[18,21,23]. Formulae to predict the expected change in serum cholesterol with changes in SFAs, PUFAs, and cholesterol were developed separately by Keys et al [22,24,25] and Hegsted et al [26,27]. A recent meta-analysis of 27 trials[28], on the effects of dietary fatty acids on serum lipids and lipoproteins produced an equation which was in close agreement with those of Keys et al and Hegsted et al.

These studies showed that serum cholesterol is much more responsive to changes in dietary SFAs than either dietary PUFAs or cholesterol. In the studies by Hegsted et al[26] the changes in SFAs accounted for over 70% of the variations in serum cholesterol. Dietary cholesterol has a significant, although minor contribution to serum cholesterol changes. Although both the equations of Keys et al[25] and Hegsted[27] were able to predict well the effects of changes in dietary fat on serum cholesterol, several investigators have found large individual variability in response to changes in dietary SFAs, PUFAs[24,29], and especially to dietary cholesterol[30,31].

The question of the appropriate ratio of PUFAs to SFAs (P:S ratio) has been addressed by Gustafsson et al[32,33]. In these studies, diets with different P:S ratios were compared with respect to serum lipoprotein changes. It was found that increasing the P:S ratio above 0.7 did not improve serum lipoproteins in patients with moderate hyperlipidaemia. Most of the benefits in relation to the lipoproteins were therefore gained with a shift in the P:S ratio up to 0.7. However, this level might depend upon factors affecting dietary responsiveness.

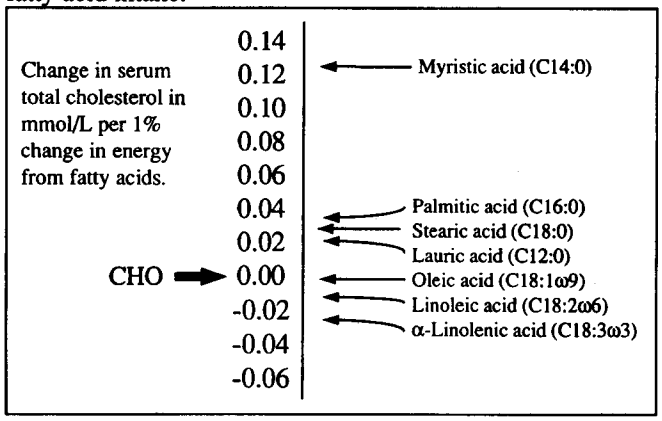
There is also evidence in support of the relationship between increasing the P:S ratio and improving serum lipoproteins in a large scale study. In the Lipid Research Clinics Primary Prevention Trial, in which over 6000 hypercholesterolaemic men were advised to adopt a diet lower in SFAs and cholesterol and relatively higher in PUFAs, SFAs were directly related and PUFAs were inversely related to LDL cholesterol lowering[34].

Apart from the specific fatty acid composition of the diet, several other dietary factors are important determinants of effects on serum lipids and lipoproteins. The most important of these is probably the background diet. The prevailing level of SFAs in the diet, for example, might influence the degree to which a reduction of SFAs will reduce LDL cholesterol. In addition, the structure of the triglyceride in the fat being consumed can also influence serum lipid and lipoprotein responses[35,36].

Saturated fatty acids

Myristic acid (C14:0) has the greatest cholesterol elevating effects[25,26] and has been estimated to be four to six times as cholesterol raising as either lauric (Cl2:0) or palmitic (C16:0) acid[37]. However, the effects of individual fatty acids on serum cholesterol can still only be estimated. Refinement of the Keys and Hegsted equations is proceeding with more metabolic studies. The more recent studies indicate that a change in palmitic acid intake has relatively little effect on LDL cholesterol concentration, particularly when compared to change in myristic acid ingestion[38-40]. A number of experiments have indicated that stearic acid (C18:0) does not elevate cholesterol[25,26,41]. Saturated fatty acids of chain length less than C10 produce little or no cholesterol elevation [25,42,43]. These results are summarised in Figure 3.

Figure 3 Response of serum total cholesterol to changes in fatty acid intake.



Estimates taken from meta-analysis of Mensink and Katan (28).
Figure adapted from Grundy (44).

Monounsaturated fatty acids (MUFAs)

The major MUFA in the diet is oleic acid (18:1 n-9). It is widespread in the food supply, the richest sources being olive oil and canola oil. The effects of MUFAs on serum cholesterol have been examined in a number of studies[45-47], and it was found in all of these studies that MUFAs did not elevate serum cholesterol concentrations as did SFAs, and that diets high in MUFAs did not lower HDL cholesterol concentrations, as did substitution of SFAs with carbohydrates. It has been estimated from a meta-analysis[28] that if monounsaturated fatty acids replace carbohydrate in the diet then a relatively small decrease in LDL cholesterol and a small increase in HDL cholesterol is expected.

Polyunsaturated fatty acids (PUFAs)

Although increasing linoleic acid will lower LDL cholesterol, its effects are less than half that of lowering dietary saturated fatty acids[28]. The serum cholesterol lowering potential of linoleic acid is shown in Figure 3.

Fish and fish oils are major sources of omega-3 (ω3) fatty acids. Fish oils consistently reduce serum triglyceride concentrations, particularly in hypertriglyceridaemic subjects[48-50]. Although substitution of SFAs with long chain ω3 PUFAs has been found to result in a fall in total cholesterol[19,21] and LDL cholesterol, this effect seems to be due to reduced SFAs. Supplementation with ω3 PUFAs has also been reported not to lower LDL cholesterol[51], and lowering of serum triglycerides with fish oils is often associated with an increase in LDL cholesterol[52], particularly in association with diabetes[53]. However, different ω3 PUFAs may have different effects on serum cholesterol concentrations.

Fish oils also affect the haemostatic system and eicosanoid metabolism. The overall result of an increase in the intake of ω3 fatty acids is a beneficial change in the haemostatic balance towards a more vasodilatory state, with reduced platelet aggregation. There is evidence that much of the proposed beneficial effects of the ω3 fatty acids on cardiovascular disease may operate through the haemostatic system and eicosanoid metabolism rather than through lipoproteins, thereby reducing the risk of MI through influencing thrombosis.

Trans-fatty acids (TFAs)

Many vegetable oils require partial hydrogenation to attain properties needed for particular food uses. This process generates a variety of *trans* and uncommon *cis*-fatty acid isomers. The other major source of TFAs is from ruminant animal origins.

A number of studies have examined the relationship between TFAs in the diet and serum lipids and lipoprotein concentrations. Many of these studies, conducted during the 1960s, produced inconsistent findings. More recently, well-designed studies have found that TFAs increase LDL cholesterol[54,55] and Lp(a)[38,56], and reduce HDL cholesterol[54,55], and overall are approximately as unfavourable on serum lipoproteins as SFAs in general. It is not known whether particular TFAs are responsible for the observed effects.

Modification of other macronutrient intakes and hyperlipidaemia

Carbohydrates

The effects of dietary fatty acids on serum lipids and lipoproteins are often measured in relation to carbohydrate intakes, which are assumed to be neutral in these analyses. However, high carbohydrate diets reduce LDL cholesterol[46], although their beneficial effects seem to be secondary to a reduction in dietary SFAs. High carbohydrate diets may also be associated with increased VLDL production and elevated triglyceride levels, and falls in HDL cholesterol[28,57]. It must be kept in mind however, that serum lipoproteins are not the most important outcome. Cardiovascular disease and death are obviously more important.

Protein

There is some evidence which suggests that the source of protein (animal vs plant) has differential effects on serum lipoproteins. Soy protein based diets have been shown to lower serum LDL cholesterol in hyperlipidaemic subjects[58-61]. However, the effect is less consistent in normocholesterolaemic people[62-64].

Alcohol

Alcohol consumption produces an increase in serum triglyceride concentrations as a result of elevation of VLDL and chylomicron levels[65]. There is also some elevation of serum cholesterol levels. A proportion of this is due to an increase in HDL cholesterol[66,67]. The rise in HDL cholesterol occurs only in inactive individuals, not in runners where HDL levels are already raised[68].

There is also some evidence for an inverse association between alcohol intake and LDL cholesterol. In the Lipid Research Clinics Coronary Primary Prevention Trial, change in alcohol intake was associated inversely with change in LDL cholesterol levels among men in the placebo group after adjustment for body mass index and dietary lipids[69].

Fibre

Numerous studies have suggested that an increased consumption of fibre-rich foods can reduce serum cholesterol levels[70-72]. However, not all dietary fibre appears to influence serum lipoproteins. Insoluble fibre (such as wheat bran) has little influence on serum lipoproteins[73]. Soluble fibres appear to favourably affect serum lipoproteins. However, the effects are variable depending on the type of soluble fibre used. For example, guar gums tend to lower LDL cholesterol, but not influence HDL cholesterol, whereas oat bran will lower LDL cholesterol as well as increase HDL cholesterol[74]. Oat bran may also lower triglycerides in hypercholesterolaemic people[75].

Micronutrients

Niacin in doses used to lower serum cholesterol should be regarded as a pharmacological rather than a nutritional approach. There is little evidence that other micronutrients can influence serum lipid and lipoprotein concentrations. However, there may be several micronutrients which

influence atherosclerosis via effects on lipoproteins without significantly altering lipoprotein concentrations[76].

Non-nutrient food components and hyperlipidaemia

There is growing interest in various non-nutrient components of food which favourably influence plasma lipoprotein status. At the moment, these identified components should be regarded as indicative of new ways of looking at food from the point of view of the management of hyperlipidaemia. The components include:

- a lipid soluble fraction from boiled coffee[77],
- allicin from garlic[78,79],
- saponins from foods like chick peas[80],
- tocotrienols from barley and palm oil, which appear to have HMG CoA reductase inhibitor activity[81,82]
- and plant sterols which may be handled alternatively to cholesterol[83].

With the growing evidence for physiological effects of phytoestrogens in humans[84] and serum cholesterol-lowering properties in experimental animals of certain natural food colours like anthocyanins[85,86], there may be an ever wider range of foods of value in the management of lipid disorders. Although the effects of individual food components may be relatively small (say a 1-3% lowering of LDL cholesterol) cumulatively, several components could be important.

Diet and cardiovascular disease

Cardiovascular end points which have been used in dietary intervention studies include CAD, MI, CVD mortality, and total mortality.

Coronary artery disease

Coronary angiography has been used to assess CAD progression or regression in humans in several studies. However, detailed analysis of nutritional variables, including fatty acids, has only been performed in two quantitative angiographic studies[87,88].

The influence of diet on the appearance of new lesions in human coronary arteries was examined in the placebo arm of the Cholesterol Lowering Atherosclerosis Study (CLAS) study by Blankenhorn et al[89]. Coronary angiograms along with 24-hour dietary recall information were used to examine the relationships between change in diet and the appearance of new lesions. The placebo group was given dietary goals: to reduce total fat to less than 26% (5% SFAs, 10% MUFAs and 10% PUFAs). It was found that increased intake of total fat, PUFAs, linoleic acid (18:2ω6), oleic acid (18:1ω9), and lauric acid (12:0), was associated with a significant increase in risk of new lesions. The results in this study indicated that when total dietary fat and SFAs are reduced, the preferred substitutes may be protein and carbohydrate rather than PUFAs and MUFAs[89].

More comprehensive dietary data was collected in the St Thomas' Atherosclerosis Regression Study (STARS)[90]. Dietary assessments were performed using a dietary history method on all patients at least twice during the study. Pooled data from the usual care and lipid lowering diet groups were used to assess the relationships between nutrient intake and CAD. Total fat and SFA were the nutrients most closely (positively) associated with CAD progression. MUFAs were also positively associated with CAD progression, but this may have been due to a close relationship with total and SFA intake. PUFAs were not significantly related to CAD progression.

Other angiographic trials with dietary interventions, with or without additional interventions[91-93], are in general agreement with the CLAS[89] and STARS[90], and indicate that lower total and saturated fat intakes may result in reduced progression, or regression of CAD. The results are also consistent with an effect of SFA intake on atherosclerosis operating through serum lipoproteins. The relationships of MUFAs and PUFAs with CAD progression is less clear. The lack of a negative relationship between PUFAs and CAD progression in the STARS[90], and the positive relationship between both PUFA and linoleic acid intake and CAD in the CLAS[89] suggests that SFAs may be more important in relation to CAD. The results of the CLAS[89] are consistent with results from a recent cross-sectional study where a positive relationship between linoleic acid and CAD was found[94]. The results from both the STARS[90] and the CLAS[89] are at variance with data finding negative relationships between linoleic acid and CVD events[95-97]. These varying results may reflect a beneficial influence of dietary PUFAs, including linoleic acid, on processes other than atherosclerosis which influence CVD events.

Cardiovascular disease events and mortality

Primary intervention trials

Studies of diet as the only intervention, aiming for a

Table 1. Primary prevention trials of dietary intervention aiming for a reduction in cardiovascular mortality or incidence.

Study/ Author	Randomised	Study Population	Diet	Cholesterol Reduction	Major Findings
Los Angeles Veterans Administration Study Dayton et al 1969	Yes	846 men aged 55 to 89	High P:S ratio	13% (7 years).	31% reduction in all cardiovascular events No reduction in total mortality
Finnish Mental Hospital Study Miettinen et al 1972	No (Cross-over)	1900 men	High P/S ratio(1.42-1.78)	15% (12 years).	Reduced mortality from CHD No reduction in total mortality
Minnesota Coronary Survey Frantz et al 1989	Yes	4393 men & 4664 women	High P:S ratio (0.28[control] c.f1.67[treatment])	15% (1 year)	No significant reduction in CVD events, CVD mortality or total mortality