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Which cardiovascular risk factors matter in chronic kidney disease?

Colin Baigent and Martin Landray

Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Oxford, UK

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Why measure risk factors for vascular disease?

Identifying cardiovascular risk factors among patients with chronic kidney disease (CKD) is potentially useful for two main reasons. First, such risk factors may be used to predict the future risk of an event, which may help physicians to plan treatment. Second, they may be targets for intervention to prevent such events. It is now clear that a large number of risk factors independently predict the risk of cardiovascular outcomes among dialysis patients [1] and among patients with lesser degrees of renal impairment [2]. But, although a risk score based on independent risk factors can be assembled without particular regard to whether they are causal, treatments which modify a particular risk factor will only be effective for the prevention of vascular disease if that risk factor is a cause of such disease.

Limitations of dialysis studies for identifying causes of vascular disease

The starting point for identifying risk factors that might prove to be possible targets for intervention in CKD is population-based observational studies. But we face an immediate difficulty when evaluating observational studies among dialysis patients because such studies are especially prone to confounding, thereby distorting epidemiological associations. The problem is that dialysis patients have a complex array of different metabolic disorders, comorbid conditions and treatments, so that characterizing them with a limited number of measurements is virtually impossible. Even after correction for measured confounding variables, therefore, substantial 'residual' confounding is likely to be present. An illustration of this difficulty is provided by the phenomenon of 'confounding by disease', or 'reverse causality'. Disorders such as malnutrition, for example, may influence the metabolism of risk factors so profoundly that genuinely causal associations are obscured. If we take the example of cholesterol [or more specifically low-density lipoprotein (LDL) cholesterol], which is known to be an important cause of atherosclerosis, negative associations have been observed between cholesterol and mortality in epidemiological studies among people who are very elderly [3], or who have advanced heart failure [4], cancer [5] or AIDS [6]. We find exactly the same phenomenon in dialysis patients [7,8]. These negative associations should not, however, be taken as evidence that higher cholesterol protects patients from atherosclerotic disease in these conditions. Instead, a more plausible explanation is that down-regulation of hepatic lipoprotein production in those at highest risk of death results in low cholesterol levels [9]. Evidence that such patterns are most likely the result of confounding comes from studies in the very elderly, in which the negative associations in observational studies [3] are strongly refuted by the unconfounded evidence from large-scale randomized trials. A meta-analysis of 90 000 patients in 14 statin trials has shown clearly that each 1 mmol/l reduction in LDL cholesterol resulted in a one-fifth reduction in major vascular events [myocardial infarction or death from coronary heart disease (CHD), stroke or coronary revascularization] in those aged 75 or over ($P = 0.0001$) [10].

Alternative strategies for identifying causes of vascular disease in CKD

A more reliable strategy for identifying risk factors relevant to vascular disease in patients with CKD may be to extrapolate information from observational studies conducted in non-renal populations. Several aetiologically distinct vascular pathologies are found among patients with CKD, including atherosclerosis, vascular stiffness, calcification and left-ventricular hypertrophy. Registry studies have shown, for example, that left-ventricular hypertrophy

Correspondence and offprint requests to: Prof Colin Baigent, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK. Email: colin.baigent@ctsu.ox.ac.uk

is present in about three-quarters of patients commencing dialysis [11] and congestive heart failure is the most common recorded type of morbidity for inpatients with CKD [12]. Atherosclerotic conditions such as myocardial infarction and stroke account for about one-third of vascular deaths [12]. Of these pathologies, left-ventricular hypertrophy and atherosclerosis occur commonly in non-renal populations, and observational studies have identified potentially causal risk factors for them. Whilst the *strength* of any such association might differ in CKD, it is unlikely to be completely abolished. Hence, in renal populations, randomized trials to test treatments that modify risk factors identified in non-renal populations should be a starting point in the effort to prevent vascular disease in CKD.

Average levels of risk factors may to be too high for CKD patients

In non-renal populations, blood LDL cholesterol is positively and continuously associated with the risk of CHD across a wide range of cholesterol levels, with no increase in risk of CHD at low LDL concentrations. Randomized trials in non-renal populations have shown that lowering LDL cholesterol reduces this risk [10], thus demonstrating that LDL cholesterol is a cause of CHD. Since the absolute risk of CHD is higher among CKD patients than among those without CKD, if we were able to correct completely for confounding then we might hypothesize that the association between usual LDL cholesterol and CHD would run parallel but higher than the association in a non-renal population (Figure 1). This implies that a large absolute reduction in CHD may be possible by reducing LDL cholesterol among patients with CKD

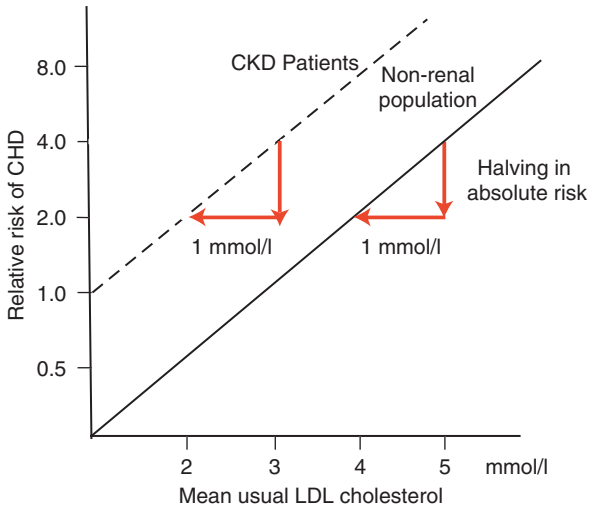

Fig. 1. Potential benefits of lowering cholesterol at below average cholesterol levels in high-risk population of patients with CKD.

even in those with 'normal' (i.e. average) LDL cholesterol levels. For LDL-cholesterol, the key point is that the level of the risk factor does not have to be 'abnormal' to be a potentially important target for intervention: all that matters is that the risk factor is causal, and that the causal association is continuous right down to the lowest levels that can be achieved safely. (This is not intuitive, because as physicians we are trained to correct abnormal levels, and leave normal levels well alone.) Since there are no known hazards of reducing LDL cholesterol to very low levels, at least in non-renal populations [10], the ongoing randomized trials of cholesterol-lowering treatments in patients with CKD (SHARP [13] and AURORA [14]) do not have any lower threshold for LDL cholesterol in their eligibility criteria.

A similar argument can be applied to blood pressure, since observational studies in non-renal populations have demonstrated positive associations between blood pressure and the risk of CHD, stroke and congestive heart failure [15], and randomized trials of blood pressure–lowering regimens have shown that lowering blood pressure reduces the risk of these outcomes [16,17]. Hence, it may be hypothesized that lowering blood pressure might be beneficial to patients with CKD even when blood pressure control is regarded as adequate, provided such reductions can be tolerated by patients. Testing this hypothesis among patients with CKD is especially important because raised blood pressure is associated with three important vascular outcomes (CHD, stroke and heart failure) as well as progression of renal disease, so the potential absolute benefits of further reductions in blood pressure in high-risk patients with CKD who have 'well controlled' blood pressure are substantial.

Assessing risk factors which are specific to CKD

Some risk factors which have been implicated in the pathogenesis of vascular disease in CKD may be difficult to study in observational studies among non-renal patients because the range of usual values in non-renal patients does not extend to the values which occur in advanced CKD. For example, the usual values for haematocrit in the general population are ~39–49% in men and 33–43% in women [18], but haematocrit falls below these ranges once CKD becomes established. Observational studies examining the association between haematocrit and CHD have been performed in healthy people, and a meta-analysis of 16 such studies showed that, as compared with those in the bottom tertile of haematocrit values (mean 41.7%), the relative risk for CHD among those in the top tertile (mean 46.3%) was 1.16 (95% CI 1.05–1.29) [19]. But, in contrast to studies of cholesterol or blood pressure, these studies do not tell us very much about the nature of any association in people with much

lower haematocrit levels, such as those prevailing in patients with CKD, in whom it is likely that low haematocrit is associated with higher risk. In these circumstances, the lack of relevant information from non-renal observational studies and the potential for residual confounding in observational studies of dialysis patients [20] makes randomized trials of erythropoietin essential if we are to determine whether low haematocrit is a cause of vascular disease in CKD.

Summary

Risk factors for vascular disease in CKD can be useful both for assessing the level of risk of vascular disease and as potential targets for the prevention of such disease. Only those risk factors which cause a major component of vasculopathy in CKD are likely to be worth modifying. Owing to unavoidable residual confounding, observational studies in dialysis patients (or patients with advanced CKD) may provide misleading information about the strength and direction of associations. Better control of this confounding may be possible for particular risk factors in non-renal populations, but ultimately randomized trials will be essential, both for establishing the causal relevance of candidate risk factors for vascular disease in renal failure, and for determining the size of any clinical benefit.

Conflict of interest statement. None declared.

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