Case report

Unexpected benefits of participation in a clinical trial: abdominal aortic aneurysms in patients with chronic kidney disease

C.D. CHUE¹, W.E. MOODY¹, R.P. STEEDS¹, J.N. TOWNEND¹ and C.J. FERRO²

From the ¹Department of Cardiology, University Hospital Birmingham NHS Foundation Trust and University of Birmingham and ²Department of Renal Medicine, University Hospital Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK

Address correspondence to Dr C.D. Chue, Department of Cardiovascular Medicine, School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK. email: colin.chue@nhs.net

Case report 1

A 75-year-old man was referred to renal services in 2008 with a creatinine of 168 µmol/l and an estimated glomerular filtration rate (eGFR) of 35 ml/min/1.73 m². He had a past history of hypertension and carcinoma of the prostate previously treated with radiotherapy. There was no history of diabetes or cardiovascular disease. On referral, he was taking perindopril 8 mg, doxazosin 4 mg and bendroflumethiazide 2.5 mg with well-controlled blood pressure at 119/67 mmHg. Total cholesterol was 4.9 mmol/l. An abdominal ultrasound scan showed two kidneys (right 10.3 cm and left 11.6 cm) with moderate cortical thinning and no other pathology. He was followed up infrequently in the renal clinic as his renal function remained stable, his blood pressure was satisfactory and his cholesterol remained <5 mmol/l.

In June 2009, he agreed to participate in the CRIB-PHOS randomized controlled trial (evaluating the effects of sevelamer carbonate on cardiovascular structure and function in Chronic Renal Impairment in Birmingham).¹ A lateral lumbar spine radiograph was performed to semi-quantitatively assess the presence and extent of abdominal aortic calcification at baseline as part of the study protocol.² This showed heavy abdominal aortic calcification and a probable infra-renal aortic aneurysm measuring up to 6 cm (Figure 1a). Three days later, still as part of the trial, he underwent cardiac magnetic resonance imaging. With the patient’s consent, images were obtained of the abdominal aorta, which confirmed the presence of an infrarenal abdominal aortic aneurysm measuring 4.4 cm in the antero-posterior diameter with a rim of intraluminal thrombus (Figure 1b).

The patient is now on the aneurysm surveillance programme having been urgently referred for a vascular surgical opinion and informed that a repair is likely to be required within 2 years.

Case report 2

A 78-year-old man was referred to renal services in 2010 with a creatinine of 150 µmol/l and an eGFR of 38 ml/min/1.73 m². He was not diabetic. He had a past medical history of hypertension and hypercholesterolaemia but no known cardiovascular disease. He was taking losartan 25 mg, amlodipine 10 mg, bendroflumethiazide 2.5 mg and simvastatin 40 mg. On referral, his blood pressure was satisfactory at 126/56 mmHg while his cholesterol measured 3.9 mmol/l. An abdominal ultrasound showed two
kidneys (right 9.4 cm and left 10.2 cm) with bilateral diffuse cortical thinning but nothing else of note.

In February 2011, he agreed to participate in the CRIB-PHOS trial. The lateral lumbar spine radiograph showed extensive calcification of the abdominal aorta as well as a large infra-renal aortic aneurysm (Figure 2a). Nine days later, he underwent cardiac magnetic resonance imaging, which confirmed the presence of a 6.6-cm abdominal aortic aneurysm (Figure 2b). He was urgently referred for a vascular surgical opinion and subsequently listed for elective endovascular stenting of the aneurysm.

**Discussion**

It is generally accepted that clinical trials are good for us as a society. A common perception is that participants sacrifice their time and undertake risks for the good of future patients, but usually obtain no direct personal benefit. There is, however, evidence that individuals can also benefit from taking part in a trial. There are fewer reported randomized controlled trials in nephrology than in most other internal medicine specialities, and lack of willing participants has been postulated to be one potential cause. Here we report two patients with
Stage 3 chronic kidney disease (CKD) participating in the CRIB-PHOS trial\(^1\) whose clinical management was dramatically altered following a lateral lumbar spine radiograph performed purely as part of the study protocol.

There is no evidence that outcomes are worsened by trial participation\(^5,11\) and several studies have demonstrated improved outcomes compared with those receiving standard care.\(^6,7,11–13\) A number of potential sources of a trial effect have been identified.\(^14\) These include the ‘Hawthorne effect’, whereby merely the process of being observed leads to benefit; the ‘treatment effect’, resulting from the treatment under study being superior to the standard alternative, and the ‘care effect’, where the trial protocol requires more comprehensive care. The ‘protocol effect’, in which trial patients have very similar outcomes to non-trial patients treated according to systematized protocols,\(^5,11\) strongly suggests that adherence to protocols may be a major factor in explaining the improved outcomes in trial participants.

Male gender and age are the only two risk factors consistently shown to increase the risk of developing an aortic aneurysm.\(^15–17\) Patients with known cardiovascular risk factors for atherosclerosis such as hypertension, smoking or diabetes mellitus are also thought to be at increased risk of developing an aortic aneurysm, although the evidence is inconsistent.\(^15,18–22\) Thus, although the development of atheroma may be critical to the initial development of aortic aneurysms, additional processes are important in determining the progression of aneurysmal disease as evidenced by epidemiological, histological and macroscopic differences.\(^18,23–25\) Family history is also a recognized risk factor for the development of abdominal aortic aneurysms,\(^22\) and it has even been demonstrated that patients undergoing inguinal hernia repair are at increased risk.\(^26\) It has been postulated that these associations may be explained by increased elastin and collagen degradation.\(^23,27\)

The presence of CKD is not only associated with the development of atheromatous cardiovascular disease,\(^28\) but also with increased arterial stiffness.\(^29\) Uraemia appears to increase the degeneration of both arterial wall elastin and collagen leading to this increased arterial stiffness.\(^29\) With an elevated risk of atheroma, increased arterial stiffness and the almost ubiquitous presence of hypertension, it is reasonable to hypothesize that CKD patients have an increased risk of abdominal aortic aneurysms. Despite this, the incidence or prevalence of abdominal aortic aneurysms in this population is unknown. In our cohort of 65 male patients, two had abdominal aortic aneurysms detected using a plain lateral abdominal radiograph. Although anecdotal, this rate is higher than that has been found in conventionally screened high-risk male populations with published rates of 0.8 and 0.6\% for medium (4.4–5.4 cm) or large (>5.5 cm) aneurysms, respectively.\(^17\) This is especially so given that a plain lateral lumbar spine radiograph is not a recognized screening tool for abdominal aneurysms. The use of more sensitive techniques such as ultrasound or computed tomography would likely have only further increased the detection rate. Interestingly, both of our subjects had undergone renal ultrasound scanning as part of their routine investigations for CKD. It is important that physicians potentially suspecting an abdominal aortic aneurysm in patients are not falsely reassured by non-targeted ultrasonography. We recommend that imaging of the aorta should also be performed during renal ultrasonography to facilitate detection of abdominal aortic aneurysms in this patient group.

The two cases described illustrate two important points. Firstly, doctors, particularly renal physicians, should continue to enrol patients into trials and be reassured that their participation may result, for a variety of reasons, in improved outcomes. It should, however, be remembered that the Helsinki Declaration precludes using the ‘protocol’ or ‘Hawthorne effects’ as tools to promote trial participation. Secondly, there is surprisingly little known about the incidence or prevalence of abdominal aortic aneurysms in patients with CKD. There are strong theoretical reasons to suggest that this population might be at high risk, and renal function may be a factor worth investigating in order to define populations at sufficient risk to prioritize future screening schemes. If CKD is indeed a risk factor for the development of abdominal aortic aneurysms, then consideration might also need to be given to the opportunistic screening of these individuals when routine renal ultrasonography or cardiac echocardiography are performed.

Acknowledgements
We are grateful to the two patients presented for permission to use their cases in this report. We are also grateful to all patients participating in the CRIB-PHOS study.

Funding
Unrestricted educational grant from Genzyme Corporation.

Conflict of interest: None declared.
References


