Renal function, revascularization and risk

Graham S. Hillis¹*, Brian H. Cuthbertson², and Bernard L. Croal³

¹Department of Cardiology, Aberdeen Royal Infirmary; ²Health Services Research Unit, University of Aberdeen; and ³Department of Clinical Biochemistry, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, UK

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This editorial refers to 'Renal insufficiency and long-term mortality and incidence of myocardial infarction in patients undergoing coronary artery bypass grafting' by M.J. Holzmann et al., on page 865.

In 1974, 14 years after the advent of regular maintenance haemodialysis, Linder et al. first reported the powerful relationship between end-stage renal failure and cardiovascular complications. This is now generally recognized, and the statistics quantifying this excess risk, such as the 100-fold increase in cardiovascular mortality associated with a requirement for chronic dialysis below the age of 45 years, are frequently quoted. More recently, however, clinicians have become aware of the association between milder degrees of renal dysfunction and cardiac morbidity and mortality.

There are several reasons for an increased interest in the relationship between kidney and cardiovascular disease. An ageing population with a greater prevalence of obesity, hypertension, and diabetes has resulted in rising levels of chronic renal disease. Among 6233 participants in the Framingham Heart Study, 8% had mild renal insufficiency based on measures of serum creatinine. Likewise, the third National Health and Nutrition Examination Survey estimated that, in the USA, almost 10% of men and 2% of women have creatinine levels of 1.5 mg/dL (≈133 μmol/L) or greater.

The association between renal impairment and cardiovascular outcome has also been emphasized in recent reports by several authoritative working groups. These, combined with several large cohort studies, have highlighted the problem and confirmed the importance of renal dysfunction in multiple patient populations.

Another factor may be the increasing utilization of more precise estimates of renal function. In particular, the Modification of Diet in Renal Disease formula allows estimation of glomerular filtration rate (GFR) on the basis of a patient’s age, serum creatinine, gender, and racial background—facilitating its use in everyday clinical practice. If the estimated GFR is used, many more individuals will be identified as having chronic renal insufficiency. For example, Holzmann et al. demonstrate that, in a cohort of 6575 patients undergoing isolated first coronary artery bypass grafting (CABG), 21% would be identified as having chronic kidney disease on the basis of an estimated GFR < 60 mL/min/1.73 m². Only 6% of patients would have been identified as having renal dysfunction using the commonly accepted cut-off of creatinine > 1.5 mg/dL. Thus, the estimated GFR allows clinicians to make a much more precise estimate of kidney function, identifying subtle, but prognostically important, renal impairment. As one would expect, estimated GFR is, therefore, a better discriminator of risk than serum creatinine and is now generally accepted as the preferred measure in this context.

Renal dysfunction in patients undergoing myocardial revascularization

During myocardial revascularization, even mild degrees of renal dysfunction are increasingly recognized as a key prognostic indicator. Several studies have demonstrated that end-stage renal failure predicts a worse outcome from CABG. A poorer prognosis has also been described among patients with renal dysfunction not requiring dialysis. Most such studies have included patients with moderate to severe elevations of creatinine, dichotomized on the basis of largely arbitrary cut-off levels. Recently, several authors have demonstrated that milder degrees of renal impairment, identified using the estimated GFR, are also important determinants of outcome. As noted above, Holzmann et al. studied patients undergoing isolated first CABG at the Karolinska Hospital, Stockholm, between 1980 and 1995. Their principal finding was that, even after correction for confounding variables, the hazard of death and/or myocardial infarction increased as the estimated GFR fell: an association that was similar in both men and women. Interestingly, the percentage of patients with chronic kidney disease (< 60 mL/min/1.73 m²) undergoing CABG between 1990 and 1995 (26%) was double that among those operated on between 1980 and 1984 (13%). Importantly, this study excluded an additional 136 patients who died within the initial 30 days of surgery and does not assess the impact of renal function on early outcome after CABG. Other recent data confirm that estimated GFR is a
very powerful, independent, predictor of early morbidity and mortality.\textsuperscript{5,6} Renal dysfunction is also an important determinant of outcome following percutaneous coronary intervention where, as in patients undergoing CABG, even mild impairment is associated with a considerable increase in 1-year mortality, independent of other factors.\textsuperscript{7} Studies in the 1990s suggested that patients with severe kidney disease treated with balloon angioplasty had a poor procedural outcome and high restenosis rates. More recent data suggest that in patients with milder degrees of renal dysfunction, treated predominantly with intra-coronary stents, rates of restenosis and acute myocardial infarction are no higher than those in patients with normal renal function, after an average follow-up of 9 months.\textsuperscript{8}

**Relationship between estimated GFR and outcome**

Holzmann \textit{et al.} did not specifically address the pattern of the relationship between declining GFR and outcome. Nonetheless, their data are in keeping with the observations of others that the risk is non-linear.\textsuperscript{5,6} A GFR of 90 mL/min/1.73 m\textsuperscript{2} or above is regarded as normal. Patients at high-risk of, or with pre-existing, cardiovascular disease who have mild renal dysfunction (estimated GFR 60–89 mL/min/1.73 m\textsuperscript{2}) are at slightly increased risk of adverse events. There appears, however, to be a threshold effect whereby risk increases greatly as the estimated GFR falls below 60 mL/min/1.73 m\textsuperscript{2}—the level at which a patient is regarded as having ‘chronic kidney disease’ and at which the regulatory functions of the kidney begin to fail, with an associated increase in the prevalence of ‘renal-specific’ cardiovascular risk factors.

**Mechanisms whereby pre-procedural renal function influences outcome**

The mechanisms whereby minor abnormalities in renal function mediate a worse outcome are complex. Renal function tends to decline with age, and dysfunction is a consequence of several conventional cardiovascular risk factors, such as diabetes mellitus and hypertension. Likewise, impaired kidney function exacerbates the effects of these conditions and is associated with dyslipidaemia plus a variety of other less well-defined risk factors such as increased acute-phase proteins, reduced antioxidants, and hyperhomocysteinemia. It has been suggested that reductions in haemoglobin and abnormalities of calcium/phosphate homeostasis might also be contributory and, although more pronounced in advanced renal disease, such changes can be observed in patients with relatively modest reductions in GFR.

Renal dysfunction is a common consequence of reduced left ventricular systolic function and heart failure. This, most likely, reflects a combination of factors including the direct relationship between impaired haemodynamic status and renal function, neurohormonal activation, effects of medications, and the results of the underlying disease processes. Not only can left ventricular impairment result in reduced renal function, but the converse may also occur: chronic kidney disease is itself a risk factor for left ventricular hypertrophy, dilatation, and dysfunction.

In summary, the prognostic utility of renal function is assumed in part to be due to its association with, and exacerbation of, established and suspected risk factors for accelerated atherosclerosis and left ventricular dysfunction. In addition, the kidney is particularly sensitive to the effects of generalized vascular dysfunction and haemodynamic disturbances, and may therefore serve as a useful ‘barometer’ of cardiovascular health. Finally, there are extensive data demonstrating that patients with even mild renal impairment are less likely to receive therapies that can improve cardiac outcome.

**Effects of post-procedural renal function on outcome**

Relatively few studies have assessed the impact of post-operative renal function on long-term outcome. Those data that are available confirm that pre-operative renal impairment is a major predictor of peri-procedural deterioration and that, both after CABG and PCI, this is associated with a worse outcome.\textsuperscript{9,10} Indeed, in this setting, even relatively minor changes predict a higher mortality. The mechanisms underlying this are poorly defined but may include a decreased renal reserve (with increased susceptibility to the effects of haemodynamic compromise), worse underlying cardiac disease, a higher prevalence of diabetes, increased age, and poorer systolic function or clinical heart failure. In addition, renal dysfunction is a common consequence of many other post-operative complications, such as sepsis, that in turn have profound implications for outcome.

**Clinical implications**

The data presented by Holzmann \textit{et al.} add to the growing literature demonstrating that renal dysfunction, particularly when measured accurately using the estimated GFR, is a potent predictor of outcome following CABG. The underlying mechanisms are multifaceted and include both direct and indirect effects. Thus, renal dysfunction can be regarded both as a marker and a mediator of increased risk.

Despite the impact of kidney disease on the outcome from CABG, current risk-prediction models either exclude renal function altogether or rely on serum creatinine used as a dichotomous variable, the need for renal replacement therapy or poorly defined criteria such as ‘renal failure’. Further work is required to assess whether the inclusion of more discriminatory measures of renal function might improve pre-operative risk stratification. Greater use of the estimated GFR would also increase the recognition of renal dysfunction and, hopefully, encourage the use of therapies proven to improve cardiovascular outcome. Ultimately, prospective studies are required to devise strategies that reduce the risk associated with renal dysfunction in this setting.

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**References**


Clinical vignette

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Aneurysm of the membranous septum causes pre-syncopes and transient bilateral blindness

Christoph Langer*, Dieter Horstkotte, and Cornelia Piper

Department of Cardiology, Heart Center North Rhine-Westphalia, Ruhr University Bochum, Georgstr. 11, 32545 Bad Oeynhausen, Germany

* Corresponding author. Tel: +49 5731 971258; fax: +49 5731 972194. E-mail address: clanger@hdz-nrw.de

A 33-year-old female presenting with a 3-year history of fatigue, palpitations, and dyspnoea on exertion revealed a 1/6 systolic murmur. ECG demonstrated premature beats, whereas echocardiography (Panel A) identified an aneurysm of the membranous septum (AMS) not considered relevant. A complete AV-block developed, but the implanted two-chamber pacemaker did not bring relief. While walking fast, the patient suffered pre-syncopes and transient bilateral blindness. A cardiac CT scan (Panel B) demonstrated an isolated AMS (3 × 3 × 4 mm) consisting of three pouches free of thrombus and calcifications prolapsing into the right ventricular outflow tract. Heart catheterization (Panel C) confirmed a Type B AMS, resulting in a functional stenosis measuring a gradient of 12 mmHg at rest and in supine position. After complete resection of the aneurysmal sac, the patient has remained asymptomatic so far (24 months).

Pre-syncopes and amaurosis fugax can be caused by different pathologies. AMS are generally regarded as developmental malformations and thought to result from spontaneous partial or complete closure of congenital ventricle septal defect. Mostly associated with other cardiac anomalies, isolated AMS are rare and often asymptomatic.