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# RENAL FUNCTION, REVASCULARISATION AND RISK.

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In 1974, 14 years after the advent of regular maintenance haemodialysis, Linder and colleagues first reported the powerful relationship between end-stage renal failure and cardiovascular complications.[1] This is now generally recognised, 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 more 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 an increased prevalence of obesity, hypertension and diabetes has resulted in rising levels of chronic renal disease. Among 6,233 participants in the Framingham Heart Study, 8% had mild renal insufficiency based on measures of serum creatinine.[2] Likewise, the third National Health and Nutrition Examination Survey estimated that, in the United States, almost 10% of men and 2% of women have creatinine levels of 1.5mg/dL (~133µmol/L) or greater.[3]

The association between renal impairment and cardiovascular outcome has also been emphasised 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 utilisation 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, in this issue of the *Journal*, Holzmann and colleagues demonstrate that, in a cohort of 6,575 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 <60mL/min/1.73m$^2$. Only 6% of patients would have been identified as having renal dysfunction using the commonly accepted cut-off of creatinine >1.5mg/dL.[4] 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 revascularisation**

During myocardial revascularisation even mild degrees of renal dysfunction are increasingly recognised 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, dichotomised 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.[5,6] One such study is published in this issue of the *Journal*. As noted above, Holzmann and colleagues 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.[4] Interestingly, the percentage of patients with chronic kidney disease (<60mL/min/1.73m$^2$) undergoing CABG between 1990 and 1995 (26%) was double that among those operated on between 1980 and 1984 (13%).[4] 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.[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.[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 with normal renal function after an average follow-up of 9 months.[8]

**Relationship between estimated GFR and outcome**

Holzmann and colleagues did not specifically address the pattern of the relationship between declining GFR and outcome. Their data are, however, in keeping with the observations of others that the risk is non-linear.[5,6] A GFR of 90mL/min/1.73m$^2$ or

above is regarded as normal. Patients at high-risk of, or with pre-existing, cardiovascular disease who have mild renal dysfunction (estimated GFR 60-89mL/min/1.73m$^2$) are at slightly increased risk of adverse events. There appears to be a threshold effect whereby risk increases greatly as the estimated GFR falls below 60mL/min/1.73m$^2$ – 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 (see below).

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

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 in addition is associated with dyslipidaemia plus a variety of other less well-defined risk factors such as increased acute phase proteins, reduced antioxidants and hyperhomocysteinaemia. It has been suggested that reductions in haemoglobin and abnormalities of calcium/phosphate homeostatis 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, therefore, the powerful 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 generalised 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.[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 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 and colleagues 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. It appears, however, that 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 in cardiac surgery 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 result in improved pre-operative risk stratification. Increased use of the estimated GFR would also increase the recognition of otherwise unapparent renal dysfunction and, hopefully, encourage the use of therapies already proven to improve cardiovascular outcome. Ultimately, prospective studies are required to devise strategies that reduce the risk associated with renal dysfunction in this setting.

## References

1. Linder A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med.* 1974;**290**:697-701.

2. Culleton BF, Larson MG, Evans JC, Wilson PW, Barrett BJ, Parfrey PS, Levy D. Prevalence and correlates of elevated serum creatinine levels: the Framingham Heart Study. *Arch Intern Med.* 1999;**159**:1785-1790.

3. Jones CA, McQuillan GM, Kusek JW, Eberhardt MS, Herman WH, Coresh J, Salive M, Jones CP, Agodoa LY. Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis.* 1998;**32**:992-999.

4. Holzmann M, Hammar N, Ahnve S, Nordqvist T, Pehrsson K, Ivert T. Renal insufficiency and long-term mortality and incidence of myocardial infarction in patients undergoing coronary artery bypass grafting. *Eur Heart J.* 2007; *To be completed.*

5. Hillis GS, Croal BL, Buchan KG, El-Shafei H, Gibson G, Jeffrey RR, Millar CG, Prescott GJ, Cuthbertson BH. Renal function and outcome from coronary artery bypass grafting: impact on mortality after a 2.3-year follow-up. *Circulation.* 2006;**113**:1056-1062.

6. Cooper WA, O'Brien SM, Thourani VH, Guyton RA, Bridges CR, Szczech LA, Petersen R, Peterson ED. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation.* 2006;**113**:1063-1070.

7. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, Berger PB. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol.* 2002;**39**:1113-1119.

8. Best PJ, Berger PB, Davis BR, Grines CL, Sadeghi HM, Williams BA, Willerson JT, Granett JR, Holmes DR,Jr, PRESTO Investigators. Impact of mild or moderate chronic kidney disease on the frequency of restenosis: results from the PRESTO trial. *J Am Coll Cardiol.* 2004;**44**:1786-1791.

9. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR,Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation.* 2002;**105**:2259-2264.

10. Thakar CV, Worley S, Arrigain S, Yared JP, Paganini EP. Influence of renal dysfunction on mortality after cardiac surgery: modifying effect of preoperative renal function. *Kidney Int.* 2005;**67**:1112-1119.