Editorial

Looking for people at high cardiovascular risk?
Look at serum-creatinine

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When patients present to hospital with an acute myocardial infarction, the major long-term aims are to preserve myocardial function and to prevent cardiovascular events. To this end and beyond, the corrected interpretation of serum-creatinine as a marker of glomerular filtration rate (GFR) as well as of future cardiovascular and renal events is helpful. In this issue, Hillege and collaborators\textsuperscript{1} provide compelling evidence for people with acute myocardial infarction (a) that even mildly reduced GFR is highly predictive for the development of heart failure and (b) that ACE inhibition with captopril preserves renal and cardiac function better than placebo over 1 year. The data apply to people without severe heart failure or hypotension on admission and are restricted to those with a serum-creatinine below 180 µmol l\textsuperscript{-1} (about 2 mg dl\textsuperscript{-1}), thus a selective group. The authors calculated GFR from serum-creatinine by the Cockcroft–Gault formula, which provides a clinically useful estimate of GFR based on patient age, body weight, and gender \(\text{GFR}=(140−\text{age, years})\times\text{body weight, kg}/72\times\text{serum-creatinine, mg dl}^{-1}\). Especially in the elderly, clinicians tend to overestimate GFR when looking at serum-creatinine alone. The calculated GFR of a 68-year-old, 50-kg woman with a serum-creatinine 2 mg dl\textsuperscript{-1} (180 µmol l\textsuperscript{-1}) is in the range of only 20 ml min\textsuperscript{-1}!

The observations of Hillege et al. are in line with a recent report by Al Suwaidi et al.\textsuperscript{2} Their analysis encompassed the GUSTO trials, the PARAGON-A investigation, and the PURSUIT study. Of over 18 000 patients, almost half had reduced renal function in these studies. Creatinine clearance was independently associated with risk of short-term mortality in the ST segment elevation infarction group and in the non-ST segment elevation infarction group. The authors indicated that patients presenting with acute coronary syndromes frequently have abnormal renal function. Abnormal function is a marker of adverse baseline clinical characteristics and is independently associated with increased risk of death and myocardial infarction death.

Hillege et al. excluded people with a serum-creatinine >180 µmol l\textsuperscript{-1}. A third of the trial participants had a GFR<80 ml min\textsuperscript{-1} and 8%≤60 ml min\textsuperscript{-1}. Reduced GFR was an impressive predictor of congestive heart failure. In fact, GFR was the only independent predictor, apart from the wall motion score index. The multivariate analysis included many variables from the patients’ history and haemodynamic cardiac findings. However, the data are limited by the inclusion of only 298 people with anterior myocardial infarction with no information on metabolic and inflammatory parameters. Even mild renal insufficiency is associated with proatherogenic changes such as increased night time blood pressure, elevated serum level of LP(a), C-reactive protein, homocysteine, fibrinogen, parathyroid hormone and decreased insulin sensitivity, impaired NO production, lowered HDL-cholesterol etc.\textsuperscript{3} It may be useful to take all these parameters into account when analysing the predictive power of serum-creatinine or of GFR for cardiovascular disease. Some might explain, at
least in part, the strong influence of GFR on cardiovascular risk.

Hillege et al. studied a highly selected group of people with acute, but haemodynamically stable, myocardial infarction with only mild renal impairment. This selection allows the conclusion that even in rather mildly affected people, congestive heart failure develops in the presence of renal insufficiency at a surprisingly high rate of about 40% in 1 year. This high risk suggests that cardiovascular intervention studies in people with renal insufficiency are warranted. Renal insufficiency is, in fact, much more common in less selected samples of people with acute myocardial infarction and in people with chronic coronary and other cardiovascular diseases. In the latter populations, as well as in those with documented congestive heart failure, with hypertension, and with diabetes, there is a striking 1.5–3-fold increase in cardiovascular risk in the presence of mild renal insufficiency.

Mild renal insufficiency affects 15–30% of people with atherosclerotic end-organ disease and is highly predictive for further cardiovascular risk. However, the data are less clear in populations with a low prevalence of cardiovascular disease. At the other extreme, people with end-stage renal disease die from cardiovascular disease at a prodigious rate. Age-adjusted cardiovascular mortality is about 30 times higher in end-stage renal disease than in the general population.

All too often, ACE inhibitors are withheld because of mild renal insufficiency. Hillege et al. provide arguments that this practice is not indicated. The lower the GFR in their study, the higher was the heart failure risk and the higher was the preventive effect of ACE inhibition on heart failure. This experience is in line with previous findings from the HOPE study where all major cardiovascular outcomes were prevented by ACE inhibition in the sub-group with mild renal insufficiency. The enhanced activation of the renin–angiotensin system may be the reason, why ACE inhibition is effectively preventing heart failure after myocardial infarction in renal insufficiency. However, Hillege et al. did not administer beta-blockers routinely in their patients. Beta-blockers, which are indicated in most people after myocardial infarction, definitely enhance the efficacy of ACE inhibition and reduce clinical consequences by reducing renin release.

Adverse renal effects do not counterbalance the cardiovascular preventive effect of ACE inhibition in renal insufficiency. On the contrary, renal function was better preserved after acute myocardial infarction with ACE inhibition than with placebo. ACE inhibitors can provoke a sudden decrease in GFR but GFR usually reverts to basal levels after the drug has been discontinued. The phenomenon suggests possible overzealous use of diuretics, renal artery stenosis or a too generous initial ACE inhibitor dose. Large randomized controlled trials in patients with renal insufficiency or in people with widespread atherosclerotic cardiovascular damage reassuringly indicate that ACE inhibitors were stopped no more frequently than placebo because of an acute increase in serum-creatinine. Nevertheless, when starting therapy with ACE inhibitors, we must be prepared to accept a slight increase in serum-creatinine that is best explained by the physiological dilatation of the efferent glomerular arteriole. This fact is highlighted by the data of Hillege et al. and confirms previous data. The initial decrease in GFR by 10–20% is a rule after beginning ACE inhibition. The decrease is most pronounced when there is intravascular volume depletion, e.g. by high doses of diuretics. Long-term, there is unequivocal evidence that inhibition of the renin–angiotensin system blunts the progressive loss of renal function that is found in many renal diseases. This evidence was confirmed by Hillege et al.

The rate at which GFR declined after myocardial infarction was fast, about 5 ml min⁻¹ year⁻¹. The usual rate in middle-aged healthy people is 1 ml min⁻¹ year⁻¹. When renal function is moderately impaired at baseline, the rapid rate of GFR loss places the population post-myocardial infarction at risk for end-stage renal disease, i.e. dialysis. However, we are not told about proteinuria, the most important renal parameter that predicts progression of renal failure.

Simply by looking more closely than usual at serum-creatinine, the cardiologists has the opportunity to define a high-risk sub-group among people with cardiac disease. This highly informative sub-group, especially of chronic and acute coronary and heart failure patients, is defined at a minimum cost, by calculating GFR. Inhibition of the renin–angiotensin system, especially with ACE inhibitors, is protective for the heart and the kidneys at the same time. Future research should explore the experimental and clinical foundations of the cardio-renal axis. The benefit of ACE inhibition is not accompanied by severe side-effects if some clinical precautions are taken.

References

1. Hillege HL, van Gilst WH, van Yelshuisen DJ et al. Accelerated decline and prognostic impact of renal function after myocardial infarction with ACE inhibition than with placebo. ACE inhibitors can provoke a sudden decrease in GFR but GFR usually reverts to basal levels after the drug has been discontinued. The phenomenon suggests possible overzealous use of diuretics, renal artery stenosis or a too generous initial ACE inhibitor dose. Large randomized controlled trials in patients with renal insufficiency or in people with widespread atherosclerotic cardiovascular damage reassuringly indicate that ACE inhibitors were stopped no more frequently than placebo because of an acute increase in serum-creatinine. Nevertheless, when starting therapy with ACE inhibitors, we must be prepared to accept a slight increase in serum-creatinine that is best explained by the physiological dilatation of the efferent glomerular arteriole. This fact is highlighted by the data of Hillege et al. and confirms previous data. The initial decrease in GFR by 10–20% is a rule after beginning ACE inhibition. The decrease is most pronounced when there is intravascular volume depletion, e.g. by high doses of diuretics. Long-term, there is unequivocal evidence that inhibition of the renin–angiotensin system blunts the progressive loss of renal function that is found in many renal diseases. This evidence was confirmed by Hillege et al. The rate at which GFR declined after myocardial infarction was fast, about 5 ml min⁻¹ year⁻¹. The usual rate in middle-aged healthy people is 1 ml min⁻¹ year⁻¹. When renal function is moderately impaired at baseline, the rapid rate of GFR loss places the population post-myocardial infarction at risk for end-stage renal disease, i.e. dialysis. However, we are not told about proteinuria, the most important renal parameter that predicts progression of renal failure.

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References

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