

## EDITORIAL

# Minor renal dysfunction: an emerging independent cardiovascular risk factor

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Because of the excessive cardiac risk, treating a patient with renal dysfunction should no longer be regarded as primary, but rather as secondary prevention

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Following the seminal observation of Lindner and colleagues<sup>1</sup> on the excessive cardiovascular mortality in patients with end stage renal disease on renal replacement therapy, this observation has been repeatedly confirmed. It is currently known that in patients on renal replacement therapy the relative risk of dying from cardiac causes is higher by a factor of 10–100, depending on age.<sup>2</sup>

It has only recently been recognised that even minor renal dysfunction, as reflected by an increase in urinary albumin excretion and/or a decrease in glomerular filtration rate, is an independent cardiovascular risk factor<sup>3</sup> which should be added to the known factors contributing to the Framingham risk score.

This has again been confirmed and extended by the present study of Santopinto and colleagues,<sup>3</sup> published in this issue of *Heart*, who report on an impressively large prospective multicentre observational study covering 11 774 patients in 14 countries hospitalised for acute coronary syndromes. It is commonly agreed upon that the serum creatinine concentration is a non-reliable estimate of glomerular filtration rate. The sensitivity of the estimate can be increased with the so called Cockcroft Gault formula which gives an estimate of creatinine clearance. Santopinto and collaborators found that the in-hospital mortality in patients with moderate renal dysfunction (creatinine clearance 30–60 ml/min) is higher by a factor of two (adjusted relative risk (RR) 2.01), while it was higher by a factor of almost four in patients with severe renal dysfunction (odds ratio 3.71). Confirming previous observations,<sup>4,5</sup> they also noted that in-hospital medication (interestingly enough not medication taken before admission) was suboptimal, with less intensive use of antiplatelet agents, angiotensin converting enzyme (ACE) inhibitors, and  $\beta$  blockers—presumably because of a perceived greater risk. That the risk is definitely greater is illustrated in this study by the observation of a higher rate of bleeding, presumably explained by the known platelet dysfunction in renal failure.

Both Shlipak and colleagues<sup>4</sup> and Wright and associates<sup>5</sup> had noted that patients with renal dysfunction had received less diagnostic and therapeutic interventions, such as coronary angiography, coronary angioplasty or coronary bypass graft surgery, again because of an assumed

(and real) higher risk of complications—for example, bleeding, radiocontrast renal failure, etc. The documentation of such enormous excess mortality justifies future efforts to provide a detailed and reliable quantitative risk benefit estimate—for example, for the administration of radiocontrast, for administration of antiplatelet agents, etc. Nevertheless it remains difficult to understand why physicians hesitate to administer ACE inhibitors or  $\beta$  blockers to these patients.

## ADVERSE EFFECT ON SURVIVAL

The highly welcome information from the present GRACE (global registry of acute coronary events) study is in perfect agreement with other observations that mild to moderate renal dysfunction has an adverse effect on survival in the general population,<sup>6,7</sup> in hypertensive individuals examined in the HOT study,<sup>8</sup> in the high cardiovascular risk population of the HOPE study,<sup>9</sup> and in patients with congestive heart failure.<sup>10</sup>

While the epidemiological relationship appears now certain beyond any reasonable doubt, the underlying pathophysiological mechanisms have certainly not yet been sufficiently clarified. Nevertheless, recent studies have provided several hints pointing to an increased risk of accelerated atherosclerosis with minor renal dysfunction—for example, uninephrectomy in the apo-E knock out mouse,<sup>11</sup> increased concentrations of the nitric oxide (NO) synthase inhibitor ADMA in renal patients even when inulin clearance is still within the normal range,<sup>11</sup> early increase of blood pressure and left ventricular remodelling with evidence of impaired left ventricular diastolic function in renal patients with normal inulin clearance,<sup>12</sup> insulin resistance with minor renal dysfunction,<sup>13,14</sup> and sympathetic overactivity in renal patients even with normal glomerular filtration, as documented by microneurographic measurements of action potentials in the sural nerve by Klein and colleagues.<sup>15</sup> Atherogenesis, NO inhibition, increase in blood pressure and cardiac dysfunction, insulin resistance, and sympathetic overactivity undoubtedly provide an unhealthy mix, but which of the factors is (are) truly culpable (and susceptible to intervention) remains to be shown.

**Abbreviations:** ACE, angiotensin converting enzyme; GRACE, global registry of acute coronary events; HOPE, heart outcomes prevention evaluation; HOT, hypertension optimal treatment; NO, nitric oxide

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## RENAL DYSFUNCTION: THE CINDERELLA OF CARDIOVASCULAR RISK

There is no doubt, however, that renal dysfunction has remained the Cinderella of the cardiovascular risk profile. There are recent efforts to give renal dysfunction the status of a major cardiac risk factor, similar to diabetes mellitus, where Haffner and colleagues<sup>16</sup> had shown that mortality in diabetics without a history of cardiac events was equal to that in non-diabetic patients surviving a myocardial infarction. As a result, in diabetic patients cardiovascular prophylaxis, including administration of ACE inhibitors (independent of blood pressure) and of statins (independent of low density lipoprotein cholesterol values) has been advocated. It will have to be seen whether renal dysfunction will be given a similar status. Nevertheless, in my opinion, because of the excessive cardiac risk, treating a patient with renal dysfunction should no longer be regarded as primary, but rather as secondary prevention.

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### Identifying long QT syndrome using genotypic-phenotypic correlations is a life saver



Please visit the *Heart* website [[www.heartjnl.com](http://www.heartjnl.com)] for link to this full article.

Many young patients at risk of sudden death from long QT syndrome (LQTS) would benefit from a more efficient screening strategy, say the authors of a prospective study. Replacing mutation analysis with genotype-phenotype correlations would enable timely diagnosis and earlier prophylaxis for index cases and their affected relatives.

The study was performed in 40 unrelated consecutive patients using clinical and ECG data available for the index patients and their relations up to the time of referral. It assessed whether diagnosis based on the first gene elected for analysis could be increased by using known genotype-phenotype correlations and the impact on yield of positive results and on cost. It compared screening all five known causal genes for LQTS with screening for the most eligible gene first, according to published prevalences in LQTS or to phenotypic data on the index case and relatives. The data included patient age, sex, treatment and data on age at onset, triggers, and relatives' ECG results and medical history.

Incorporating phenotypic data significantly improved the yield of positive results—70% versus 45% for published data—only slightly below the optimum yield with screening for all genes and at 80% less cost. It predicted 90% of all genotyped cases correctly.

LQTS affects 1:5–7000 people, and 6–13% of patients have affected relatives. Testing for all causal mutations is labour intensive and slow; even screening for the most likely first usually entails two screenings to get a positive result.

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