Kidney Diseases beyond Nephrology

Kidney disease in cardiology

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Keywords: acute kidney injury; chronic kidney disease; end-stage renal disease; ischaemic heart disease; statins

Introduction

Once again the Twin Cities of St Paul and Minneapolis are resplendent in their brilliant Minnesota fall foliage (and presidential election campaign signs). A new bridge over the Mississippi River has been raised and opened since last year. The detritus of the Republican convention 4 weeks ago has been swept away; the same cannot yet be said for the mess arising from the current financial crisis. In light of current events, the focus of my third annual column highlighting publications in non-nephrology journals dealing with cardio-renal issues relevant to nephrologists may seem curiously irrelevant. The clinical importance of the topic, however, remains undiminished by Wall Street meltdowns, so once again, a potpourri of articles of interest is submitted for your approval. The clinical topics highlighted in these articles include acute kidney injury (AKI), statins in chronic kidney disease (CKD) and ischaemic heart disease in end-stage renal disease (ESRD) patients.

AKI I: contrast-induced nephropathy

Contrast-induced nephropathy (CIN) continues to be a vexing clinical issue for cardiologists and nephrologists managing patients with CKD and ischaemic heart disease. Peri-procedure volume expansion and contrast parsimony are universally accepted treatment strategies to reduce the risk of CIN, but as highlighted in the papers of interest, much uncertainty in clinical management remains. Weisbord et al. [1] showed that implementation of evidence-based strategies known to reduce CIN (i.e. pre-procedure volume expansion) is frequently not used in clinical settings, as only 43% of 660 patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² receiving intravenous radiocontrast media also received pre-procedure intravenous fluids. Although clinical studies frequently use a dichotomous cut-point of eGFR ≤60 mL/min/1.73 m² to define populations at risk for AKI after contrast administration, residual risk may remain for diabetic patients undergoing percutaneous coronary intervention with less severe renal impairment [2].

The route of administration (intravenous versus higher-risk intra-arterial sites) is another variable that may alter the risk for CIN. Kuhn et al. [3] report equal rates of CIN in patients with CKD and diabetes undergoing computed tomography with intravenous iopamidol (a low osmolar agent) or ioxolane (an iso-osmolar agent); however, these rates may be difficult to generalize to other higher risk settings, such as percutaneous coronary intervention. As reported in a recent series by El-Hajjar et al. [4], the incidence of CIN in 400 patients with baseline serum creatinine 1.5–2.5 mg/dL receiving ‘non-invasive’ multidetector computed tomographic coronary or peripheral arterial studies (with ‘preventive’ measures of N-acetylcysteine, sodium bicarbonate and iso-osmolar intravenous contrast) was surprisingly low, 1.75%. One excellent recent review framing the contrast controversy (drawing on the comprehensive work of the CIN Consensus Working Panel) was published by McCullough [5].

Sodium bicarbonate has been promoted for its prophylactic benefit in attenuating the risk of CIN [6]; a recent retrospective observational study from the Mayo Clinic, however, instead suggested an increased incidence of CIN associated with intravenous sodium bicarbonate [7]. Brar et al. [8], in a single-blind study of 353 patients with eGFR ≤60 mL/min/1.73 m² and one risk factor (congestive heart failure, diabetes, hypertension or age >75 years) undergoing non-emergent cardiac catheterization, prospectively randomly assigned patients to intravenous sodium chloride or sodium bicarbonate (with stratification by diabetic status and use of N-acetylcysteine) administered at the same rate (3 mL/kg for 1 h before coronary angiography, 1.5 mL/kg/h during the procedure and for 4 h after completion of angiography). The primary endpoint (≥25% decrease in eGFR 1–4 days after the procedure) was met in 13.3% of patients assigned to sodium bicarbonate and 14.6% of patients assigned to sodium chloride [relative risk (RR) 0.94, 95%
confident interval (CI) 0.55–1.60]. Importantly, the groups were well matched clinically (including mean left ventricular end-diastolic pressure of 17 mmHg in both groups, implying comparable ‘volume status’). The trial design of the Brar et al. study [8] is considerably different from the design of the RENO study [9], in which patients undergoing emergency percutaneous coronary intervention received either pre-procedure sodium bicarbonate and post-procedure volume expansion or no pre-procedure volume expansion and post-procedure sodium chloride. The purported benefit of sodium bicarbonate in RENO is difficult to accept, as the volume status of the treatment groups was not comparable at the time of angiography. I suspect that the results of the Brar et al. study [8] will dampen enthusiasm for the indiscriminate use of sodium bicarbonate, but I would predict more publications on this topic in the near future.

The concept of contrast parsimony to reduce AKI is intuitively logical, and data from Kane et al. [10] lend credence to the ‘less is better’ credo. These investigators found that the incidence of CIN (defined as absolute serum creatinine increase of ≥0.5 mg/dL, occurring in 15% of patients) was directly associated with contrast volume (in a patient cohort with mean eGFR 31 mL/min/1.73 m² undergoing coronary angiography), with an incremental odds ratio of CIN 2.12 (95% CI 1.4–3.4) associated with each additional 20 cc of contrast. Interestingly, 53.6% (n = 15) of patients who developed CIN required dialysis within a year, compared to 5.7% (n = 9) of patients with no CIN (P < 0.0001).

Finally, readers are urged to read a provocative, disturbing observational paper by Newhouse et al. [11] and the accompanying editorial by Baumgarten and Ellis [12] for a ‘revisionist’ interpretation of CIN. Newhouse et al. identified 32,161 patients in an electronic medical record with serial creatinine levels recorded on 5 consecutive days and no prior radiocontrast administration in the previous 10 days. More than half of the patients showed a change of at least 25%. Among patients with baseline creatinine values of >2.0 mg/dL, increases of at least 25% occurred in 16% of patients and of 50% in 7% of patients, and increases of 0.6 mg/dL occurred in 26% of this group. Newhouse and colleagues are suggesting that the background incidence of ‘hospital-induced nephropathy’ (or more accurately, comorbidity-associated nephropathy) confounds the hazard estimates of developing CIN (and the attenuation of risk by diverse preventive strategies), because of the implicit absence of a true control group (i.e. sham control) in most studies on CIN.

**AKI II: cardiac surgery**

AKI after cardiac surgery is associated with increased mortality. Brown et al. [13] previously published data on the association of postoperative rise in serum creatinine and 90-day mortality in patients after cardiac surgery. These authors have now extended their analysis to include long-term follow-up (mean 2.7 years) of 13,748 patients (who did not require dialysis preoperatively) undergoing surgical coronary revascularization without concomitant valve surgery, in northern New England, USA, from 2001 to 2006 [14]. Patients were stratified by postoperative eGFR categories (≥90, 60–89, 30–59, 15–29 and <15 mL/min/1.73 m²), and incident death rates were calculated after adjustment for demographic and clinical variables, including preoperative renal function. In the cohort, 62% of patients had a postoperative reduction in renal function, 18% had no change and 20% had improved renal function (based on last preoperative serum creatinine and highest postoperative serum creatinine). The estimated incident death rates per 100 patient-years were respectively 1.4, 1.8, 3.9, 12.4 and 21.2 for the five categories of postoperative renal function. The adjusted hazard ratios (95% CI), with eGFR ≥90 mL/min/1.73 m² as reference, for all-cause mortality were respectively 1.07 (0.82–1.39), 1.76 (1.34–2.30), 4.42 (3.27–5.96) and 7.03 (4.93–10.04). Interestingly, postoperative renal function (i.e. eGFR) was marginally more predictive of 5-year mortality than preoperative renal function, with, surprisingly, no apparent mortality risk associated with the magnitude of acute renal function deterioration; that is, the mortality risk is equivalent for an acute drop in eGFR from 90 to <15 mL/min/1.73 m² and from 30 to <15 mL/min/1.73 m². Importantly, exactly what is mediating this deadly outcome in some patients with AKI, and how to prevent it, is still unclear.

My colleagues at the Minneapolis Veterans Affairs Medical Center recently published results of their prospective, randomized placebo-controlled trial of oral N-acetylcysteine for prevention of AKI in CKD patients undergoing cardiac surgery [15]. Patients requiring urgent surgery, with renal transplants or previous dialysis, or with prior radiocontrast administration within 4 days before surgery were excluded. A total of 102 patients with eGFR <60 mL/min/1.73 m² for at least 3 months were randomized. The primary outcome variable was maximal change in creatinine from baseline within 7 days after surgery, and secondary outcomes were development of AKI (rise in serum creatinine of >0.5 mg/dL or ≥25%), frequency of postoperative dialysis, operative mortality and length of stay. At postoperative Day 5, AKI occurred in 41 patients (22 N-acetylcysteine, 19 placebo). There was no significant difference related to treatment for any outcome variable. Although the results are disappointing, they are not completely unexpected, given the small sample size and the uncertain relative contribution of oxygen free-radicals to the clinical syndrome of AKI, in humans. At present, the role of N-acetylcysteine for prevention or amelioration of AKI in a variety of clinical settings remains controversial. Future clinical trials testing interventions to prevent AKI are warranted.

**Statins in CKD**

Statins play an important role in the primary and secondary prevention of cardiovascular disease in the general population. Patients with CKD face increased vulnerability to cardiovascular morbidity and mortality, with a graded incremental risk inversely related to the level of renal function. The assumption that statins should be particularly efficacious in CKD patients seems reasonable, but remains unsupported in prospective clinical trials specifically
targeting CKD patients, including the negative result of the 4D study in diabetic dialysis patients [16]. Subgroup analyses in the Heart Protection Study (HPS) and Cholesterol and Recurrent Events (CARE) study [17,18] suggest improved outcome for CKD patients receiving statins; management of dyslipidaemia in CKD is nicely framed in a recent review by Harper and Jacobson [19]. A recent meta-analysis by Strippoli et al. [20] provides additional support for the putative benefit of statins for reducing cardiovascular events (but not all-cause mortality) in CKD patients. Fatal cardiovascular events were reduced by 19% (RR 0.81, 95% CI 0.73–0.90) and non-fatal events by 22% (RR 0.78, 95% CI 0.73–0.84) in patients receiving statins in this meta-analysis. All-cause mortality, however, was reduced by a non-significant 8% (RR 0.92, 95% CI 0.82–1.03) in a pooled analysis comprising 44 studies and 23,665 patients.

The best inferential support for the role of statins in reducing cardiovascular events in CKD patients is provided by a post hoc analysis of the presciently yclept (in the context of the worldwide financial implosion occurring at the time this review was prepared) TNT (Treating to New Targets) study [21]. Of 10,001 patients with clinically evident coronary heart disease (CHD) prospectively randomized to double-blind therapy with either 10 or 80 mg of atorvastatin daily, 9,656 patients had complete data regarding renal function; 3,107 had CKD, defined as eGFR < 60 mL/min/1.73 m$^2$. The primary outcome measure of major cardiovascular events was defined as CHD, death, non-fatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest or fatal or nonfatal stroke. Median follow-up was 5 years; 351 patients with CKD (11.3%) and 561 patients without CKD (8.6%) experienced the primary endpoint [hazard ratio (HR) for CKD patients: 1.35, 95% CI 1.18–1.54]. Compared to 10 mg of atorvastatin, in the high-dose arm, the relative risk of major cardiovascular events was reduced by 32% in CKD patients (HR 0.68, 95% CI 0.55–0.84) and 15% in non-CKD patients (HR 0.85 95% CI 0.72–1.00).

It has been suggested that statins may retard the rate of progression of renal function decline in CKD patients [22–25], but this issue remains unsettled [20]. The TNT study had no control group; the treatment arms were either 10 or 80 mg of atorvastatin per day. Both groups showed small increases in eGFR, rather than the ‘expected’ decline over time, suggesting indirect support for the renoprotective effect of statins. Although I am leery of divination of future clinical trial results (or the performance of financial markets), it is a reasonable wager that the completion of the ongoing SHARP (Study of Heart and Renal Protection) trial will help clarify the issue of statins in renal disease.

Ischaemic heart disease in dialysis patients

Three interesting studies from Japan pertaining to diagnosis and treatment of ischaemic heart disease in dialysis patients merit mention. On the treatment side, there has been a great interest (including by this author) in the efficacy of drug-eluting stents (DES) for the treatment of obstructive coronary artery disease in dialysis patients, especially as prior data suggested superior outcomes with surgical coronary revascularization compared to non-drug-eluting (bare metal) stents in these patients [26]. Few data exist on the rate of restenosis in dialysis patients after DES, particularly due to incomplete angiographic follow-up (and potential unreliability of using surrogate measures to detect occult restenosis). Ishio et al. [27] retrospectively matched 54 dialysis patients treated with DES to a comparator group of 54 patients treated with non-DES. Angiographic follow-up was obtained for 80% of the DES group and 86% of the non-DES group. In the DES group, 31% had angiographic restenosis (22% in-stent and an additional 9% at the stent edge) versus 20 patients (37% of 54, but reported as 43%) with restenosis (19 due to in-stent restenosis) in the non-DES group. Aoyama et al. [28] retrospectively compared 88 patients (121 lesions) receiving DES to 78 patients (95 lesions) receiving bare metal stents. Angiographic follow-up was obtained in ~85% of both groups. Angiographic restenosis occurred in 22% of the DES group and 24% of the bare-metal-stent group. Although the sample size is small, these studies are concerning as they cast doubt on the assumed (ESRD patients were typically excluded from clinical trials) superiority of DES in ESRD patients.

Nishimura et al. [29] offer a novel diagnostic strategy for identifying dialysis patients at risk for cardiac events. Single-photon emission computed tomography (SPECT) using I-123 labelled beta-methyl iodophenylpentadecanoic acid (BMIPP) reflects fatty acid metabolism in the myocardium (and myocardial ischaemia). The investigators followed 375 haemodialysis patients without chest symptoms after resting 123I-BMIPP and Thallium-201 dual myocardial scintigraphy on a non-dialysis day. Fifty-seven patients receiving coronary revascularization within 60 days were excluded; the remaining 318 patients were followed for a mean of 3.6 years, with the survival endpoint of cardiac death. There were 50 cardiac deaths. Using a BMIPP summed score of 12 (reflecting a more severe derangement in myocardial fatty acid metabolism) as a cut-off value, the hazard ratio for cardiac death was 21.9 (95% CI 8.5–56.1). Cardiac-event-free survival at 3 years was 61% for patients with BMIPP summed scores of $\geq 12$ ($n = 98$) and 98% for those with scores $< 12$ ($n = 220$). Of note, some of these patients may have suffered from ischaemia mediated by microvascular disease occurring in uraemic cardiomyopathy (e.g. myocardial fibrosis and inadequate capillary reserve for perfusion of hypertrophied hearts), a process that might escape detection with conventional angiographic methods. The work of Nishimura et al. [29] offers a new window on our clinical understanding of ischaemic heart disease in dialysis patients, because it potentially encompasses both large vessel epicardial coronary artery disease and microvascular disease.

Conclusion

A continued and expanding interest in cardiorenal disease, and in understanding the formidable cardiovascular risk for CKD patients, is apparent. Designs for new clinical trials targeting cardiovascular disease in CKD patients are eagerly anticipated (along with a return to economic stability).
Conflict of interest statement. The author is on the scientific advisory board (SAB) of CorMedix.

References

Received for publication: 15.10.08 Accepted in revised form: 21.10.08