Kidney Diseases Beyond Nephrology

Kidney disease in cardiology

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Introduction

It is a balmy Armistice Day in the Twin Cities of St. Paul and Minneapolis, but the dense carpet of fallen leaves on umber lawns is a harbinger of another imminent Minnesota winter. The arrival of the snow flurries, however, seems benign in comparison to the current national discourse on health care reform; predicting the first blizzard seems a lot easier than divining the outcome of this fractious debate. Although the focus of my fourth annual column is narrow (reviewing cardiology papers that are relevant to nephrologists but appeared in non-nephrology journals), the topic remains clinically relevant, as chronic kidney disease (CKD) is such a powerful predictor of adverse cardiovascular outcome. The arc of this column covers acute kidney injury (AKI), acute myocardial infarction (AMI), statins, CKD biomarkers and risk stratification and hypertensive cardiovascular disease.

Contrast-induced acute kidney injury

The recent volume of publications, particularly randomized clinical trials, regarding the prevention of contrast-induced acute kidney injury (CI-AKI) in cardiology journals may be surprising to nephrologists. The topic is challenging for clinicians (and authors of practice guidelines) striving to practice or promote ‘evidence-based’ medicine. Iloprost, a prostacyclin analogue, has been shown to protect against radiocontrast media renal toxicity in rats. Spargias et al. [1] compared iloprost (infused 30–90 min before, ending 4 h after intervention) to placebo in a trial of 208 patients with serum creatinine ≥1.4 mg/dL undergoing coronary angiography and/or percutaneous coronary intervention (PCI). The primary outcome was the ‘classic’ CI-AKI definition, absolute serum creatinine increase ≥0.5 mg/dL or relative increase ≥25%. These patients were at high risk for CI-AKI; 50% were diabetic, and contrast volumes were large (mean approximately 250 cc). Use of N-acetylcysteine (in only 9% of patients) and type of contrast agent were determined by the interventional cardiologist. Surprisingly, the study gave no information regarding the administration of sodium bicarbonate. Of patients randomized to iloprost, 8% developed CI-AKI versus 22% of control patients (odds ratio [OR] 0.29, confidence interval [all reported at 95%] 0.12–0.69). Although promising, these findings need independent confirmation. One bothersome aspect of the study is that, despite the procedure being solely diagnostic for half the patients, the contrast volume was unusually large; contrast parsimony should be an essential part of clinical management in the cardiac catheterization laboratory.

This issue is nicely framed by Morikawa et al. [2], testing the efficacy of atrial natriuretic peptide (ANP; initiated 4–6 h before, continued for 48 h after coronary angiography or intervention) in a randomized placebo-controlled trial of CI-AKI prevention in 254 patients with serum creatinine ≥1.3 and <6 mg/dL. Independent predictors of CI-AKI were contrast volume ≥155 cc (OR 6.89, 2.4–19.3) and ANP infusion (OR 0.24, 0.07–0.77). Although the protective effect of ANP is physiologically interesting, a drug infusion protocol requiring 2 days of continuous intravenous therapy will not be greeted enthusiastically by practicing cardiologists. Scrupulous attention to contrast volume and pre-procedural intravascular volume expansion remain the cornerstones of CI-AKI prevention.

There remains no dearth of new papers on the comparative efficacy of iso-osmolar versus low-osmolar contrast media (LOCM) for CI-AKI prevention. Laskey et al. [3] prospectively compared the ‘iso-osmolar’ ioxigalex to the ‘low-osmolar’ iopamidol in 526 patients (of whom 418 were ‘eligible’) with diabetes and CKD. Median baseline estimated creatinine clearance was 45.5 mL/min for the ioxigalex and 47.9 mL/min for the iopamidol groups (P = ns). Peri-procedural intravascular volume expansion was employed, but without sodium bicarbonate or other putative ‘nephroprotective’ agents. Contrast volume was similar in both groups and not unduly large (mean approximately 120 cc). Incidence of CI-AKI (defined as increase in serum creatinine ≥0.5 mg/dL from baseline within...
3 days of receiving contrast) after coronary angiography with or without PCI was 11.2% in the ioxixanol and 9.8% in the iopamidol groups ($P = ns$). As the study population would be legitimately considered to be at increased risk for CI-AKI, the findings are noteworthy, with the caveat that creatinine clearance was $< 30$ mL/min for relatively few patients (10%).

Another smaller trial by Mehran et al. [4] compared 72 patients (51% with diabetes) receiving ioxixanol to 74 patients (41% with diabetes) receiving the low-osmolar agent ioxaglate. Mean baseline creatinine clearance in both groups was about 45 mL/min, and about two-thirds of each group underwent PCI. The contrast volume was large (55% of ioxixanol and 51% of ioxaglate patients received at least 200 cc). A peak increase in serum creatinine of $≥ 0.5$ mg/dL occurred in 15.9% of ioxixanol and 18.2% of ioxaglate patients ($P = ns$), and an increase of at least 25% in 15.9% of ioxixanol and 24.2% of ioxaglate patients ($P = ns$). A recent meta-analysis by Reed et al. [5] of 16 trials comparing CI-AKI incidence with ioxixanol and other LOCM found no difference overall for ioxixanol versus LOCM (relative risk [RR] 0.79, 0.56–1.12). However, when individual agents were compared, the conclusion was somewhat different: ioxixanol versus ioxaglate, RR 0.58, 0.37–0.92; versus iohexol, RR 0.19, 0.07–0.56; versus iopamidol, RR 1.20, 0.66–2.18; versus iopromide, RR 0.93, 0.47–1.83; versus ioversol, RR 0.92, 0.60–1.39. Unfortunately, no compelling data could resolve this agent-specific versus class-specific conundrum for CI-AKI, but this is not a unique clinical problem. At present, a fair conclusion is that the benefit of ioxixanol for reducing CI-AKI risk is, at best, modest. Furthermore, the nagging issue of a ‘standard’ CI-AKI definition remains, as reported incidence can vary depending on endpoint definitions [4,6].

As prophesized in last year’s column, more publications on the role of sodium bicarbonate for preventing CI-AKI have appeared, but, like the local weather, the issue remains unsettled. Maioli et al. [7] randomized 502 patients with estimated creatinine clearance $< 60$ mL/min to open-label isotonic saline 1 mL/kg/h 12 h before and after coronary angiography/PCI or sodium bicarbonate (154 mEq/L in dextrose and water) 3 mL/kg/h 1 h before contrast administration and 1 mL/kg/h 6 h after the procedure. All patients received oral N-acetylcysteine and ioxixanol. Commendably, all had echocardiographic evaluation of left ventricular (LV) function (with reduced hydration rate in patients with LV ejection fraction $< 40%$ or Class III–IV congestive heart failure). Mean contrast volume was 170 mL in the saline and 160 mL in the bicarbonate groups. Only 24% of patients were diabetic; mean basal creatinine clearance was 42 mL/min in the saline and 43 mL/min in the bicarbonate group ($< 30$ mL/min for only 15% of all patients). CI-AKI ($≥ 0.5$ mg/dL increase in serum creatinine within 5 days after contrast) occurred in 11.5% of the saline and 10.0% of the bicarbonate groups ($P = 0.60$). The secondary endpoint, $≥ 25%$ relative increase in serum creatinine, occurred for 20.6% of the saline and 15.2% of the bicarbonate groups ($P = 0.13$). This trial is ‘negative’, but one paradoxical outcome may be increased sodium bicarbonate use; a 7-h infusion of sodium bicarbonate would be more palatable to cardiologists (and hospital administrators) than a 24-h infusion of saline.

For this reason, the findings of Tamura et al. [8] are interesting, but tangential to clinical practice. They found that a single-bolus intravenous administration of 20 mEq of sodium bicarbonate 5 min before contrast exposure further reduces CI-AKI risk when added to ‘conventional’ isotonic saline administration, given 12 h before and after contrast; however, infusion time was not shortened in the bicarbonate arm. In this small trial (72 patients in each arm), incidence of reported CI-AKI ($≥ 25%$ rise in serum creatinine or $> 0.5$ mg/dL within 3 days) was 1.4% in the saline/bicarbonate arm versus 12.5% in the saline-only arm ($P = 0.017$). As predicted in columns of yesteryear, more trials on the role of sodium bicarbonate in preventing CI-AKI are likely.

**Acute kidney injury II: cardiac surgery**

Pre-operative renal function and AKI in the setting of cardiac surgery have been shown to independently predict outcome [9,10], but less is known about long-term survival after complete recovery from AKI. Hobson et al. [11] retrospectively analysed the 10-year survival of 2973 patients with no CKD history undergoing cardiac surgery 1992–2002, stratified by the presence of AKI and Risk, Injury, Failure, Loss, and End-stage (RIFLE) classification of severity. In a Cox model, compared with patients without AKI, hazard ratios (HR) were 1.23 (1.06–1.42) for the least severe and 2.14 (1.73–2.66) for the most severe RIFLE classes. The most interesting finding, however, was that, even for patients with ‘complete renal recovery’ (defined as serum creatinine at hospital discharge $< 50%$ above baseline), the HR for death was 1.28 (1.11–1.48) compared with patients without AKI. One could argue that some of these patients did not experience ‘complete renal recovery’; nevertheless, the persistent hazard at 10 years further validates the long-term clinical importance and ‘downstream’ consequences of AKI.

**Acute kidney injury III: advanced decompensated heart failure/congestive kidney failure**

Mullens et al. [12] challenged the conventional paradigm of low cardiac output as the main determinant of acute renal function deterioration in advanced decompensated heart failure. In their provocative invasive study of 145 patients, they argue for the key concept of ‘congestive kidney failure’: venous congestion, assessed by central venous pressure (CVP), is a predictor (and cause) of acute renal function deterioration in advanced decompensated heart failure (an idea with experimental support dating back seven decades). Prospectively testing CVP-guided (as assessed non-invasively by inferior caval sonography) treatment strategies in these ill patients would be interesting, particularly coupled with ultra-filtration.
Chronic kidney disease I: biomarkers and risk stratification

CKD and biomarkers reflecting renal disease severity are independent predictors of cardiovascular morbidity and mortality. Keller et al. [13] studied 1827 patients (previously enrolled in the AtheroGene registry) with estimated glomerular filtration rate (eGFR, reported in millilitres per minute per 1.73 m²) >60 and assessed the cardiovascular mortality risk related to plasma cystatin C levels. Logarithmically transformed, standardized cystatin C predicted cardiovascular death (HR 1.94, 1.59–2.37), with mortality risk 3.87-fold (2.33–6.42) higher for the upper quartile, suggesting a potential ‘threshold effect’.

Go et al. [14] analysed the relation of proteinuria and eGFR and risk of thromboembolism in patients with chronic non-valvular atrial fibrillation (not receiving anticoagulation) enrolled in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. During 33 165 patient-years without anticoagulation for 10 908 patients, 676 new thromboembolic events occurred. In a multivariate regression model, urine dipstick proteinuria (≥30 mg/dL) was associated with a 54% increased risk of thromboembolism (RR 1.54, 1.29–1.85). A graded, increased risk of stroke was associated with progressively lower eGFR; compared with eGFR ≥60ml/min, RR for eGFR <45 ml/min was 1.39 (1.13–1.71).

Finally, Hakeem et al. [15] examined the prognostic utility of myocardial perfusion single-photon emission computed tomography for predicting cardiac death in 1652 patients with preserved renal function or CKD (eGFR <60). Unsurprisingly, cardiac death risk increased with worsening levels of perfusion defects across the spectrum of renal function, and inducible ischaemia independently predicted death. The most important finding, however, was the cardiac death rate in patients with entirely normal nuclear studies: negative predictive value was markedly attenuated by CKD. The annual cardiac death rate for patients with normal studies was 0.4% for eGFR 90 ml/min, 0.9% for 60–89 ml/min, 2.2% for 59–30 ml/min and 4.7% for <30 ml/min. This study confirms the powerful independent cardiac risk associated with CKD and casts doubt on the clinical utility of myocardial perfusion studies for cardiac risk stratification in CKD patients.

Chronic kidney disease II: acute myocardial infarction

Convincing data relate diminished renal function and adverse outcome in CKD patients with AMI. Evidence-based therapies beneficial for non-CKD patients with AMI are assumed (not necessarily based on CKD-specific data) to be efficacious in CKD patients. Szummer et al. [16] reported 1-year mortality hazards for early revascularization versus conservative (medical) management of non-ST-elevation MI patients (in the SWEDHEART registry), stratified by eGFR ranges. In patients with eGFR ≥90, 60–89 and 30–59 ml/min, an invasive (early revascularization) strategy was associated with reduced mortality (42 to 32% from highest to lowest eGFR, P = 0.001), but it was of no benefit in patients with eGFR 15–29 and <15 ml/min or on dialysis [HR 0.91 (0.51–1.61) and 1.61 (0.84–3.09), respectively].

Medi et al. [17] analysed the relative benefit of acute coronary reperfusion (with PCI or fibrinolitics) in patients enrolled in the Global Registry of Acute Coronary Events (GRACE) registry, stratified by eGFR ≥60, 30–59 or <30 ml/min. Fibrinolysis was not associated with decreased in-hospital or 6-month mortality in any group. PCI outcomes were better for patients with eGFR ≥60 ml/min in hospital (OR 0.54, 0.38–0.78) and for patients with eGFR 30–59 ml/min at 6 months (OR 0.41, 0.22–0.75). However, for patients with eGFR <30 ml/min, there was no in-hospital benefit and a suggestion of harm at 6 months (OR 2.73, 1.01–7.36).

Finally, Lambert et al. [18] retrospectively analysed outcomes for non-stage 5 CKD patients with AMI receiving coronary stents regarding eGFR and dipstick proteinuria. As expected, presence of eGFR 15–59 ml/min and dipstick proteinuria predicted stent thrombosis (HR 3.69, 1.54–8.89) and mortality (HR 2.68, 1.34–5.37). Diminished eGFR alone also predicted stent thrombosis (HR 2.61, 1.22–5.10). Changing practice guidelines to reduce PCI use for AMI treatment in severe CKD patients based on these observational data would be premature; however, these studies mandate further clinical trials and careful attention to haemorrhage and other complications of invasive therapy in this high-risk population.

Statins (or 4D redux: the record of null trials in dialysis patients remains unbroken)

Concordant with the 4D Study findings [19], the astronomically cycled A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) reported a null result for rosuvastatin benefit in reducing occurrence of the primary combined endpoint of cardiovascular death, non-fatal MI, and non-fatal stroke or the secondary endpoint of all-cause mortality [20]. Taken together, 4D and AURORA raise the issue of primary mechanistic differences in cardiovascular death in dialysis patients: in contrast to the general population where the hazard of ‘atherosclerotic heart disease/coronary heart disease’ is reduced by statins, reducing low-density lipoprotein cholesterol in dialysis patients does not result in improved cardiovascular outcome. We have speculated that one major reason is that sudden death (accounting for about 26% of deaths in 4D) is not a consequence of ‘coronary heart disease’, but of LV hypertrophy and myocardial fibrosis [21]. An interesting footnote is the preliminary post hoc analysis, finding reduced MI (a ‘coronary’ event) with rosuvastatin in diabetic patients in AURORA [22].

The eagerly anticipated release of the Study of Heart and Renal Protection (SHARP) trial data at the end of 2010 will complete the landmark trilogy of statin trials in CKD.
Hypertensive cardiovascular disease

A trio of stimulating papers is recommended for careful review. Aldosterone has been implicated as a cause of decreased arterial compliance and LV hypertrophy. Edwards et al. [23] compared the aldosterone antagonist spironolactone to placebo in normotensive stage 2 and 3 patients already treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. After 40 weeks, LV mass was reduced and measures of aortic distensibility improved in the spironolactone group, a finding not attributable to lower blood pressure. Continuing the ongoing assault on ‘conventional’ (e.g. atenolol) beta-blocker therapy for hypertension, Bangalore et al. [24] examined the relation of resting heart rate to outcome in a meta-analysis of beta-blocker trials for hypertension. Lower attained heart rate in patients receiving beta-blockers was associated with adverse outcome: increased risk of all-cause mortality, cardiovascular mortality, MI, stroke or heart failure. The authors suggest that bradycardia may ‘paradoxically’ increase central aortic pressure by a temporally inappropriate delay of reflected aortic pressure waves and resultant dys-synchrony of outgoing and reflected wave.

Whatever the mechanism, the analysis of Bangalore torpedoed the concept of therapeutic bradycardia in treating hypertension.

Drawing on the classic work of Gerald DiBona (one of my medicine chiefs three decades ago) on renal sympathetic activity, Krum et al. [25] performed a proof-of-concept trial of therapeutic renal sympathetic denervation by catheter-based percutaneous radiofrequency ablation to treat resistant hypertension in 50 patients. In 10 patients studied, mean reduction of renal noradrenaline spillover after ablation was 47% (28–65%). Mean reduction in blood pressure (baseline 177/101 mmHg, standard deviation 20/15) at 9 months was 47% (28–65%). Mean reduction in blood pressure (baseline of therapeutic renal sympathetic denervation by catheter-based percutaneous radiofrequency ablation to treat resistant hypertension).

Conclusion: can you mend a broken heart?

Divination of future events (e.g. the next great clinical advance) is fraught with difficulty, but elegant, innovative research may provide a fleeting glimpse of what lies beyond our current event horizon. My favourite paper in 2009 was the stunning work by Bergmann and colleagues [26] on cardiomyocyte renewal in humans. Whether people can regenerate myocardial cells in adult life (a profoundly important question in the context of the large cardiac disease burden in CKD patients) has been conjectural. Although the authors found that fewer than the 50% of cardiomyocytes are exchanged during a normal life span (using the integration of 14C generated by nuclear bomb testing during the Cold War into genomic DNA of human myocardial cells to gauge rates of renewal), the unequivocal demonstration of this regenerative capacity (by literally using fallout from weapons of mass destruction) may be a catalyst for translational research on how to mend a broken heart. One thing, however, is certain. Spring will come next year (and, hopefully, health care reform and economic stability).

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References

Kidney disease in diabetology: lessons from 2009

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Introduction

Diabetic nephropathy (DN) is the worldwide most common cause of renal failure requiring renal replacement therapy, but today most patients have type 2 and not type 1 diabetes. During the last 30 years the rate of type 1 diabetic patients requiring renal replacement therapy decreased continuously due to significant improvement of antidiabetic and antihypertensive treatment strategies. The landmark study DCCT (Diabetes Control and Complications Trial) showed that a mean reduction in HbA1C by 2% reduced the incidence of nephropathy by 54% and retinopathy by 76% [1]. A recent report [2] from the DCCT indicates that after 30 years of diabetes, the cumulative incidences of proliferative retinopathy, DN, and cardiovascular disease (CVD) were as high as 50%, 25% and 14% in the conventional treatment group (mean HbA1c: 9%), but only 21%, 9% and 9% in the intensive treatment group (mean HbA1c: 7%). Interestingly, less than 1% in the intensive treated patient group became blind, required kidney replacement or needed an amputation because of diabetes during that time. The increased burden arriving from type 2 diabetes is explained not only by the worldwide pandemia of that disease, but also by the much longer life expectancy. Before 1980 most patients with type 2 diabetes died before they progressed to end stage renal disease (ESRD). Recently, good news were reported from the Framingham study [3] indicating that type 2 diabetic patients had a 69% decline in CVD mortality similar to patients without diabetes (62% decline) during the last 25 years (1976–2005) compared with the earlier period between 1950 and 1975. Compared with individuals without diabetes mellitus, individuals with diabetes experienced a greater increase in body mass index, a greater decrease in low-density lipoprotein cholesterol and a similar magnitude of decline in systolic blood pressure [4]. However, diabetic individuals have not experienced the necessary declines in CVD risk factors to overcome this increased CVD risk and to protect them from progressing to ESRD after long duration of diabetes.

Chronic kidney disease is a dominant predictor for excess mortality in type 1 diabetes

Despite modern therapeutics, type 1 diabetes continues to be associated with premature death. Mortality in individuals with type 1 diabetes is about 3–4 times higher than in the...