Editors' view

Novel therapeutic approaches to chronic kidney disease

Neeraj Dhaun¹ & David J. Webb²¹Department of Renal Medicine, Royal Infirmary of Edinburgh and ²Clinical Pharmacology Unit, University of Edinburgh, The Queen's Medical Research Institute, Edinburgh, UK

Chronic kidney disease (CKD) is a major health problem that affects 10–16% of the general adult population in Asia, Europe, Australia and the USA [1–6]. Progression to end-stage renal disease (ESRD) remains a major clinical problem, and there are currently over a million patients worldwide on dialysis, with the number continuing to increase by ~7% yearly [7]. Dialysis is expensive, costing ~£30 000 per patient per year in the UK [8]. Furthermore, survival once on dialysis is poor.

Cardiovascular disease (CVD) commonly accompanies CKD. While many patients with CKD have other risk factors for CVD, with hypertension being the commonest and much of the increased risk being attributable to these other risk factors, repeated studies demonstrate that CKD itself is an independent risk factor [9]. Mortality from CVD is 10–20 times greater in dialysis patients than in the general population; for a patient under 45 years of age, this rises to 100 times [10]. As renal function declines, the association with CVD increases, and patients with nondialysis-requiring CKD are more likely to die from CVD than to develop ESRD [11]. Furthermore, not only are individuals with CKD at increased risk of adverse cardiovascular events, but their outcome after these events is worse than those without CKD [12]. Such figures have led the US National Kidney Foundation Task Force on CVD in Chronic Renal Disease to recognize that patients with CKD should be considered in the 'highest risk group' for subsequent cardiovascular events [13].

Microalbuminuria (and overt proteinuria) is a marker of renal dysfunction and is well recognized as an adverse prognostic indicator for poor CVD outcomes in both diabetic [14, 15] and nondiabetic patients, with the HOPE study demonstrating a >60% increased risk of stroke, myocardial infarction or cardiovascular death in nondiabetic subjects with microalbuminuria [16]. Albuminuria is incrementally associated with increased cardiovascular risk both in individuals with pre-existing risk (such as hypertensive patients) [17] and in individuals with no known risk factors [18]. This is true even in the presence of normal

renal function [19]. Importantly, a reduction in proteinuria is associated with a reduction in the rate of decline of glomerular filtration rate (GFR) in patients with CKD [20, 21], while in patients with hypertension it confers cardiovascular protection [17]. The prevalence of hypertension ranges from about 22% in stage 1 CKD to >80% in stage 4 disease [5, 22]. This increases with both decreased GFR and increased proteinuria [22].

Both epidemiological and clinical data show that damage to large arteries contributes to the increased cardiovascular risk observed in CKD [23]. Atherosclerosis is the most frequent cause of arterial damage in the general population [24]. Additionally, medial calcification, associated with CKD, leads to arterial stiffening associated with arteriosclerosis [25]. Arterial calcification and stiffness are independent predictors of all-cause and cardiovascular mortality in patients with CKD [26]. In their review, Goldsmith and colleagues discuss vascular calcification and its potential for reversal in patients with CKD. The endothelium is an important regulator of vascular tone [27], and endothelial dysfunction is associated with increased cardiovascular risk [28]. Both endothelial dysfunction and increased arterial stiffness commonly coexist in CKD patients.

There is an important unmet need for treatments that can slow the rate of progression of renal impairment, delaying the onset of dialysis in CKD. Given that CKD is characterized by arterial stiffening and endothelial dysfunction and is commonly associated with hypertension [29] and atherosclerotic vascular disease [10], therapies that might offer additional cardiovascular protection are particularly attractive. The reviews presented in this series look at novel therapeutic strategies that may be added onto current standard treatments in patients with CKD.

Some of the agents discussed in these series of reviews are licensed drugs for indications other than CKD, for which there may be renal benefits. Kohan and colleagues discuss the potential of endothelin receptor antagonists. These drugs are currently licensed for the orphan indication of

pulmonary arterial hypertension but may provide benefits for both diabetic and nondiabetic CKD patients in terms of blood pressure (BP) and proteinuria reduction. This treatment is in addition to standard therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Similar BP and proteinuria benefits are discussed in a review in the journal *Hypertension* on the phosphodiesterase-5 inhibitors [30], currently licensed for pulmonary arterial hypertension and erectile dysfunction. In the current series, Persson and colleagues focus on the direct renin inhibitors, which are licensed for hypertension. In addition to their effects on BP and proteinuria, these agents may provide wider cardiovascular benefits.

In addition to existing drugs with off-label indications, there have recently been some altogether new therapeutic strategies that may be of benefit in CKD. Not only is hypertension a frequent finding in patients with CKD but it is difficult to control, with over 75% of patients with a GFR <30 ml min⁻¹ having a BP >140/90 mmHg [1]. Despite treatment with multiple antihypertensive agents, the majority of CKD patients fail to reach target BP [31]. Thus, the review of renal sympathetic denervation for the treatment of resistant hypertension by Krum is of great interest. To date, the studies of this technique have excluded those patients with significant CKD, and the renal community remains sceptical about the benefit of this technique for its patients, in particular with regard to safety and preservation of longer-term renal function.

Autosomal dominant polycystic kidney disease (ADPKD) affects approximately one of every 1000 persons in the general population and develops, by means of slowly progressive renal cyst growth, to ESRD in over 50% of patients [32]. ADPKD is the commonest inherited kidney disorder and is the cause for ESRD in 7–10% of patients requiring dialysis [32]. Although several drugs effectively suppress cyst growth in cystic animal models, until recently there has been a lack of medical therapy proven to slow the progression of ADPKD. The review by Ong focuses on the recently published TEMPO study [33], which showed that the vasopressin antagonist tolvapatan reduced cyst growth and decline in renal function over the study period, a breakthrough for this disorder.

In order to improve outcomes for patients with CKD, new treatments will need to be translated into clinical practice and public health. Nephrology has the lowest number of clinical trials of the major specialties [34], and few treatments have been shown to enhance clinical outcomes [35]. There are a number of substantial challenges to the conduct of clinical trials of CKD. First, the average rate of progression of most kidney diseases is slow, needing a long follow-up period or a large study population to test the effectiveness of interventions to slow progression. Death from CVD is a competing event, especially in older patients with early stage CKD, in whom the rate of death far exceeds the rate of ESRD. Second, the high prevalence of comorbid disorders in CKD patients suggests that

multifaceted interventions and co-ordination of medical care might be needed to improve outcomes. Third, despite the large number of uraemic complications in CKD, most patients do not have specific symptoms until late stages of disease, and few studies have recorded patient-reported outcomes [36]. The review by de Zeeuw elaborates on these challenges to trials in CKD and offers guidance on future directions.

Finally, there is the issue of suitable end-points in trials of CKD. A doubling of serum creatinine or reaching ESRD have been accepted as surrogate end-points for progression of CKD, but a change in GFR that is smaller than this change in serum creatinine is not accepted [37]. Changes in serum creatinine are not sensitive to the early decline in GFR, which limits drug development to patients with severe disease. The multiple methods of measuring renal function both in the clinic and for research purposes are discussed in the review by Sandilands. Whilst an increase in GFR might, at first thought, be considered beneficial, the trials using bardoxolone methyl in patients with diabetic nephropathy show this not to be the case [38], highlighting the uncertain nature of drug development in this area. Re-evaluation of whether some asymptomatic disease complications might be considered as clinical end-points in CKD could be worthwhile. Indeed, Remuzzi and colleagues discuss the ongoing issue of proteinuria as a potential surrogate end-point in CKD trials.

The increased prevalence of kidney failure and early stages of CKD constitute a worldwide public health threat. Costs for dialysis and transplantation are high compared with the costs of managing other chronic diseases [39]. Newer treatments that slow CKD progression and reduce the associated CVD risk are urgently needed.

Competing Interests

There are no competing interests to declare.

REFERENCES

- 1 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39: 1–266.
- 2 Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, Atkins RC. Prevalence of kidney damage in Australian adults: the AUSDIAB kidney study. *J Am Soc Nephrol* 2003; 14: S131–138.
- 3 Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; 298: 2038–47.
- 4 Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, Hallan HA, Lydersen S, Holmen J.

- International comparison of the relationship of chronic kidney disease prevalence and esrd risk. *J Am Soc Nephrol* 2006; 17: 2275–84.
- 5** Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, Chiang PH, Hsu CC, Sung PK, Hsu YH, Wen SF. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in taiwan. *Lancet* 2008; 371: 2173–82.
- 6** Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a kdigo controversies conference report. *Kidney Int* 2011; 80: 17–28.
- 7** Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. *J Am Soc Nephrol* 2002; 13: S37–408.
- 8** NHS Blood and Transplant. Cost-effectiveness of transplantation. Available at http://www.organdonation.nhs.uk/newsroom/fact_sheets/cost_effectiveness_of_transplantation.asp (last accessed 12 April 2013).
- 9** Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the american heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 2003; 108: 2154–69.
- 10** Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32: S112–119.
- 11** Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, Schneider KA. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The hypertension detection and follow-up program cooperative group. *Hypertension* 1989; 13: 180–93.
- 12** Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; 351: 1285–95.
- 13** Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT Jr. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National kidney foundation task force on cardiovascular disease. *Am J Kidney Dis* 1998; 32: 853–906.
- 14** Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286: 421–6.
- 15** Agewall S, Wikstrand J, Ljungman S, Fagerberg B. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk factor intervention study group. *Am J Cardiol* 1997; 80: 164–9.
- 16** Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. *N Engl J Med* 2000; 342: 145–53.
- 17** Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension* 2005; 45: 198–202.
- 18** Wang TJ, Evans JC, Meigs JB, Rifai N, Fox CS, D'Agostino RB, Levy D, Vasan RS. Low-grade albuminuria and the risks of hypertension and blood pressure progression. *Circulation* 2005; 111: 1370–6.
- 19** Freedman BI, Langefeld CD, Lohman KK, Bowden DW, Carr JJ, Rich SS, Wagenknecht LE. Relationship between albuminuria and cardiovascular disease in type 2 diabetes. *J Am Soc Nephrol* 2005; 16: 2156–61.
- 20** R Ruggenenti P, Perna A, Gherardi G, Benini R, Remuzzi G. Chronic proteinuric nephropathies: outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. *Am J Kidney Dis* 2000; 35: 1155–65.
- 21** Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of esrf in non-diabetic proteinuric chronic nephropathies. *Kidney Int* 1998; 53: 1209–16.
- 22** Collins AJ, Foley RN, Herzog C, Chavers BM, Gilbertson D, Ishani A, Kasiske BL, Liu J, Mau LW, McBean M, Murray A, St Peter W, Guo H, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers PW, Agodoa L. Excerpts from the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis* 2010; 55: 1–420.
- 23** Collins AJ, Kasiske B, Herzog C, Chavers B, Foley R, Gilbertson D, Grimm R, Liu J, Louis T, Manning W, Matas A, McBean M, Murray A, St Peter W, Xue J, Fan Q, Guo H, Li S, Li S, Roberts T, Snyder J, Solid C, Wang C, Weinhandl E, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Johnson R, Sheets D, Forrest B, Berrini D, Constantini E, Everson S, Frederick P, Eggers P, Agodoa L; United States Renal Data System. Excerpts from the United States Renal Data System 2004 annual data report: atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 2005; 45: 1–280.
- 24** Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; 290: 697–701.

- 25** Moody WE, Edwards NC, Chue CD, Ferro CJ, Townend JN. Arterial disease in chronic kidney disease. *Heart* 2013; 99: 365–72.
- 26** Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 2001; 38: 938–42.
- 27** Haynes WG, Webb DJ. Contribution of endogenous generation of endothelin-1 to basal vascular tone. *Lancet* 1994; 344: 852–4.
- 28** Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, Kiowski W, Luscher TF, Mancia G, Natali A, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Spieker LE, Taddei S, Webb DJ. Endothelial function and dysfunction. Part ii: association with cardiovascular risk factors and diseases. A statement by the working group on endothelins and endothelial factors of the european society of hypertension*. *J Hypertens* 2005; 23: 233–46.
- 29** Ljutic D, Kes P. The role of arterial hypertension in the progression of non-diabetic glomerular diseases. *Nephrol Dial Transplant* 2003; 18: 28–30.
- 30** Drummond I, Dhaun N, Goddard J, Webb DJ. Phosphodiesterase (PDE)-5 inhibition in chronic kidney disease. *Hypertension* 2013; in press.
- 31** Peralta CA, Hicks LS, Chertow GM, Ayanian JZ, Vittinghoff E, Lin F, Shlipak MG. Control of hypertension in adults with chronic kidney disease in the united states. *Hypertension* 2005; 45: 1119–24.
- 32** Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet* 2007; 369: 1287–301.
- 33** Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367: 2407–18.
- 34** Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. *J Am Soc Nephrol* 2004; 15: 411–9.
- 35** Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012; 379: 165–80.
- 36** US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. December, 2009. Available at <http://www.Fda.Gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm193282.Pdf> (last accessed 12 April 2013).
- 37** Levey AS, Cattran D, Friedman A, Miller WG, Sedor J, Tuttle K, Kasiske B, Hostetter T. Proteinuria as a surrogate outcome in ckd: report of a scientific workshop sponsored by the national kidney foundation and the us food and drug administration. *Am J Kidney Dis* 2009; 54: 205–26.
- 38** REATA Pharmaceuticals. Company statement: termination of the BEACON Trial. Available at <http://www.reatapharma.com/investors-media/news/news-timeline/2012/company-statement-termination-of-beacon-trial.aspx> (last accessed 12 April 2013).
- 39** Yach D, Hawkes C, Gould CL, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. *JAMA* 2004; 291: 2616–22.

RECEIVED

22 JANUARY 2013

ACCEPTED

23 JANUARY 2013

CORRESPONDENCE

Dr Neeraj Dhaun MD, The Queen's Medical Research Institute, 3rd Floor East, Room E3.23, 47 Little France Crescent, Edinburgh EH16 4TJ, UK.
Tel.: (+44) 131 242 9210
Fax: (+44) 870 1342778
E-mail: bean.dhaun@ed.ac.uk