Chronic kidney disease (CKD) and its progression to the need for renal replacement therapy (RRT) are important causes of distress for patients and their families, but also a very important economic and logistic burden for society. Even more importantly, a great majority of CKD patients die due to cardiovascular disease (CVD) before reaching the need for RRT. Thus, nephrologists should focus their efforts not only on preventing or at least delaying CKD progression, but also in reducing the risk of CVD.

Unfortunately, CKD is not a homogeneous disease and its progression varies considerably, even among patients with the same underlying disease and the same level of renal function, making its therapeutic approach more and more complicated. This complexity in outcomes has led to vigorous efforts of groups of outstanding nephrologists and their collaborators working within the realm of basic science, clinical research and knowledge translation. The high impact that CKD and its complications have on organizational and economic systems has prompted enquiry into all aspects of care delivery from screening to multidisciplinary care.

Given the breadth and depth of the problem internationally, the current special issue of NDT is focused entirely on the public health and research agenda for CKD. It is hoped that this edition will increase the awareness of readers regarding the immensity of problems still facing the nephrology community while acknowledging the strides made to date.

In the last 30 years, important progress has been made regarding the physiology of CKD progression and treatment.

The seminal paper by Brenner [1] about the relevance of hyperfiltration in damaging the glomeruli and in CKD progression was a true corner stone in this respect.

The Lewis study on type 1 diabetes [2] and the AIPRI study [3], mainly on non-diabetic patients, were the first demonstrations of the possibility of significantly slowing down CKD progression, independently of the underlying disease, using angiotensin-converting enzyme (ACE) inhibitors, both of which changed the practice dramatically.

Data from the REIN study [4] in more proteinuric, non-diabetic patients and from the RENAAL [5] and IDNT [6] trials using angiotensin-II receptor blockers (ARBs) in type 2 diabetic CKD patients further confirmed these beneficial effects in different populations with different agents. The accruing data on the efficacy of ACE-I and ARBs in slowing down the progression of CKD was attributable in large part to the antiproteinuric effect of these drugs, which are most effective in those patients with higher baseline proteinuria. The subsequent practice of up-titrating the drugs to normalize the proteinuria levels led to some unintended side effects such as hypotension and hyperkalaemia, which became the limitations to using the drugs in high doses. Furthermore, the recognition that hyperkalaemia was a consequence of these medications led many to stop them as kidney function declined, despite data often suggesting the contrary, although conflicting results have been reported [7].

As clinicians strived for better control of proteinuria, the combination of ACE-I and ARBs (dual Renin Angiotensin Aldosterone System (RAAS) blockade) was suggested, as was the addition of a third agent, such as aldosterone antagonists (to obtain triple RAAS blockade). While small studies were encouraging [8], larger randomized, controlled trials have not been able to demonstrate a benefit of these strategies, and in fact, have suggested that harm could derive from dual or triple RAAS blockade [9].

Given the increasing prevalence of ageing populations, diabetes, hypertension and CVD, arteriosclerosis and atherosclerosis are major contributors to progressive kidney decline in these populations. Interestingly, these conditions are not typically characterized by heavy proteinuria.

The ONTARGET trial [9], which was designed to test whether the combination of ACE-I and ARBs reduces cardiovascular events or death, was negative, and in fact...
showed harm (the need for acute dialysis was seen in a group of patients). Of note, the population of interest here consisted of individuals coming from general practice who had cardiovascular comorbidities and/or type 2 diabetes and very low proteinuria. The use of this aggressive dual blockade protocol without cautiously titrating the dosage of these drugs and monitoring is obviously not appropriate. However, this population is not necessarily representative of the CKD population, so it is not clear whether, with appropriate patient selection and monitoring, there may be a reduction in the risks as well as some benefits. Nonetheless, a similar study, the ALTITUDE [10], which was designed to test the utility of ARBs in addition to a direct renin inhibitor in type 2 diabetic patients with CKD, has been stopped prematurely due to a high incidence of side effects.

In the context of the above studies, and in consideration that many of our patients are nowadays affected by renal atherosclerotic lesions (diabetic or non-diabetic), there is a need to develop new therapies for slowing down CKD progression. While the use of ACE-I and ARBs is certainly of benefit for our patients, from a cardiovascular perspective as well as in delaying progression to some extent, there is clearly a need for other agents. ACE-I and ARBs are able to significantly slow down CKD progression in proportion to the patient baseline proteinuria. However, it remains a ‘residual risk’ and many patients still progress to end-stage renal disease, despite optimal treatment and diet control. Thus, it is clear that new alternative approaches should be explored using different drugs including antifibrotic, antioxidative and anti-inflammatory agents and combinations thereof. Some of these studies are ongoing or being planned as we collate this edition of NDT.

There is undoubtedly a need for well-conducted trials to ensure that the balance of benefit and risk for these new agents is understood. However, these trials are difficult to design (given the variability of outcomes in this population) and even more difficult to implement and conduct, due to expense and the regulatory environment that exists in different countries.

The identification and validation of appropriate surrogate or better intermediate end points remain a quest to help design and test new therapies at potentially lower costs. The validation of these appropriate end points in CKD remains a science and research agenda in and of itself.

In the current era, while we await the results of ongoing trials and drug development for testing in new trials, it is important to remember that hypertension and proteinuria remain the major factors affecting CKD progression, and so attention to these two factors is critical. In the era of increasingly scarce resources, we should at least ensure that basic evidence-based care is being delivered.

On the background of what is known, and as we move forward in better defining the different patterns of progression in well-characterized groups of patients, we are challenged to take better care of patients in the present, while awaiting answers of future research.

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References


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