
CKD is a major burden for the individual patient as well as for society in general. Whereas only 2% of all patients with CKD eventually reach the stage of dialysis dependency, cardiovascular risk rises steadily with the decline in kidney function, resulting in a robust increase in morbidity and mortality. Morphologically, chronic renal failure is most often characterized by glomerulosclerosis, tubular atrophy, and tubulointerstitial fibrosis, the latter often being the most prominent feature.1 Tubulointerstitial fibrosis consists of proliferation and activation of various cells to so-called myofibroblasts and synthesis of extracellular matrix by these cells. A long-standing controversy surrounds which cell type is the main precursor of these matrix-producing cells, including resident fibroblasts, fibrocytes, pericytes, endothelial cells, and epithelial cells. However, the individual contribution of these various cell types to myofibroblast formation may vary according to the method and model examined, pointing to a certain heterogeneity of these cells.2 However, once matrix-synthesizing myofibroblasts have been formed, renal interstitial fibrosis represents a final common pathway for a plethora of CKDs. Thus, renal interstitial fibrosis is a worthwhile target because antifibrotic therapy would make almost all patients with CKD suitable candidates for therapy. Moreover, antifibrotic therapy may also be of clinical importance in other organs, such as the lung and the liver.

Initial antifibrotic strategies focused mainly on the neutralization of profibrotic cytokines or the application of antifibrotic cytokines.3 However, in recent years the focus of antifibrotic therapy has shifted to antioxidant therapy. Although oxidation was thought to be of primary importance for inflammatory processes, recent evidence has shown that it is also critical for organ fibrosis in general and the liver and the kidney in particular.4 Many of these potential therapeutic agents have been tested experimentally and clinically in diabetic kidney disease.5 One of the more interesting substances in this regard is pirfenidone, which has antifibrotic, anti-inflammatory, and antioxidant properties. The drug was used successfully to treat many fibrotic disorders, not only in the kidney but also in the lung and the liver. Furthermore, the drug has already been approved for use in patients with idiopathic pulmonary fibrosis; it is in clinical use in Europe but not the United States (the Food and Drug Administration has withdrawn approval in the United States). However, one clinical trial in patients with diabetic nephropathy gave only mixed results,6 whereas a second trial in patients with FSGS is still ongoing.7 Another interesting antioxidant and again antifibrotic agent is tranilast. This synthetic compound attenuates the induction of thioracoxid–interacting protein and oxidative stress. It is used as an antifibrotic agent in Southeast Asia for the treatment of keloid formation. In addition, the drug has been evaluated experimentally8 as well as clinically in diabetic nephropathy,9 although clinical use was confined to only a few patients. Pentoxifylline is a methylxanthine phosphodiesterase inhibitor that has been evaluated in more than 20 studies, mostly in patients with diabetic nephropathy. Unfortunately, most of these studies included only a handful of individuals and were of short duration.10 There was a tendency toward decreased serum creatinine values but no significant effects on proteinuria, and the current evidence does not support the use of the drug in patients with diabetic kidney disease.5

See related article, “Targeted Glomerular Angiopoietin-1 Therapy for Early Diabetic Kidney Disease,” on pages 33–42.

**Antifibrotic Therapy: Is an Antioxidative Regimen the Answer?**

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Published online ahead of print. Publication date available at www.jasn.org.

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Another antioxidative and antifibrotic therapeutic agent is bardoxolone methyl. This synthetic compound is an antioxidative agent that mediates at least part of its effects by induction of nuclear factor erythroid 2–related factor 2, a transcription factor that downregulates NF-kB signaling, resulting in a robust decrease in inflammatory response. The drug was very effective in the initial BEAM (Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes) phase 2b trial during 24 weeks in patients with diabetic nephropathy.11 However, the large subsequent phase 3 BEACON (Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events) trial had to be terminated because of an increase in serious adverse effects, including an increased mortality rate.12 The premature termination of this trial raised many questions, including the design of experimental studies before embarking on a clinical trial and advocacy of a more careful approach in clinical studies with novel compounds.13 Despite the failure of bardoxolone, the potential of antioxidative therapy in CKD in animal models is evident; however, the definite clinical efficacy of any of these antioxidant therapies has yet to be demonstrated.

Now comes another antioxidant therapy. In this issue of JASN, Okamura and colleagues describe the effects of the antioxidative cysteamine bitartrate as a potential antifibrotic agent.14 Cysteamine bitartrate is an established agent for patients with nephropathic cystinosis, a rare autosomal recessive lysosomal storage disease, but it may have potential in other diseases, such as chronic liver disease, neurodegenerative disease, and even cancer. The authors tested the drug in two established models of chronic progressive renal disease: the model of unilateral ureteral obstruction and the renal ischemia reperfusion model. Animals treated with cysteamine bitartrate did have considerably less renal interstitial fibrosis compared with sham-treated animals, although matrix accumulation could not be inhibited completely. The authors carefully analyzed the dosing but were able to achieve drug levels considered therapeutic in patients only at night. Thus, a higher dose associated with higher levels of the drug could be even more effective as an antifibrotic agent. In this regard, it is also noteworthy that a new enteric-coated form of cysteamine may be reproduced in pericyte-derived fibroblasts but not in tubular epithelial cells. In addition, some inhibition of macrophage accumulation was observed, although treatment did not affect the synthesis of cytokines. There was, however, a reduced generation of reactive oxygen species. Clearly, more studies are needed to confirm the status of cysteamine as a novel antifibrotic agent. In addition, the recent experience with bardoxolone should caution against a premature clinical trial. Still, cysteamine is one of the better hopes for an effective antifibrotic therapy in the relatively near future, and the authors should be applauded for bringing us this hope.

DISCLOSURES
None.

REFERENCES
Older Adults with CKD and Acute Kidney Failure: Do We Know Enough for Critical Shared Decision Making?

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doi: 10.1681/ASN.2013090981

Most medical providers argue that they practice patient-centered care; incorporating evidence-based best practices in the context of patient preferences, capacity, and healthcare goals. However, to accomplish true patient-centered care, we must transition from disease-oriented care to patient-oriented care. The foundation of this is shared decision making in which evidence-based best practices are adapted within the patient’s context, which is referred to as contextualized care.1,2 The end result is individualized care that enables patients to achieve the best outcomes based on what is important to them, rather than what is important to the healthcare provider or system.3 When this approach is successful, it improves overall patient outcomes and possibly decreases unnecessary testing, procedures, and therapy.3,4

We also know that our patients want and expect accurate, transparent information about their disease trajectory, including symptoms and symptom management, survival, cost of care, and quality of life for each therapy choice. Unfortunately, nephrologists and other providers have not consistently met this expectation.5–8 Certainly this gap in information exchange may be due to the nephrology team’s lack of awareness, communication skills, or time to spend with the patient; however, it may also be due to the lack of available trusted data that can be interpreted relative to certain subsets of CKD patients. This is particularly true for the older adult with advanced CKD or AKI.

A clinical commentary by Rosansky and Clark9 highlights the recent decline in the number of patients starting renal replacement therapy in the United States. The data presented indicate that the decrease in early dialysis starts (with an estimated GFR ≥10 ml/min per 1.73 m²) accounts for a large part of this change. Interestingly, there has been a slow-down in early dialysis starts even for individuals aged >75 years, whose increasing incidence of dialysis has outpaced other age groups. Changes in practice patterns leading to the decrease in early starts were influenced by well designed, patient-oriented research informing conversations with patients around the timing of and need for renal replacement therapy.9–19 The knowledge gained from these studies and others about the pros and cons of therapy options, including maximum conservative management, should be incorporated into patient-centered, age-relevant decision aids, a tool that is successful in helping patients understand the effect of various options on their healthcare goals and personal priorities.20,21 Unfortunately, many elderly patients do not decide whether to pursue renal replacement therapy while they are in calm, controlled preemptive settings. Rather, patients often must make this decision at the time of an acute illness or decompensation of a complex chronic illness, when time pressures and lack of prognostic data hinder the decision making process.22,23 In these acute situations, especially for very elderly individuals (aged ≥85 years) with limited baseline overall survival, there are many questions regarding survival predictions, subsequent quality of life, burden of the therapy, intensity of medical services needed, degree of recovery expected, and so forth, for which we have little data. This knowledge gap in critical health status transitions has often left providers, patients, and surrogate healthcare decision makers with difficult decisions without evidence-based data on which to make a truly informed patient-centered decision. The consequence is a nonstandard approach to therapy, as shown by the wide variation in the percentage of older patients in dialysis programs throughout the United States and worldwide.15,24–28

In this issue of JASN, Wong et al.29 use 2010 US Renal Data System data30 to retrospectively determine the association of intensity of care at the time of dialysis initiation with survival and the need for subsequent intensive medical services. Primary outcome measures were time to death after initiating dialysis and time spent in the hospital during the follow-up period with the future use of intensive procedures as a secondary outcome measure. The authors found significantly higher