Kidney fibrosis is a hallmark of chronic kidney disease (CKD) and a potential therapeutic target. However, there are conceptual and practical challenges to directly targeting kidney fibrosis. Whether fibrosis is mainly a cause or a consequence of CKD progression has been disputed. It is unclear whether specifically targeting fibrosis is feasible in clinical practice because most drugs that decrease fibrosis in preclinical models target additional and often multiple pathogenic pathways (eg, renin-angiotensin-aldosterone system blockade). Moreover, tools to assess whole-kidney fibrosis in routine clinical practice are lacking. Pirfenidone, a drug used for idiopathic pulmonary fibrosis, is undergoing a phase 2 trial for kidney fibrosis. Other drugs in use or being tested for idiopathic pulmonary fibrosis (eg, nintedanib, PRM-151, epigallocatechin gallate) are also potential candidates to treat kidney fibrosis. Novel therapeutic approaches may include antagonists (eg, lademirsen) or drugs targeting interleukin 11 or NKD2 (WNT signaling pathway inhibitor). Reversing the dysfunctional tubular cell metabolism that leads to kidney fibrosis offers additional therapeutic opportunities. However, any future drug targeting fibrosis of the kidneys should demonstrate added benefit to a standard of care that combines renin-angiotensin system with mineralocorticoid receptor (eg, finerenone) blockade or with sodium/glucose cotransporter 2 inhibitors.

Chronic kidney disease (CKD) is one of the fastest growing causes of death worldwide, expected to become the fifth most common cause of death globally by 2040 and, by the end of the century, the second leading cause of death in countries with long life expectancy.1,2 Factors contributing to these dismal predictions are the late diagnosis of CKD and suboptimal therapeutic tools. As a hallmark of CKD, kidney fibrosis has relevance to diagnosis and monitoring of CKD, and antifibrotic agents may have potential for treatment of CKD. In this review, we discuss current therapeutic approaches for CKD that interfere with kidney fibrosis in preclinical studies, therapeutic approaches that target kidney fibrosis and are being investigated in clinical trials, drugs undergoing clinical trials for pulmonary fibrosis that may be of interest for kidney fibrosis, and some key preclinical findings closer to clinical translation. An in-depth review of the recent preclinical literature can be found elsewhere.3

**Features and Assessment of Kidney Fibrosis**

Kidney fibrosis has 3 main components: glomerular (called glomerulosclerosis), interstitial, and vascular fibrosis. It is intrinsically linked to simultaneously ongoing processes such as kidney cell injury and inflammation. Whether fibrosis is mainly a cause or a consequence of CKD progression has been disputed. There is preclinical evidence that hyperactivation of a single receptor (platelet-derived growth factor [PDGF] receptor β [PDGFR-β]) in mesenchymal cells may drive glomerular and interstitial fibrosis, preceding tubular atrophy, interstitial inflammation, and decreased glomerular filtration rate in the absence of hypertension or albuminuria.4,5 In mice, targeting PDGFR-β or its ligands PDGF-B and PDGF-D has been reported to protect against mesangial proliferation, unilateral ureteral obstruction, and unilateral ischemia/reperfusion injury.4 However, evidence that fibrosis can trigger kidney disease in an animal model does not necessarily imply that it is a key driver of CKD in humans.

Aside from uncertainty regarding the pathogenic role of kidney fibrosis, its relevance in diagnosis and monitoring of CKD remains to be specified. In particular, although the diagnostic criteria for CKD in the KDIGO (Kidney Disease: Improving Global Outcomes) guideline recommendations include persistent kidney damage as evidenced by histology or imaging, KDIGO does not detail how fibrosis can be ascertained by these methods.6

Similarly, there is no optimal method to assess kidney fibrosis in clinical practice, and only one ongoing clinical trial has a primary end point of kidney fibrosis (Fig 1; Table 1).7 Kidney biopsies are invasive, but glomerulosclerosis or interstitial fibrosis has been found to predict progressive CKD after unilateral nephrectomy and in native kidneys and kidney graft biopsies.8-10 Although molecular imaging of fibrosis proteins is still preclinical,11-15 whole-kidney fibrosis may be assessed by noninvasive tools such as urine biomarkers and magnetic resonance imaging. In kidney allografts, magnetic resonance imaging parameters of fibrosis have been reported to correlate with histological kidney fibrosis and to predict estimated glomerular filtration rate (eGFR) decrease.16

Whether fibrosis itself is a bona fide target in the clinic, independent from parenchymal cell injury or inflammation, remains to be demonstrated by clinical trials that specifically target mediators of fibrosis. The therapeutic targeting of kidney fibrosis is complicated by the reality that some drugs purportedly targeting fibrosis have poorly understood mechanisms of action (eg, pirfenidone) or multiple targets (eg, nintedanib). Additionally, most clinical trials exploring antifibrotic therapy lack an assessment of kidney fibrosis as an end point and recruit
participants with late stages of CKD, thus limiting the potential to interfere with early drivers of kidney fibrosis.

**Current Nephroprotective Drugs and Kidney Fibrosis**

Preclinical studies have identified multiple therapeutic approaches that decrease kidney fibrosis. However, preclinical promise does not mean clinical success, and, even if a certain therapeutic approach decreases fibrosis, this does not necessarily imply that the mechanism of the therapeutic effect is directly related to fibrosis, because fibrosis may be indirectly modified by approaches that directly prevent acute kidney cell injury or decrease inflammation. As an example, targeting TWEAK, a proinflammatory cytokine, has been reported to decrease kidney fibrosis through a combined lowering of kidney fibroblast proliferation, tubular cell death, and inflammation.\(^\text{17}\) Several drugs in clinical use, some of them for kidney protection, decrease kidney fibrosis in animal models of kidney disease or are under study for kidney fibrosis in clinical trials (Box 1; Table 2).

**Renin-Angiotensin System Blockers**

Renin-angiotensin system (RAS) blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers decreases kidney fibrosis in multiple animal models of kidney disease.\(^\text{1}^-^\text{3}\) However, directly targeting fibrosis is not the main mechanism of kidney protection. Moreover, antifibrotic effects were not formally tested in clinical trials. The RAS has direct profibrotic actions and also increases hyperfiltration and blood pressure, enhances inflammation, and decreases expression of Klo-tho, a protein expressed in the kidney that has antiaging and antifibrotic actions.\(^\text{18}\)

**Mineralocorticoid Receptor Antagonists**

Mineralocorticoid receptor antagonists decrease kidney fibrosis in murine kidney disease. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, may have a better safety profile than spironolactone and eplerenone in terms of gynecomastia and hyperkalemia, although head-to-head comparisons are lacking.\(^\text{19}\) In in vitro binding assays of mineralocorticoid receptor transcriptional cofactors, finerenone shows higher potency/efficacy than eplerenone; in addition, finerenone displays inverse agonism, leading to differential mineralocorticoid receptor cofactor modulation that may provide an antifibrotic advantage. Moreover, finerenone was observed to improve kidney outcomes in diabetic kidney disease in the phase 3 FIDELIO trial, even though that study did not include kidney fibrosis as an end point.\(^\text{19^-^2^2}\) Finerenone is more expensive than prior mineralocorticoid receptor antagonists; however, these older drugs are not approved for kidney protection.

**Sodium/Glucose Cotransporter 2 Inhibitors**

In clinical use to treat diabetic and nondiabetic CKD, sodium/glucose cotransporter 2 (SGLT2) inhibitors have
been reported to decrease kidney fibrosis in nondiabetic rodents with kidney ischemia/reperfusion or cyclosporin nephrotoxicity.\textsuperscript{23-25} The mechanism of the antifibrotic action is unclear, but SGLT2 inhibitors may protect podocytes from the adverse impact of hyperfiltration and tubular cells from the adverse effects of albuminuria (eg, inflammatory response, decreased Klotho), glucose toxicity (eg, inflammatory and profibrotic responses), and energy expenditure in kidneys with deficient microvasculature.\textsuperscript{26,27}

\textbf{Pentoxifylline}

Pentoxifylline is not approved for kidney protection, but it preserved kidney function and increased Klotho levels in an open-label trial.\textsuperscript{28} An ongoing placebo-controlled pentoxifylline phase 4 trial (PENFOSIDINE; ClinicalTrials.gov identifier NCT03664414) with a recruitment target of 196 participants and an estimated completion time of December 2021 has a primary end point of estimated glomerular filtration rate (eGFR) at 24 months and lists NT-proBNP (N-terminal fragment of the prohormone brain natriuretic peptide) as a fibrosis marker, albeit in the context of myocardial fibrosis rather than a kidney fibrosis endpoint.

\textbf{Novel Drugs Undergoing Trials for Kidney Fibrosis}

In 2017, there were 6 agents in clinical development for kidney fibrosis (Table 3).\textsuperscript{29-32} As of October 2021, ClinicalTrials.gov listed 6 intervention studies for fibrosis in native kidneys, 4 of which are already completed. Ongoing trials are testing pirfenidone and, as indicated above, pentoxifylline. In addition, lademirsen is also undergoing clinical trials for CKD.

\textbf{Pirfenidone}

Pirfenidone is an antifibrotic drug with a poorly understood mechanism of action. In preclinical studies, it inhibited expression of transforming growth factor β1 (TGF-β1) and its downstream actions in cell culture and in vivo. However, it also has anti-inflammatory actions such as inhibition of tumor necrosis factor (TNF) expression. Anti-inflammatory and antifibrotic effects were demonstrated in multiple animal models of kidney disease.\textsuperscript{33,34} Systems biology studies disclosed multiple effects of pirfenidone administration on proteins and metabolites that may be a result of altered regulation of messenger RNA processing.\textsuperscript{35} In mouse lung, 129 molecules, mostly

\begin{table}
\centering
\caption{Examples of Tools for Assessment of Whole-Kidney Fibrosis}
\begin{tabular}{|l|l|l|l|l|}
\hline
\textbf{Approach} & \textbf{Information Provided} & \textbf{Setting} & \textbf{Advantages} & \textbf{Drawbacks} \\
\hline
Kidney biopsy & Conventional histology: current kidney fibrosis; systems biology: identification of active profibrotic pathways & Clinical & Widely available; allows assessment of activity and diagnosis of cause/underlying condition & Limited kidney sample size; may not be representative of whole kidneys or both kidneys; invasive; concomitant systems biology not in routine use for clinical care \\
\hline
Fluid biomarkers, eg, urinary peptidomics and others (eg, PIIINP) & Current kidney fibrosis, matrix remodeling\textsuperscript{a} & Clinical & Noninvasive; urine can be shipped for analysis elsewhere & Limited information on natural history and response to therapy; does not provide information on unilateral vs bilateral disease; limited external validation \\
\hline
US/MRI elastography & Strain, shear wave velocity: current fibrosis & Clinical & Noninvasive & Native kidney not easily accessible; influenced by hemodynamics \\
\hline
MRI & Increased cortical apparent diffusion coefficient and decreased T1 correlate with current fibrosis & Clinical & Noninvasive; may be combined with information from other MRI parameters & Not widely available; limited information on natural history and response to therapy; reflect kidney function and perfusion rather than fibrosis \\
\hline
CT scan & Current fibrosis & Clinical & Noninvasive & Radiation exposure; limited information on fibrosis in the absence of contrast media, natural history, and response to therapy \\
\hline
Molecular imaging & Current fibrosis (eg, fluorescent CNA35 CT, ESMA-based molecular MRI of elastin) & Preclinical & Noninvasive; specific imaging of extracellular matrix molecules deposited during fibrosis & Performance not assessed in humans \\
\hline
\end{tabular}
\begin{flushleft}
Abbreviations: CNA35, collagen-binding adhesion protein 35 (binds to fibril-forming collagens); CT, computed tomography; ESMA, elastin-specific magnetic resonance contrast agent; MRI, magnetic resonance imaging; PIIINP, collagen type III aminoterminal propeptide; US, ultrasound. \\
\textsuperscript{a}Decreased amounts of collagen peptides in kidneys with fibrosis may represent decreased matrix remodeling.
\end{flushleft}
\end{table}
corresponding to unknown metabolites, were differentially expressed 45 minutes after pirfenidone administration. No significant effects on known metabolic pathways were identified. Taken together, the observation of a positive impact of pirfenidone on acute conditions and the evidence for multiple targets draw into question the widely held notion that pirfenidone is mainly an antifibrotic drug.

Pirfenidone was first approved for idiopathic pulmonary fibrosis (IPF). As of May 2021, it was undergoing US Food and Drug Administration priority review for unclassifiable interstitial lung disease. For IPF, pirfenidone dose is increased over a period of 2 weeks to reach 801 mg 3 times daily (2,403 mg/d). Pirfenidone is excreted predominantly in the urine (80% of the dose within 24 hours) as its metabolite 5-carboxy-pirfenidone, which accumulates when kidney function is decreased. The Food and Drug Administration indicates caution with pirfenidone when creatinine clearance is <80 mL/min and refers to clinical pharmacokinetics data on potential metabolite accumulation. The European Medicines Agency indicates caution when creatinine clearance is 30-50 mL/min and avoidance when creatinine clearance is <30 mL/min. Both agencies contraindicate pirfenidone in persons undergoing dialysis. The main adverse effects are increased liver enzyme levels, photosensitivity and rash, and gastrointestinal disorders (nausea, vomiting, diarrhea, dyspepsia, gastroesophageal reflux disease, and abdominal pain), which may require temporary dosage reductions or discontinuations of the drug. Recent and ongoing pirfenidone trials are defining its role in other forms of lung fibrosis.

As of October 2021, ClinicalTrials.gov listed 52 completed pirfenidone studies, of which 3 phase 1 and/or 2 trials studied kidney disease, totaling 127 participants followed for as long as 3 years. It also listed 23 ongoing studies, of which 2 phase 1/2 trials with known status target kidney disease, totaling 224 participants to be followed for as long as 3 years (Table 4). An open-label study evaluated the safety and efficacy of pirfenidone in patients with idiopathic and post-adaptive focal segmental glomerulosclerosis, most of them undergoing RAS blockade. The annualized change in eGFR improved from a median of –7.3 mL/min/1.73 m² before pirfenidone to –5.4 mL/min/1.73 m² while taking pirfenidone. In an extension phase beyond 12 months, the decrease in eGFR was similar to the eGFR slope before pirfenidone. Overall, there were no statistically significant differences in blood pressure, proteinuria, or the projected time to initiation of kidney replacement therapy. Adverse events included dyspepsia, sedation, photosensitive dermatitis, and biopsy-proven toxic hepatitis, all causing drug discontinuation. Therapy was stopped within 4 months in 3 of 21 (14%) participants.

In a double-blind study, participants with diabetic nephropathy, most undergoing RAS blockade, were randomized to receive placebo (n = 26) or pirfenidone 1,200 mg/d (n = 26) or 2,400 mg/d (n = 25). Among the 52 participants who completed the study, mean eGFR increased at 1 year in the pirfenidone 1,200-mg/d group (+3.3 ± 8.5 mL/min/1.73 m²; P = 0.026 vs placebo) and decreased in the placebo and pirfenidone 2,400-mg/d groups (–2.2 ± 4.8 and –1.9 ± 6.7 mL/min/1.73 m², respectively). The dropout rate was high for both pirfenidone groups: 9 of 26 (35%) and 11 of 25 (44%).
Table 2. Completed Trials With Primary Kidney End Points of Drugs in Clinical Use Other Than Pirfenidone That Are Undergoing Clinical Trials for Kidney Fibrosis or That Decrease Fibrosis in Preclinical Models

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>N</th>
<th>Disease</th>
<th>Notable Inclusion Criteria</th>
<th>Notable Exclusion Criteria</th>
<th>Arms</th>
<th>Primary End Point/Effect Size</th>
<th>Key Secondary End Point/Effect Size</th>
<th>Post Hoc Analyses</th>
<th>Key Limitations</th>
<th>Key Safety Concern</th>
<th>Dosing Considerations in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>PREDIAN</td>
<td>169</td>
<td>DKD</td>
<td>CKD 3-4; UAE &gt;30 mg/d</td>
<td>DM1</td>
<td>1,200 mg/d or placebo</td>
<td>Progression of DKD (difference in ΔeGFR from BL): 4.3 (3.1-5.5); P &lt; 0.001</td>
<td>ΔUAE</td>
<td>Increase in serum/urine Klotho</td>
<td>Small sample size, open label</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>CREIGENCE</td>
<td>4,401</td>
<td>DKD</td>
<td>eGFR 30-&lt;90, UACR 300-5,000</td>
<td>DM1</td>
<td>100 mg/d or placebo</td>
<td>Kidney end point: HR, 0.66 (0.53-0.81); P &lt; 0.001</td>
<td>–</td>
<td>Stopped early</td>
<td>DKA</td>
<td>Initiation NR if eGFR &lt;45</td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>DAPA-CKD</td>
<td>4,304</td>
<td>DKD and nondiabetic CKD</td>
<td>eGFR 25-75, UACR 200-5,000</td>
<td>DM1</td>
<td>10 mg/d or placebo</td>
<td>Kidney end point: HR, 0.56 (0.45-0.68); P &lt; 0.001</td>
<td>–</td>
<td>Stopped early</td>
<td>Volume depletion</td>
<td>Contraindicated in KF/dialysis</td>
<td></td>
</tr>
<tr>
<td>Finerenone</td>
<td>FIDELIO</td>
<td>5,734</td>
<td>DKD</td>
<td>UACR 30-300 and eGFR 25-60 or UACR 300-5,000 and eGFR 25-75</td>
<td>Serum K+ &gt;4.8 mmol/L</td>
<td>10-20 mg/d or placebo</td>
<td>Kidney end point: HR, 0.82 (0.73-0.93); P = 0.001</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Hyperkalemia</td>
<td>Dose 10 mg/d if eGFR 25-60, NR for eGFR &lt;25</td>
</tr>
</tbody>
</table>

Data shown are intention-to-treat. Abbreviations: BL, baseline; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m²); HR, hazard ratio; KF, kidney failure; MOA, mechanism of action; NR, not recommended; Scr, serum creatinine; UACR, urinary albumin-creatinine ratio (in mg/g); UAE, urinary albumin excretion.

*Values in parentheses are 95% CIs.
*Fibrosis-related.
*KF, 50% decrease in eGFR, or renal death.
Table 3. 2021 Status of Drugs Identified in 2017 as Being in Clinical Development for Kidney Fibrosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Current Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone</td>
<td>Trials ongoing for kidney disease.</td>
</tr>
<tr>
<td>Fresolimumab, LY2382770</td>
<td>A phase 2 trial for steroid-resistant FSGS was underpowered (it recruited 36 of 88 prespecified patients) and did not meet primary or secondary end points of partial or complete remission of proteinuria or eGFR change up to day 112.40,42 Trials are ongoing for osteogenesis imperfecta or malignancy.</td>
</tr>
<tr>
<td>FG-3019 (pamrevlumab)</td>
<td>Phase 2 program in DKD (NCT00913393) and phase 1 in FSGS (NCT00782561) terminated for business reasons. Trials are ongoing for idiopathic pulmonary fibrosis30 (NCT04419558, NCT03955146), Duchenne muscular dystrophy, and malignancy, but not for kidney disease.</td>
</tr>
<tr>
<td>STX-100 (BG00011)</td>
<td>Phase 2 in chronic allograft dysfunction (NCT00878761) withdrawn. Phase 2 program in pulmonary fibrosis stopped because of safety concerns.</td>
</tr>
<tr>
<td>GCS-100</td>
<td>Phase 2 studies for CKD completed (NCT02155673, NCT01843790) or withdrawn because of corporate decision (NCT02333955); no results available. No ongoing trials listed on ClinicalTrials.gov.</td>
</tr>
</tbody>
</table>

Abbreviations: DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis. *Based on ClinicalTrials.gov as of October 20, 2021.

respectively. Gastrointestinal symptoms, fatigue, and nonadherence were causes for study noncompletion. Dialysis was initiated in 4 of 26 (15%) persons in the placebo group, 1 of 25 (4%) in the pirfenidone 2,400-mg/d group, and none in the pirfenidone 1,200-mg/d group. There were no significant differences in urinary albumin-creatinine ratio response or levels of urinary or circulating TGF-β1 or inflammatory biomarkers.37 Thus, a benefit on eGFR was noted for participants randomized to receive pirfenidone 1,200 mg/d that did not appear to be hemodynamic in nature, as it was observed only after 6 months of therapy and not at 3 months. However, the acute effect on eGFR was not studied. Overall, pirfenidone appears to have been started too late in the course of CKD, because this trial and the aforementioned open-label study observed at least transient slowing of eGFR loss. However, the transient benefit in one trial and poor tolerance are concerning; moreover, no evidence was generated to support that any benefit was dependent on kidney fibrosis, sample size was limited, and dropout was high for a drug that would need to be taken for years. Although the highest dose is comparable to the dosing regimen for IPF, the poorer tolerance in patients with kidney disease may lead to dose limitations that may limit the efficacy for kidney fibrosis.

The ongoing phase 2 TOP-CKD trial enrolling 200 participants will be completed by December 2024 (Table 4). As the largest pirfenidone trial to date for kidney fibrosis and the only trial for any kidney fibrosis drug actually assessing kidney fibrosis by imaging or urinary markers as a primary outcome, TOP-CKD will be decisive in determining the viability and design of an eventual phase 3 trial.

**Lademirsen**

Lademirsen (SAR339375) is an antagonir (ie, micro-RNA inhibitor) targeting miR-21. MicroRNA are small, noncoding RNAs that repress the translation or induce the degradation of specific messenger RNA targets. ProfibromiRs regulate kidney fibrosis.40-42 The profibrogenic TGF-β1/Smad3 pathway promotes miR-21 expression, and miR-21 silencing has been reported to improve survival of Alport mice and reduce glomerulosclerosis, interstitial fibrosis, tubular injury, and inflammation.41 Focal segmental glomerulosclerosis is a common histological presentation of Alport syndrome.44 The protective effect is related to improved cell metabolism through enhanced PPARα/RXR (peroxisome proliferator-activated receptor α/retinoid X receptor) activity and improved mitochondrial function. However, adverse glomerular responses to miR-21 targeting were observed in preclinical diabetes.45

Lademirsen is undergoing a phase 2 clinical trial for Alport syndrome (HERA; trial ID NCT02855268), which plans to recruit 45 adults with eGFR 36-89 mL/min/1.73 m² at risk of rapid progression despite RAS blockade. The primary end points are safety and change in GFR from baseline to 48 weeks. No secondary end point specifically addresses kidney fibrosis, but blood and urine TGF-β1 will be assessed. It will be completed by June 2023.

**Other Drugs Undergoing Trials for IPF That May Be of Interest for Kidney Fibrosis**

Given that pirfenidone is indicated for IPF, and considering its promise for kidney fibrosis, it is worth reviewing the clinical experience regarding IPF therapy to obtain insights into the future of treatment for kidney fibrosis. IPF is a progressive fibrotic disorder of the lungs believed to be driven by fibroblast proliferation and collagen production, phenomena also characteristic of kidney fibrosis. Like kidney fibrosis, the histopathologic pattern (usual interstitial pneumonia) is nonspecific and is shared by other causes of lung fibrosis. As for CKD, the prevalence and incidence of IPF increase with advancing age. Thus, it may be possible to obtain insight into potential kidney-protective effects of treatments for IPF by adding kidney fibrosis outcomes to IPF trials and/or tracking eGFR in real-world experience with therapies for IPF and related conditions. This would require an effort to reach across medical specialties, as not even baseline kidney function parameters are reported in IPF clinical trials.46,47 Likewise, there is no information on eGFR slopes for patients taking pirfenidone for nonkidney indications. Nintedanib, PRM-151, and epigallocatechin gallate (EGCG) are undergoing clinical trials for IPF or other forms of lung fibrosis, whereas clinical development of zirtaxestat (GLPG1690) was recently stopped.
<table>
<thead>
<tr>
<th>Identifier</th>
<th>Condition</th>
<th>Pirfenidone Dose</th>
<th>Phase</th>
<th>N</th>
<th>Completion Date</th>
<th>Eligibility</th>
<th>Kidney Baseline</th>
<th>Primary End Point</th>
<th>Secondary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00001959</td>
<td>FSGS</td>
<td>1,200-2,400 mg/d in 2 doses</td>
<td>2</td>
<td>21</td>
<td>Oct 2008</td>
<td>Adult FSGS, eGFR&lt;sup&gt;b&lt;/sup&gt; 20-80 mL/min, eGFR ↓ of &gt;2.4 mL/min in 6 mo, stable RAS blockade unless contraindicated</td>
<td>Median eGFR 21 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;, median proteinuria 2.8 g/d</td>
<td>ΔGFR during therapy (1 y): −0.45 [−0.78 to −0.16] mL/min/1.73 m&lt;sup&gt;2/mo&lt;/sup&gt;, P &lt; 0.01 vs BL (ITT)</td>
<td>Proteinuria posttreatment</td>
</tr>
<tr>
<td>NCT00063583</td>
<td>DKD</td>
<td>1,200-2,400 mg/d in 2 doses</td>
<td>1/2</td>
<td>77</td>
<td>Mar 2009</td>
<td>Adult, T1DM or T2DM, UACR &gt;30 mg/g, eGFR 20-75 ml/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Mean eGFR 35-40 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;; median UACR 179-214 mg/g</td>
<td>Δ in kidney function (1 y): mean intergroup difference in ΔeGFR, +5.5 (1.1-9.9) mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;, P = 0.026, placebo vs 1,200 mg drug&lt;sup&gt;c&lt;/sup&gt;</td>
<td>% ΔUACR, urine and circulating TGFβ1</td>
</tr>
<tr>
<td>NCT02408744</td>
<td>CKD</td>
<td>1,200-2,400 mg/d in 2 doses</td>
<td>1/2</td>
<td>30</td>
<td>Sep 2013</td>
<td>Age 10-40 y, CKD G1-G4</td>
<td>–</td>
<td>Progression in CKD G category over 3 y</td>
<td>Kidney function (Scys, 1/Scr, 24-h CL&lt;sub&gt;cr&lt;/sub&gt; collection) over 3 y</td>
</tr>
</tbody>
</table>

The status of NCT02689778, a phase 3 trial comparing pirfenidone with placebo for DKD is listed as unknown as of October 20, 2021; it was last updated in 2019 and at that time, it was expected to be completed by December 2019. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; A1M, α1-microglobulin; BL, baseline; CL<sub>cr</sub>, creatinine clearance; DKD, diabetic kidney disease; DW-MRI, diffusion-weighted magnetic resonance imaging; FSGS, focal segmental glomerulosclerosis; ITT, intention-to-treat analysis; KFRE, Kidney Failure Risk Equation; MCP-1, monocyte chemoattractant protein 1; PIIINP, N-terminal procollagen type 3 peptide; Scys, serum cystatin C; UACR, urinary albumin-creatinine ratio.

*Values in parentheses are 95% CI, values in brackets are interquartile range.
*<sup>a</sup>By Modification of Diet in Renal Disease (MDRD) Study equation.
*<sup>b</sup>Type of analysis (ITT vs other) not specified.
*<sup>c</sup>No results reported in ClinicalTrials.gov or found in PubMed, and no results mentioned in a 2015 review on pirfenidone by the authors that discussed kidney disease.
Nintedanib
Nintedanib is a small molecule that can compete with adenosine triphosphate (ATP) for the binding pocket for the latter that is found in multiple receptor and non-receptor tyrosine kinases. Nintedanib inhibits platelet-derived growth factor receptors (PDGFRs) α and β, fibroblast growth factor receptors (FGFRs) 1-3, vascular endothelial growth factor receptors (VEGFRs) 1-3, colony-stimulating factor 1 receptor (CSF1R), Fms-like tyrosine kinase-3 (FLT-3), and Lck, Lyn, and Src kinases (Tables S1 and S2). There is preclinical evidence for antifibrotic properties in kidney disease. In mice, nintedanib slowed poly cystic kidney disease progression in 2 genetic models, but attenuated fibrosis in only one of them. In an ex vivo model of spontaneous human renal fibrosis in precision-cut kidney slices, 0.1 μM nintedanib inhibited cell proliferation and reduced accumulation of collagen type I and expression of fibrosis-related genes. In mice, nintedanib slowed glomerular microangiopathy administered immediately or 3 days after ureteral obstruction or folic acid overdosing attenuated kidney fibrosis and inhibited activation of renal interstitial fibroblasts and inflammation.

Nintedanib is marketed for treatment of IPF and other progressive chronic fibrosing interstitial lung diseases, including systemic sclerosis–associated interstitial lung disease. Ongoing trials are centered on malignancy and lung disease and are not exploring CKD. Less than 1% of the total dose of nintedanib is excreted via the kidney, and the agent can be used in those with eGFR 30–60 mL/min/1.73 m², but the safety, efficacy, and pharmacokinetics have not been studied in patients with CIcr <30 mL/min. The European label warns about cases of renal impairment/failure, in some cases with a fatal outcome. Indeed, nintedanib-induced glomerular microangiopathy and proteinuria have been reported to improve after nintedanib withdrawal. This would be unsurprising because nintedanib inhibits VEGFR. This adverse effect profile may limit its usefulness for CKD.

PRM-151
PRM-151 is a recombinant human pentraxin 2/serum amyloid P protein. Serum pentraxin 2 levels are low in fibrotic conditions, including kidney fibrosis, and recombinant human pentraxin 2 delays CKD progression in Alport mice, enhancing lifespan and decreasing kidney inflammation and fibrosis. Reduced activator protein 1 (AP-1)–driven inflammation is a key mechanism of action. PRM-151 improved IPF in a phase 2 trial and its extension to 52 weeks. It is undergoing phase 3 trials for IPF (trial ID NCT04552899) and phase 1 clinical development for kidney disease.

EGCG
A commercially available food supplement, EGCG is a fibroblast-specific, irreversible inhibitor of lysyl oxidase-like 2 (LOXL2) and TGF-β receptor 1 and 2 (TGF-βR1/2) kinase. EGCG decreased kidney cell injury, inflammation, and fibrosis in diverse preclinical kidney injury models. Recently, a study involving 10 participants with suspected IPF found that 2 weeks of EGCG treatment before lung biopsy decreased circulating and tissue biomarkers of ongoing fibrosis. A phase 1 clinical trial in IPF will be completed by December 2022 (trial ID NCT03928847).

Ziritaxestat
Ziritaxestat (GLPG1690) is an autotaxin inhibitor. Autotaxin (also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 [NPP2 or ENPP2]) is a secreted lysophospholipase D that generates lysophosphatidic acid (LPA) from lysophosphatidylcholine. Autotaxin promotes kidney fibroblast proliferation, and LAP1 and LAP2 receptors cooperate to promote TGF-β1 signaling and secretion of PDGF-B and CCN2 (connective tissue growth factor) by proximal tubule cells. Autotaxin inhibition limits progressive proteinuria and tubulointerstitial fibrosis in rat chronic allograft injury and partially attenuates obstruction-induced kidney fibrosis in mice. However, exogenous LPA is observed to provide protection from endotoxemia-induced kidney inflammation and injury, raising the possibility of cause- or timing-specific effects. In February 2021, the phase 3 ziritaxestat research program was discontinued as recommended by the independent data monitoring committee.

Potential Novel Therapeutic Targets
Some recent preclinical advances merit comment because they relate to drugs in clinical use (eg, trametinib, hypoxia-inducible factor [HIF] stabilizers), they pertain to ongoing clinical development (interleukin 11 [IL-11]), or they have identified potentially specific (NKD2 [WNT signaling pathway inhibitor]) or broad (metabolic deregancements) pathways for kidney fibrosis.

Trametinib is an inhibitor of MEK (a kinase of mitogen-activated protein kinase) in clinical use for malignancy with antifibrotic effects in murine kidney fibrosis. However, trametinib also inhibits inflammation, an expected consequence of blocking extracellular signal-regulated kinase (ERK) 1/2 signaling. Of the 125 ongoing clinical trials for trametinib (GSK1120212, JTP 74057) listed at ClinicalTrials.gov, none is targeting fibrosis in any organ.

Key to the profibrotic effect of TGF-β1 is that fibroblasts respond to this signal by secreting IL-11, which acts through autocrine activation of the IL-11 receptor-α (IL-11RA) and ERK-dependent signaling. In mice, fibroblast-specific IL-11 transgene expression or IL-11 administration causes heart and kidney fibrosis and organ failure, whereas genetic deletion of IL-11RA is protective. Neutralizing antibodies against IL-11 or IL-11RA have been developed but not yet tested in humans.
NKD2 was recently identified as a myofibroblast-specific target in human kidney fibrosis expressed by PDGFRβ-positive/high extracellular matrix myofibroblasts. NKD2 modulates the TNF and WNT pathways, and NKD2 targeting inhibits inflammation-induced expression of the α1 chain of collagen type I in human organoids. Tubular cell mitochondrial homeostasis, energy sensing, and lysosomal pathways are key drivers of kidney fibrosis (Fig 2). Proximal tubule cell dedifferentiation, formation of “mixed-identity cells” (expressing markers of different renal cell types), and proinflammatory and profibrotic phenotypes within the first 24 hours of experimental ischemia-reperfusion injury may be driven by acute mitochondrial injury that fails to fully recover. Preserving the master regulator of mitochondrial biogenesis (the transcriptional coactivator PGC1α [peroxisome proliferator-activated receptor-γ coactivator 1-α]) and increasing fatty acid oxidation are proposed avenues to combat fibrosis. Altered NAD (nicotinamide adenine dinucleotide) homeostasis has been observed in acute kidney injury and may potentially trigger late-onset fibrosis. Vitamin B3 vitamers may increase kidney NAD (nicotinamide adenine dinucleotide) availability, but studies in preclinical kidney disease have been mixed, and clinical trials in the CKD context have so far focused on treating hyperphosphatemia. The optimal approach to increase kidney NAD availability in CKD is currently unclear. Confirmation of the early role of tubular cell mitochondrial injury in kidney fibrosis may change the general approach to kidney fibrosis from treatment of late stages by focusing on fibroblasts and extracellular matrix to prevention through preservation of epithelial cell health, which is thought to be a key component of kidney protection by SGLT2 inhibition and lademirsen.

Hypoxia-inducible factor (HIF) prolyl hydroxylase enzyme inhibitors are in clinical use or development to treat anemia of CKD. Given the role of hypoxia in fibrosis and preclinical data suggesting that HIF stabilizers modulate kidney fibrosis, it was speculated that they may modulate kidney fibrosis in humans. Indeed, it was hypothesized that kidney protection by SGLT2 inhibitors may be a consequence of their promotion of oxygen deprivation signaling in the kidney. However, so far, preclinical evidence is heterogeneous regarding the direction or even the presence of an impact on kidney fibrosis, and clinical trials have yet to show modulation of CKD progression.

**Conclusions**

In conclusion, direct antifibrotic therapy remains an elusive goal in CKD (Box 2). Many nephroprotective drugs decrease
Box 2. Challenges and Opportunities in the Clinical Development of Drugs Targeting Kidney Fibrosis

1. Nephroprotective drugs that decrease kidney fibrosis in preclinical models (RAS blockers, SGLT2 inhibitors, the MRA finerenone) are already in clinical use or approved for kidney protection, so any novel therapy targeting kidney fibrosis should:
   a. Show benefit over combined RAS plus SGLT2 inhibition and/or novel MRAs or
   b. Focus on patients unable to receive these therapies.
2. Lack of kidney fibrosis outcomes end points in routine clinical practice.
   a. This poses 2 challenges:
      i. This limits the possibilities of clinical trials in early CKD stages in nonproteinuric kidney disease (ie, G1-G2/A1).
      ii. Kidney events are not suitable outcome measures for phase 2 trials or early intervention trials because of low frequency.
   b. In response, FDA- and EMA-accepted kidney fibrosis outcomes that represent whole kidney fibrosis (imaging, urinary biomarkers) should be developed.
3. Suboptimal design of clinical trials of fibrosis-targeted drugs.
   a. There are 2 key challenges facing current trials:
      i. They frequently recruit patients with advanced CKD, but earlier intervention will more likely be successful.
      ii. Kidney fibrosis outcomes would be needed to test efficacy.
   b. Ongoing and planned trials and observational intervention studies for pulmonary fibrosis offer the opportunity to simultaneously assess impact on kidney function and, ideally, on kidney fibrosis, given that the age range of participants is compatible with ongoing age-associated loss of kidney function.
4. In preclinical models, events originating in mesenchymal cells and initially causing fibrosis may evolve to secondarily cause inflammation and parenchymal cell injury. However, it remains to be demonstrated in humans that therapeutic approaches specifically targeting fibrosis add kidney protection to drugs in clinical use that also decrease fibrosis. Any therapeutic approach specifically targeting fibrosis needs to:
   a. Show kidney protection as add-on to current SOC and
   b. Demonstrate that this is associated with further decrease in fibrosis over SOC.
5. It is unclear whether there are therapeutic approaches that specifically target fibrosis without interfering with inflammation or parenchymal cell injury/dysfunction; however, this is a semantic discussion: the key issue is the end result, ie, kidney function preservation.

Abbreviations: EMA; European Medicines Administration; FDA; Food and Drug Administration; MRA; mineralocorticoid receptor antagonist; RAS, renin-angiotensin system; SGLT2, sodium/glucose cotransporter 2; SOC, standard of care.

Kidney fibrosis in preclinical studies, but whether a direct effect on fibrosis contributes to the therapeutic benefit remains unclear. Fibrosis targeting is a well-established concept in IPF. Kidney function outcomes should be added to trials and real-world studies of antifibrotic therapy for pulmonary fibrosis to gain insight into a potential impact of these drugs on kidney function in humans; eventually, this may allow design of trials with kidney outcomes. Because COVID-19 causes kidney and lung injury, the pandemic may offer the opportunity to gain insight into the impact of therapies for pulmonary fibrosis on kidney health. The optimal timing of therapy targeting fibrosis should be reassessed because some kidney fibrosis trials have enrolled participants with late-stage CKD, but the fibrosis process starts very early in the course of CKD. The availability of specific whole-kidney fibrosis outcome measures may facilitate the design of early intervention trials. In any case, these new trials should address whether interventions specifically targeting fibrosis improve kidney outcomes when added to a standard of care consisting of RAS blockers, dietary sodium restriction, and SGLT2 inhibitors or finerenone. Any trial not comparing against the new standard of therapy should be considered outdated.

Supplementary Material

Supplementary File (PDF)
Table S1: In vitro potency and selectivity of nintedanib in enzymatic assays using human recombinant kinase domains
Table S2: Potency and selectivity of nintedanib in vitro cellular assays

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