Diabetic nephropathy: landmark clinical trials and tribulations

Gary C.W. Chan and Sydney C.W. Tang
Division of Nephrology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

Correspondence and offprint requests to: Sydney C.W. Tang; E-mail: scwtang@hku.hk

ABSTRACT

Diabetic nephropathy remains the most common cause of end-stage renal disease worldwide. The current standard of therapy for diabetic nephropathy involves stringent blood pressure control via blockade of the renin–angiotensin system and control of hyperglycemia. Despite these strategies, diabetic nephropathy is still seen to progress relentlessly. A pressing need for novel therapeutic agents has fueled endless basic science research projects and clinical trials in the quest for a more specific therapy. Throughout the process, only a handful of ancillary agents have shown experimental promise and even fewer have demonstrated an impact in human trials. This review article aims to summarize the available data from landmark studies for the main therapeutic approaches investigated.

Keywords: clinical trials, diabetic nephropathy, humans

INTRODUCTION

The burden of diabetes mellitus (DM) is rapidly rising. Current projections estimate the global prevalence of diabetic individuals to rise from 6.4% (285 million) in 2010 to 7.7% (439 million) in 2030 [1]. The main problem with this disease entity is its propensity to incur macro- and microvascular complications over time, crippling both the individual and our resource restricted healthcare system.

Diabetic nephropathy (DN) is estimated to affect one-third of individuals with DM and is associated with considerable cardiovascular morbidity and mortality. It is the leading cause of end-stage renal disease (ESRD) worldwide, accounting for 42% of all patients on renal replacement therapy (RRT) in the USA [2].

Unfortunately, the magnitude of this clinical entity continues to grow in association with an expanding diabetic population and remarkably the excess mortality risk of DM is associated almost entirely with the presence of DN [3, 4]. Thus, the search for therapeutic modalities to stem this inexorable tide remains a pressing matter. Although no cure is available at present, treatment options to prevent or slow disease progression are available. In this update, we aim to address the current armamentarium in the clinical management of DN and highlight the potential novel therapies under development. The results from major clinical trials, summarized in Table 1, are presented and critically reviewed. Current established therapies, novel treatments on the horizon and investigational strategies in their infancy are illustrated in Figure 1.

CURRENT STANDARD OF APPROACH TO DN

Glycemic optimization

Direct evidence demonstrating the beneficial effect of glycemic control is derived from isolated pancreatic transplantation in patients with DN. Metabolic normalization resulted in histological regression in this cohort at 10 years following transplantation [29]. Clinical trials have consistently reverberated this notable finding in both type 1 and type 2 DM, and validate the favorable effects of stringent glycemic regulation in delaying the onset and progression of DN. The DCCT (Diabetes Control and Complications Trial) recruited 1441 patients with type 1 DM. Glycemic optimization to achieve hemoglobin A1c (HbA1c) 7.3 versus 9.1% reduced incident micro- and macroalbuminuria by 39 and 54%, respectively, at a mean follow-up of 6.5 years [5]. Furthermore, extended observational data from the EDIC (Epidemiology of Diabetes Interventions and Complications) study on the original DCCT cohort clearly exhibited durability of early intensive diabetic regulation beyond 18 years [6, 30, 31]. Comprehensive prospective data are also available for type 2 DM. The UKPDS: 33 (United Kingdom Prospective Diabetes Study: 33) randomized 3867 newly diagnosed type 2 DM patients into a treatment arm with HbA1c target of 7.0% and a control arm with no restriction of HbA1c. At 14 years follow-up, a 39% reduction in macrovascular events was seen in the Intensive group with a significant 16% reduction in microvascular events [7].
Table 1. Main results of major RCTs of various therapeutic approaches in diabetic kidney disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Design</th>
<th>FU</th>
<th>Renal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT [5]</td>
<td>1441</td>
<td>T1DM Intensive versus standard</td>
<td>6.5 years</td>
<td>Intensive glycemic control versus standard control (HbA1c 7.3 versus 9.1%) reduced incident micro- and macro-albuminuria by 39 and 54%.</td>
</tr>
<tr>
<td>EDIC/DCCT [6]</td>
<td>1441</td>
<td>T1DM Intensive versus standard</td>
<td>18 years</td>
<td>Renoprotective efficacy of intensive glycemic control persisted and resulted in 45% risk reduction of micro-albuminuria at 18 years</td>
</tr>
<tr>
<td>UKPDS 33 [7]</td>
<td>3867</td>
<td>T2DM Intensive versus standard</td>
<td>10 years</td>
<td>Intensive glycemic control versus standard control (HbA1c 7.0 versus 7.9%) led to 33% risk reduction for micro-albuminuria.</td>
</tr>
<tr>
<td>ADVANCE [8]</td>
<td>11 140</td>
<td>T2DM Intensive versus standard</td>
<td>5 years</td>
<td>Intensive glycemic control versus standard control (HbA1c 6.5 versus 7.3%) reduced risk of micro-, macro-albuminuria and ESRD by 9, 30 and 65%. For those with macro-albuminuria, number needed to treat to prevent one ESRD = 41.</td>
</tr>
<tr>
<td>ACCORD [9]</td>
<td>10 251</td>
<td>T2DM Intensive versus standard</td>
<td>Terminated at 3.5 years</td>
<td>Targeting HbA1c 6.0 versus 7.0–7.9% resulted in increased mortality (HR 1.22; 95% CI 1.01–1.46; P = 0.04).</td>
</tr>
<tr>
<td>RENAAL [10, 11]</td>
<td>1513</td>
<td>T2DM Losartan versus placebo</td>
<td>3.4 years</td>
<td>Multivariate analysis: every 10 mmHg SBP rise increased risk of ESRD by 6.7%. Losartan led to decrement of proteinuria (35%; P &lt; 0.001), risk reduction of serum creatinine doubling (25%; P = 0.006) and ESRD (28%; P = 0.002).</td>
</tr>
<tr>
<td>MARVAL [12]</td>
<td>332</td>
<td>T2DM Valsartan versus amlodipine</td>
<td>24 weeks</td>
<td>Reduction of micro-albuminuria with valsartan (44%) greater than amlodipine (8%).</td>
</tr>
<tr>
<td>IRMA-2 [13]</td>
<td>590</td>
<td>T2DM Irbesartan versus placebo</td>
<td>2 years</td>
<td>Irbesartan demonstrated renoprotective efficacy with reduction in disease progression compared with placebo (HR 0.3; 95% CI 0.14–0.61; P &lt; 0.001 for 300 mg irbesartan).</td>
</tr>
<tr>
<td>IDNT [14]</td>
<td>1715</td>
<td>T2DM Irbesartan versus amlodipine</td>
<td>2.6 years</td>
<td>Irbesartan was renoprotective with lower risk of serum creatinine doubling (33%; P = 0.003) and ESRD (23%; P = 0.07) compared with placebo.</td>
</tr>
<tr>
<td>DETAIL [15]</td>
<td>250</td>
<td>T2DM Telmisartan versus enalapril</td>
<td>5 years</td>
<td>Telmisartan and enalapril fared equally. No significant differences in level of albuminuria, rate of GFR decline and ESRD.</td>
</tr>
<tr>
<td>ROADMAP [16]</td>
<td>4447</td>
<td>T2DM Olmesartan versus placebo</td>
<td>3.2 years</td>
<td>Olmesartan resulted in a reduction in time to micro-albuminuria onset by 23% (HR 0.77; 95% CI 0.63–0.94; P = 0.01). Blood pressure was similarly controlled in both study arms.</td>
</tr>
<tr>
<td>CALM [17]</td>
<td>199</td>
<td>T2DM Candesartan/lisinopril combo versus candesartan versus losartan</td>
<td>12 weeks</td>
<td>Combination therapy more effective with greater reduction in urinary albumin: creatinine ratio (50%) compared with candesartan (24%) or losartan (39%) alone.</td>
</tr>
<tr>
<td>ONTARGET [18]</td>
<td>25 620</td>
<td>T1&amp;2DM Telmisartan/ramipril combo versus telmisartan versus ramipril</td>
<td>55 months</td>
<td>Combination therapy was associated with increased composite outcome of dialysis, serum creatinine doubling and death (HR 1.09; 95% CI 1.01–1.18; P ≤ 0.037).</td>
</tr>
<tr>
<td>VA NEPHRON-D [19]</td>
<td>1448</td>
<td>T2DM Losartan/lisinopril combo versus losartan</td>
<td>Terminated at 2.2 years</td>
<td>Combination therapy offered no renal benefit but resulted in excessive risk of hyperkalemia (6.3 versus 2.6 events per 100 person years; P &lt; 0.001) and acute kidney injury (12.2 versus 6.7 events per 100 person years; P &lt; 0.001).</td>
</tr>
<tr>
<td>AVOID [20]</td>
<td>599</td>
<td>T2DM Losartan versus aliskiren/losartan combo</td>
<td>6 months</td>
<td>Aliskiren (direct renin inhibitor)/losartan combo led to reduction of urinary albumin: creatinine ratio by 20% (95% CI 9–30; P &lt; 0.001) independent of blood pressure control.</td>
</tr>
<tr>
<td>ALTITUDE [21]</td>
<td>8561</td>
<td>T2DM RAS blockade plus aliskiren versus placebo</td>
<td>Terminated at 2.7 years</td>
<td>Addition of aliskiren to maximal ARB offered no additional benefit. Hyperkalemia and hypotension were significantly increased in the aliskiren arm.</td>
</tr>
<tr>
<td>BEAM [22]</td>
<td>227</td>
<td>T2DM Bardoxolone methyl versus placebo</td>
<td>52 weeks</td>
<td>Bardoxolone methyl at 25, 75 and 150 mg resulted in a higher GFR (5.1 mL/min/1.73 m2) compared with placebo at 52 weeks.</td>
</tr>
<tr>
<td>BEACON [23]</td>
<td>2185</td>
<td>T2DM Bardoxolone methyl versus placebo</td>
<td>Terminated at 9 months</td>
<td>Bardoxolone methyl led to a significant increase in cardiovascular morbidity (HR 1.83; 95% CI 1.32–2.55; P &lt; 0.001). Effect persisted after 8 months with 62% reduction compared with placebo (P = 0.0001).</td>
</tr>
<tr>
<td>DN.ES. [24]</td>
<td>223</td>
<td>T1&amp;2DM Sulodexide versus placebo</td>
<td>8 months</td>
<td>4 months of sulodexide (200 mg/day) significantly reduced albuminuria.</td>
</tr>
<tr>
<td>Sun-MACRO [25]</td>
<td>1248</td>
<td>T2DM Maximum ARB plus sulodexide versus placebo</td>
<td>Terminated</td>
<td>No significant benefit observed in end points of serum creatinine doubling and ESRD.</td>
</tr>
<tr>
<td>VITAL [26]</td>
<td>281</td>
<td>T2DM RAS inhibition plus paricalcitol versus placebo</td>
<td>24 weeks</td>
<td>Paricalcitol at 2 μg/day reduced albuminuria (20% compared with placebo). However, 2 μg/day was poorly tolerated and patients often reduced the dosage.</td>
</tr>
<tr>
<td>CANTATA-SU [27]</td>
<td>1450</td>
<td>T2DM Canagliflozin versus glimepiride</td>
<td>52 weeks</td>
<td>Canagliflozin caused initial decrease in GFR but subsequently stabilized while individuals in the glimepiride arm had progressive GFR decline (–1.7 versus –5.1 mL/min/1.73 m2 after 52 weeks).</td>
</tr>
<tr>
<td>ASCEND [28]</td>
<td>1392</td>
<td>T2DM Avosentan versus placebo</td>
<td>Terminated at 4 months</td>
<td>Avosentan reduced proteinuria compared with placebo, but, had excess adverse cardiovascular events; especially fluid overload (4.6%; P = 0.225), congestive heart failure (3.6%; P = 0.194) and death (2.6%).</td>
</tr>
</tbody>
</table>

ARB, angiotensin receptor blocker; RAS, renin-angiotensin system; T1DM, type 1 diabetes mellitus.
Individuals receiving either intensive glucose-lowering or conventional therapy. At a median follow-up of 10 years and an achieved 11% difference in HbA1c, the risk reduction of incident microalbuminuria was 33% in the intensive arm [7]. These results were replicated in the more recent ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, powered by 11,140 patients with type 2 DM [8]. Intensive glycemic control (HbA1c 6.5%) over a median of 5 years reduced the risk of micro- and macroalbuminuria by 9% and 30%, respectively, compared with standard control (HbA1c 7.3%). Moreover, a 65% risk reduction of ESRD was observed in the cohort and the number of participants with microalbuminuria needed to treat to prevent an ESRD event was only 41.

These encouraging data must be taken with a pinch of salt as the beneficial reduction in albuminuria may be offset by the adverse outcomes of hypoglycemia from stringent diabetic control. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was prematurely terminated because of excess mortality in the intensive therapy arm (HbA1c target <6.0%) compared with the standard arm (HbA1c 7.0–7.9%) [9]. Similarly, analyses of the ADVANCE cohort linked severe hypoglycemia with a range of adverse clinical outcomes, fueling speculation as to what constitutes an appropriately tight diabetic control [32].

The current recommendation by the American Association of Clinical Endocrinologists is to target HbA1c <6.5%, while the American Diabetes Association sets a goal of HbA1c <7% in an attempt to balance out the risk of hypoglycemia from the clear benefit of renoprotection in this cohort [33]. Caution is to be exercised when prescribing oral hypoglycemic agents in the setting of chronic kidney disease (CKD). Long-acting sulfonylureas such as chlorpropamide or glibenclamide have a propensity to induce prolonged hypoglycemia, especially in the elderly, and should be used with extreme caution. Metformin is a biguanide that may result in fatal lactic acidosis. The precise serum creatinine limits and glomerular filtration rate (GFR) thresholds for the safe use of metformin remain uncertain. In clinical practice, serum creatinine levels over 150 μmol/L have been suggested to be a contraindication [34], although this is an arbitrary limit. Some use an estimated GFR >30 mL/min/1.73 m² as a safety threshold, and an estimated GFR between 30 and 60 mL/min/1.73 m² as an indication for halving the dose. In any case, metformin should be withheld in patients who are about to receive intravenous iodinated contrast material (with potential for contrast-induced nephropathy) or undergo a surgical procedure (with potential for compromised circulation), irrespective of the baseline renal function. The dipeptidyl peptidase-4 inhibitors are structurally heterogeneous and differ in their metabolism and excretion. While sitagliptin, vildagliptin and saxagliptin have prominent renal excretion necessitating dosage reduction for GFR <60 mL/min/1.73 m², linagliptin is mainly eliminated by the enterohepatic system and does not require dosage adjustment for the level of CKD. Finally, inhibitors of the sodium-glucose co-transporter 2 interfere with renal proximal tubule glucose reabsorption and their action is understandably GFR dependent: canagliflozin and empagliflozin are not recommended for GFR <45 mL/min/1.73 m², while dapagliflozin should not be used when GFR is <60 mL/min/1.73 m².

**Blood pressure control: the renin-angiotensin system**

Hypertension is a prevalent comorbidity in diabetic individuals. Moreover, it is an independent modifiable risk factor for the development and acceleration of micro- and macrovascular complications of DM. There is no doubt that achievement of stringent blood pressure control, irrespective of the agent used, retards the onset and progression of DN to confer a survival benefit. Prospective observational data from UKPDS: 36 revealed that every 10 mmHg decrement in systolic blood pressure translated to a reduction in any DM-related complication and death by 12 and 15%, respectively [35]. Subsequently, the post hoc analyses of 1513 type 2 DM patients with established DN and hypertension in the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial...
revealed a 6.7% increased risk of ESRD or death for every 10 mmHg increment in baseline systolic blood pressure [10].

Inhibitors of the renin–angiotensin system (RAS) including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) are widely employed to control the blood pressure of diabetic patients. They are superior to other antihypertensive agents in DN by virtue of their capacity to reduce intraglomerular pressure and hence proteinuria by preferentially dilating the efferent arteriole. Their additional renoprotective benefits above and beyond blood pressure regulation are clearly demonstrated by the MARVAL (Micro-Albuminuria Reduction with Valsartan) study. For the same level of blood pressure decrease and control, valsartan was superior to amlodipine for micro-albuminuria reduction (56 compared with 92% from baseline) in 332 type 2 DM individuals after 24 weeks [12]. Meta-analysis of 698 non-hypertensive type 1 DM patients with micro-albuminuria also showed that treatment with ACEi restrained progression to macro-albuminuria by 60%. Furthermore, an increased odds ratio for regression to normo-albuminuria 3.07 [95% confidence interval (CI) 2.15–4.44; P < 0.001] was observed [36]. In addition, the effect of RAS blockade in reverting micro-albuminuria may even persist after treatment withdrawal, as demonstrated in a substudy of the IRMA-2 (Irbesartan in Patients with Type 2 Diabetes and Micro-albuminuria) trial, suggesting possible glomerular structural normalization [37]. In concert with the aforementioned effects on micro-albuminuria, the interruption of RAS is equally impressive for controlling macro-albuminuria [11, 38].

Abruption albuminuria is the cornerstone to achieving hard renal end points for RAS blockade. Simply put, the incorporation of ACEi or ARB to the treatment approach of DN slows its progression. IDNT (Irbesartan Diabetic Nephropathy Trial) recruited 1715 hypertensive type 2 DN patients and showed, after a mean follow-up of 2.6 years, that irbesartan reduced the risk of serum creatinine doubling and progression to ESRD by 33 and 23%, respectively [14]. Similarly, in the post hoc analyses of RENAAAL, every 50% reduction in albuminuria in the first 6 months of therapy with losartan was associated with a risk reduction of 45% for ESRD during subsequent follow-up [39]. A similar renoprotective effect with captopril had been noted much earlier in a study of type 1 diabetic individuals with overt nephropathy [38].

With regard to the comparative effectiveness of ACEi and ARB in DN, there is little data to favor one over the other. The general consensus is that they can be employed interchangeably as required, usually when patients develop intractable cough associated with ACE inhibition. This is supported by DETAIL (Diabetics Exposed to Telmisartan and Enalapril), which was a randomized controlled trial comparing telmisartan to enalapril in 250 type 2 DN patients. At 5 years, there were no significant differences in the rate of GFR decline, level of albuminuria and ESRD between the study arms [15].

It is prudent to note that the majority of the available evidence for RAS blockade thus far have been established in secondary prevention trials. Henceforth, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines have not enforced the implementation of ACEi or ARB for the primary prevention of DN in normotensive individuals with normo-albuminuria [40]. The ROADMAP (Randomized Olmesartan and Diabetes Micro-albuminuria Prevention) trial stands to challenge this positional statement from KDOQI. ROADMAP assigned 4447 type 2 DM patients with normo-albuminuria to receive olmesartan (40 mg daily) or placebo for a median of 3.2 years. The result was a reduction in time to micro-albuminuria onset by 23% despite equally well-controlled blood pressure in both study arms [hazard ratio (HR) 0.77; 95% CI 0.63–0.94; P = 0.01] [16].

### Further manipulation of the renin–angiotensin–aldosterone axis

Combination therapy of ACEi plus ARB has been suggested in an attempt to achieve better RAS blockade. The initial CALM (Candesartan and Lisinopril Micro-albuminuria) study found combination therapy to be more effective in retarding micro-albuminuria than either candesartan or lisinopril alone after 12 weeks [17]. However, these short-term results were never replicated by longer follow-up studies. Furthermore, no trial to date has unequivocally shown dual RAS inhibition to halt the progression of DN, with a propensity for this treatment regime to cause adverse events. ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) randomized 25 620 high vascular risk patients (37.5% diabetics) to receive ramipril, telmisartan or their combination. The composite outcome of dialysis, doubling of serum creatinine, and death was increased with combination therapy (HR 1.09; 95% CI 1.01–1.18; P ≤ 0.037), casting doubt over the use of dual blockade [18]. Such doubts were initially refuted [41] but the nail in the coffin comes from the recently published VA NEPHRON-D (Vetairs Affairs Nephropathy in Diabetes) trial, which enrolled 1448 type 2 DN patients to receive single agent losartan or in combination with lisinopril [19]. Combination therapy offered no renal benefit and the trial was prematurely stopped after just a median follow-up of 2.2 years due to excessive risk of hyperkalemia (9.9 versus 4.4%) and AKI (18 versus 11%). It must be borne in mind that only patients with estimated GFR 30.0–89.9 mL/min/1.73 m² were recruited in this study. The conceivable risk of dual RAS inhibition on the reported adverse events would only be higher in DN patients with greater renal impairment. Combination therapy is therefore not recommended in the management of DN.

A reactive increase in plasma renin activity in association with ACEi or ARB therapy has been well described. In theory, direct renin inhibition as an alternative approach for RAS downregulation may be more complete and effective by acting at a higher level within the pharmacological axis. In 2007, the direct renin inhibitor aliskiren was approved for the treatment of hypertension. Soon after, AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes) was conducted to attest whether aliskiren could confer additional renoprotection in type 2 DN patients already on maximal recommended dose of losartan. Five hundred and ninety-nine hypertensive patients with DN were enrolled and the addition of aliskiren resulted in a 20% reduction of urinary albumin-to-creatinine ratio at 24 weeks, independent of blood pressure control [20]. However,
these promising short-term data were subsequently overshadowed by the termination of ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints), based on both therapeutic futility and increased rate of adverse events that included hyperkalemia and hypotension [21]. The outcomes of ALTITUDE are reminiscent of the results from ON-TARGET and emphasize that RAS inhibition may be better confined to a single agent in DN. It is pertinent to remember that, at times of renal under-perfusion, even single agent RAS blockade can have deleterious effects and its temporary cessation pre-operatively or during times of diarrheal illnesses may help prevent the initiation and propagation of acute kidney injury (AKI).

It has also been proposed that suboptimal anti-proteinuric response to ACEi in some individuals is the result of ‘aldosterone escape’. That aldosterone antagonism may complement RAS blockade to confer plausible renoprotection has therefore subsequently been explored. Indeed, meta-analyses have demonstrated that addition of mineralocorticoid receptor antagonists (MRA) to a regimen comprising ACEi or ARB reduces proteinuria in the CKD population [42]. This beneficial effect was also exhibited in DN cohorts when non-selective (spironolactone) [43–45] and selective (eplerenone) [46] MRA were employed. However, the increased risk of hyperkalemia was evident in many of these studies that investigated the use of aldosterone antagonism in addition to RAS inhibition, and no convincing data to show a reduction in renal end points have been presented to date. As such, the jury is still out on the use of MRA in the management of DN.

**NOVEL THERAPEUTIC MODALITIES: PAST AND PRESENT**

Despite optimal RAS inhibition coupled with stringent blood pressure and glucose control, it remains evident today that many patients with DN still progress relentlessly to ESRD. The pressing search for new therapeutic drugs to effectively interrupt and ameliorate disease progression has seen novel agents stumble and disappoint. Yet, there exist several therapies on the horizon that provide potential promise to advance the current therapeutic boundaries. The following is a brief overview of the agents that have foundered in clinical trials and approaches that still bare promise under scrutiny.

Pleotropic renoprotective effects of antidiabetic drugs beyond glycemic control

Certain glucose-lowering agents have been touted to provide independent renoprotection beyond their hypoglycemic action. Abundant experimental evidence indicates that peroxisome proliferator activator receptor-gamma (PPAR-γ) agonists, also known as thiazolidinediones (TZD), have direct renoprotective effects [47–50]. However, varied outcomes have been achieved in clinical studies with some reporting favorable reduction in proteinuria [51–54], while others have demonstrated an insignificant effect [55]. In fact, post hoc analysis of PROActive (Prospective Pioglitazone Clinical Trial in Macro-vascular Events), which enrolled 5238 diabetic patients with a history of macrovascular disease, even noted a greater decline in estimated GFR with pioglitazone [56]. Among the confusion, a meta-analysis of 15 TZD trials (10 with pioglitazone; 5 with rosiglitazone) involving 2860 patients did find a significant reduction in albuminuria [57]. However, there remains a lack of TZD evidence in improving hard renal outcomes and the use of these agents have been overshadowed by multiple safety concerns, including increased cardiovascular risk [58, 59] and malignancy [60, 61]. Unless these hurdles can be surmounted, TZDs will likely remain in the background of available therapies employed in the management of DN.

Dipeptidyl peptidase-4 (DPP-4) is a regulatory enzyme that degrades glucagon-like peptide 1, an incretin released from the gut in response to food intake to stimulate insulin and suppress glucagon production [62]. Inhibitors of DPP-4 are a new class of hypoglycemic agents that have emerged in the treatment paradigm of DM, but have been shown in animal models to also harbor renoprotective potential [63, 64]. Currently, only a few clinical trials have been published, but in small uncontrolled studies, 6 months of sitagliptin [65] or 12 weeks of alogliptin [66] reduced albuminuria in type 2 DM patients. Besides a small sample size in both of these investigations, one is wary of the fact that HbA1c had appropriately lowered in response to therapy. Therein, it is difficult to delineate whether it is the agent or the improved glycemic control that has led to a reduction in albuminuria. However, a pooled analysis of four Phase III studies, which included 217 patients with DN on RAS inhibition, 24 weeks of linagliptin significantly reduced albuminuria (32% reduction; 95% CI −42 to −21; P < 0.05), independent of HbA1c [67]. The positive results of DPP-4 inhibitors thus far, coupled with their tolerability, weight neutral benefit and low risk of hypoglycemia [68, 69], have fueled interest into further research on the gut-renal axis as a putative therapeutic target [70]. Indeed, a large number of ongoing clinical trials are underway in an attempt to exploit incretin-based therapies for the management of DN.

**Bardoxolone methyl**

The increasing awareness that oxidative stress and inflammation may promote the development and progression of DN has paved the way for investigations into the use of bardoxolone methyl, an antioxidative inflammatory modulator [71]. Surprising renoprotective properties were first noticed in cancer trials. Subsequently, beneficial effects were demonstrated in small diabetic cohorts with moderate renal insufficiency [72]. The BEAM (Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes) trial randomized 227 type 2 diabetic patients with GFR 20.0–45.0 mL/min/1.73 m² to varying doses of bardoxolone methyl, an antioxidative inflammatory modulator [71]. Despite optimal RAS inhibition coupled with stringent blood pressure and glucose control, it remains evident today that many patients with DN still progress relentlessly to ESRD. The pressing search for new therapeutic drugs to effectively interrupt and ameliorate disease progression has seen novel agents stumble and disappoint. Yet, there exist several therapies on the horizon that provide potential promise to advance the current therapeutic boundaries. The following is a brief overview of the agents that have foundered in clinical trials and approaches that still bare promise under scrutiny.

Pleotropic renoprotective effects of antidiabetic drugs beyond glycemic control

Certain glucose-lowering agents have been touted to provide independent renoprotection beyond their hypoglycemic action. Abundant experimental evidence indicates that peroxisome proliferator activator receptor-gamma (PPAR-γ) agonists, also known as thiazolidinediones (TZD), have direct renoprotective effects [47–50]. However, varied outcomes have been achieved in clinical studies with some reporting favorable reduction in proteinuria [51–54], while others have demonstrated an insignificant effect [55]. In fact, post hoc analysis of PROActive (Prospective Pioglitazone Clinical Trial in Macro-vascular Events), which enrolled 5238 diabetic patients with a history of macrovascular disease, even noted a greater decline in estimated GFR with pioglitazone [56]. Among the confusion, a meta-analysis of 15 TZD trials (10 with pioglitazone; 5 with rosiglitazone) involving 2860 patients did find a significant reduction in albuminuria [57]. However, there remains a lack of TZD evidence in improving hard renal outcomes and the use of these agents have been overshadowed by multiple safety concerns, including increased cardiovascular risk [58, 59] and malignancy [60, 61]. Unless these hurdles can be surmounted, TZDs will likely remain in the background of available therapies employed in the management of DN.

Dipeptidyl peptidase-4 (DPP-4) is a regulatory enzyme that degrades glucagon-like peptide 1, an incretin released from the gut in response to food intake to stimulate insulin and suppress glucagon production [62]. Inhibitors of DPP-4 are a new class of hypoglycemic agents that have emerged in the treatment paradigm of DM, but have been shown in animal models to also harbor renoprotective potential [63, 64]. Currently, only a few clinical trials have been published, but in small uncontrolled studies, 6 months of sitagliptin [65] or 12 weeks of alogliptin [66] reduced albuminuria in type 2 DM patients. Besides a small sample size in both of these investigations, one is wary of the fact that HbA1c had appropriately lowered in response to therapy. Therein, it is difficult to delineate whether it is the agent or the improved glycemic control that has led to a reduction in albuminuria. However, a pooled analysis of four Phase III studies, which included 217 patients with DN on RAS inhibition, 24 weeks of linagliptin significantly reduced albuminuria (32% reduction; 95% CI −42 to −21; P < 0.05), independent of HbA1c [67]. The positive results of DPP-4 inhibitors thus far, coupled with their tolerability, weight neutral benefit and low risk of hypoglycemia [68, 69], have fueled interest into further research on the gut-renal axis as a putative therapeutic target [70]. Indeed, a large number of ongoing clinical trials are underway in an attempt to exploit incretin-based therapies for the management of DN.

Bardoxolone methyl

The increasing awareness that oxidative stress and inflammation may promote the development and progression of DN has paved the way for investigations into the use of bardoxolone methyl, an antioxidative inflammatory modulator [71]. Surprising renoprotective properties were first noticed in cancer trials. Subsequently, beneficial effects were demonstrated in small diabetic cohorts with moderate renal insufficiency [72]. The BEAM (Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes) trial randomized 227 type 2 diabetic patients with GFR 20.0–45.0 mL/min/1.73 m² to varying doses of bardoxolone methyl (25, 75 or 150 mg) or placebo for 52 weeks. Compared with placebo, all three doses of bardoxolone methyl significantly increased GFR [22]. However, the subsequent BEACON (Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus) trial, designed to confirm the efficacy of bardoxolone methyl in 2185 patients with type 2 DM and GFR 15.0–30.0 mL/min/1.73 m², was prematurely terminated due to safety concerns. Although GFR increased at a median of 9 months, no benefit in the composite outcome of ESRD or cardiovascular...
death was observed. The incidence of cardiovascular events was increased, as did blood pressure and albuminuria [23]. It is uncertain as to why bardoxolone methyl increased cardiovascular morbidity, but its action on PPAR-γ may partially explain fluid retention associated with hypertension and heart failure [73]. In light of these findings, further development of this drug class as a potential therapeutic modality has been placed on hold.

**Sulodexide**

Sulodexide is a purified mixture of sulfated glycosaminoglycan polysaccharides containing low-molecular weight heparin (80%), high-molecular weight heparin (5%) and dermatan sulfate (20%). This oral drug has no anticoagulant effect. Glycosaminoglycan therapy has been demonstrated to ameliorate DN in animal experiments [74–77]. After a series of encouraging small-scale pilot studies [78–82], the Di.N.A.S. (The Diabetic Nephropathy and Albuminuria Sulodexide) study was conducted to further investigate the potential renoprotective property of sulodexide [24]. Di.N.A.S. recruited 223 type 1 and 2 diabetic patients with albuminuria and mild CKD (serum creatinine ≤150 µmol/L) and demonstrated that 4 months of sulodexide 200 mg/day resulted in a persistent reduction in albuminuria. However, ensuing large randomized controlled trials failed to demonstrate a beneficial outcome with the use of this agent [25, 83]. In fact, the Sun-MACRO (Sulodexide Macro-albuminuria) trial was terminated early after 1248 enrolled type 2 DN patients showed a lack of benefit with sulodexide treatment [25].

**Pirfenidone**

The progression of DN to ESRD is characterized by pathogenic mechanisms that converge upon a common pathway leading to progressive nephron destruction with accumulative interstitial fibrosis. Pirfenidone is an anti-fibrotic agent that has shown promise in diabetic murine models [84]. A pilot study was undertaken which randomized 77 DN patients with estimated GFR 20.0–75.0 mL/min/1.73 m² to placebo or pirfenidone (1200 or 2400 mg/day). After 1 year, low-dose pirfenidone resulted in an increased estimated GFR 3.3 ± 8.5 mL/min/1.73 m² versus –2.2 ± 4.8 mL/min/1.73 m² in the placebo group (P = 0.026) [85]. However, the GFR change in the high-dose group was only comparable with placebo (–1.9 ± 6.7 mL/min/1.73 m²). It is plausible that the high dropout rate (40%) in this group may have diluted any significant observable difference. Despite these encouraging results, research into the use of pirfenidone appears to have lost momentum and further trials have yet to surface.

**Vitamin D receptor activators**

Treatment with vitamin D receptor (VDR) activators is anti-inflammatory and anti-proteinuric in animal models of DN [86, 87]. Results of the Phase III VITAL (Selective Vitamin D Receptor Activation with Paricalcitol for Reduction of Albuminuria in Patients with Type 2 Diabetes) study suggest that adjuvant paricalcitol at 2 µg/day reduces residual albuminuria in DN [26]. However, this dose of paricalcitol was poorly tolerated with 42% requiring a dose reduction. Therefore, concrete evidence demonstrating VDR activators to retard the progression of DN is still awaited. Further research is required to establish the efficacy of this therapeutic modality.

**Sodium-glucose co-transporter 2 inhibition**

Since the discovery of phlorizin in 1835, the medical community has eagerly awaited the arrival of a pharmacological agent that can harness the kidney’s ability to regulate glucose homeostasis. Selective inhibitors of the sodium-glucose co-transporter 2 (SGLT-2) have since been developed, which block the reabsorption of filtered glucose in the proximal convoluted tubule. Apart from their ability to enhance urinary glucose excretion and aid glycemic control, SGLT-2 inhibitors appear to also promote an attractive CKD portfolio that includes blood pressure and body weight optimization [88–90]. There is *in vitro* evidence to show that SGLT-2 inhibitors can attenuate the inflammatory and fibrotic responses of the human proximal tubular epithelial cells to high glucose [91]. In subsequent animal studies of experimental diabetes, SGLT-2 inhibitors demonstrated the ability to ameliorate features of DN [92–94]. At this juncture, clinical studies demonstrating their efficacy in humans are limited. The CANTATA-SU (Canagliflozin Treatment and Trial Analysis versus Sulphonylurea) study was a large Phase III randomized, double-blind, non-inferiority trial (n = 1450) comparing canagliflozin with glimepiride in patients with type 2 DM inadequately controlled with metformin [27]. Initial decreases in GFR were noted but GFR subsequently stabilized from Week 12 to 52 while the glimepiride arm showed progressive decline. A pooled analysis of four other Phase III, randomized, placebo-controlled trials involving DM patients with Stage 3 CKD concurred with this observation [95]. One of the main drawbacks of this class of drugs is the propensity of the patient to develop genitourinary infections, which appear to be mild to moderate but manageable [96–99]. A large randomized double-blind placebo-controlled trial is currently underway to investigate the effects of SGLT-2 inhibition on diabetic CKD progression. The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial should provide a clear insight into the renoprotective efficacy of SGLT-2 inhibitors. Until CREDENCE is completed, renal data will have to be extrapolated from large trials, such as CANVAS (Canagliflozin Cardiovascular Assessment Study) [100], looking at cardiovascular benefits of SGLT2 inhibition.

**Selective endothelin receptor antagonism**

Another novel approach to DN on the horizon is selective endothelin (ET) receptor antagonism. Current research has identified ET to exert its effect via two receptor subtypes, namely ET<sub>A</sub> and ET<sub>B</sub> [101]. Intra-renal ET receptor activation has been linked to play a role in promoting mesangial cell proliferation, inflammation and fibrosis [102], with several studies showing ET<sub>A</sub> antagonism to ameliorate experimental DN [103–106]. Subsequently, selective ET<sub>A</sub> inhibition with avosentan for 12 weeks was demonstrated to reduce albuminuria in 286 patients with DN [107]. These promising results led to the ASCEND (A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Effect of the Endothelin Receptor Antagonist Avosentan on Time to Doubling of Serum Creatinine, End Stage Renal Disease or
Death in Patients With Type 2 Diabetes Mellitus and Diabetic Nephropathy) trial [28]. ASCEND randomized 1392 patients with DN on ACEi or ARB to avosentan (25 or 50 mg) or placebo. Although avosentan had significantly reduced proteinuria, the trial was prematurely terminated after a median follow-up of only 4 months. This was due to strong adverse cardiovascular signals that included increased rates of congestive heart failure and fluid overload. Current postulations implicate the cardiovascular complications noted in ASCEND to be mediated by ETα inhibition. Although selective (ETα : ETβ ∼ 300:1), avosentan at high dosages used in ASCEND may result in substantial inhibition of ETβ. Subsequent investigations employing highly selective ETα blockers have achieved renal benefits while side stepping inadvertent cardiovascular adverse effects [108]. As a result, a large clinical trial is underway to determine the efficacy of atrasentan in halting the progression of DN [Study of Diabetic Nephropathy with Atrasentan (SONAR)].

**CONFLICT OF INTEREST STATEMENT**

None declared.

**ACKNOWLEDGEMENTS**

This work was supported by grants from the General Research Fund of the Research Grants Council (Grant number: HKU 779611/M) of Hong Kong, the National Basic Research Program of China 973 program no. 2012CB517600 (no. 2012CB517606), an Endowment Fund established for the ‘Yu Professorship in Nephrology’ awarded to S.C.W.T., and donations from Mr Winston Leung and the Hong Kong Concrete and the Continental Cement and Gypsum Co. Ltd.

**REFERENCES**


**FULL REVIEW**
18. Mann JF, Schmieder RE, McQueen M et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 2008; 372: 547–553


Caring for patients with kidney disease: shifting the paradigm from evidence-based medicine to patient-centered care

Ann M. O’Hare1,2,3, Rudolph A. Rodriguez1,3 and Christopher Barrett Bowling4,5

1Hospital and Specialty Medicine Service, VA Puget Sound Health Care System, Seattle, WA, USA, 2Health Services Research and Development Center of Innovation, VA Puget Sound Health Care System, Seattle, WA, USA, 3Department of Medicine, University of Washington, Seattle, WA, USA, 4Birmingham/Atlanta Geriatric Research, Education, and Clinical Center, Atlanta VA Medical Center, Decatur, GA, USA and 5Department of Medicine, Emory University, Atlanta, GA, USA

Correspondence and offprint requests to: Ann M. O’Hare; E-mail: ann.ohare@va.gov

ABSTRACT

The last several decades have witnessed the emergence of evidence-based medicine as the dominant paradigm for medical teaching, research and practice. Under an evidence-based approach, populations rather than individuals become the primary focus of investigation. Treatment priorities are largely shaped by the availability, relevance and quality of evidence and study outcomes and results are assumed to have more or less universal significance based on their implications at the population level. However, population-level treatment goals do not always align with what matters the most to individual patients—who may weigh the risks, benefits and harms of recommended treatments quite differently. In this article we describe the rise of evidence-based medicine in historical context. We discuss limitations of this approach for supporting real-world treatment decisions especially in older adults with chronic kidney disease. We discuss the limitations of this approach and the potential value of a more patient-centered paradigm, with a particular focus on the care of older adults with this condition. We conclude by outlining ways in which the evidence-base might be reconfigured to better support real-world treatment decisions in individual patients and summarize relevant ongoing initiatives.

Keywords: evidence-based medicine, patient-centered care, kidney disease, older adults, paradigm

EVIDENCE-BASED MEDICINE

In a 1992 article in the Journal of the American Medical Association, David Sackett, Gordon Guyatt and colleagues described a new paradigm for practicing and teaching medicine that had been developed over the preceding decades at McMaster University in Hamilton, Ontario [1]. Evidence-based