Diabetic Nephropathy Clinical Trials: A Critical Appraisal

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Meguid El Nahas and Bo Feldt-Rasmussen

Over the last quarter of a century, diabetic nephropathy has steadily increased in incidence and prevalence to become one of the most common causes of ESRD. Worldwide, obesity and the associated type 2 diabetes mellitus (T2DM) have reached epidemic proportions leading to a significant rise in those suffering from diabetic kidney disease (DKD) [1]. This has coincided with considerable preclinical research aimed at a better understanding of the pathophysiology of diabetic nephropathy (DN) and its progression [2].

Clearly, one of the main targets of intervention to slow the progression of DM and its complications has always focused on the optimization of glycemia control. A number of studies have explored whether intensive glycemia control offers advantages in terms of the progression of diabetic nephropathy and other vascular complications [3].

Another key focus has been the control of hypertension and the choice of anti-hypertensive agents [4]. In the 1980s, the Brenner hypothesis focused attention on the role of changes in glomerular hemodynamics, glomerular hyperperfusion-hyperfiltration, and hypertension, in the pathogenesis of diabetic nephropathy. A major role emerged for the RAAS implicating it in the initiation and progression of experimental diabetic nephropathy [5]. This has led to the clinical translation of these studies to humans with the pioneer work of Lewis and collaborators who showed for the first time in 1993 the beneficial effect of ACE inhibition of the progression of DN [6]. Since then, thousands of publications confirmed the importance of the RAAS system in the progression of DN and the beneficial impact of its inhibition [4]. Inhibition of RAAS has become the cornerstone of the management of diabetic nephropathy.

M. El Nahas, MD, PhD, FRCP
Sheffield Kidney Institute, Global Kidney Academy, Sheffield, UK
e-mail: m.el-nahas@sheffield.ac.uk

B. Feldt-Rasmussen, MD, DMSc
Department of Nephrology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, Copenhagen 2100, Denmark
e-mail: bo.feldt-rasmussen@regionh.dk

Over the last decade, other approaches based on the inhibition of putative mediators of DN and related scarring have been tested including endothelin antagonists, inhibitors of oxidative stress, as well as interventions based on vitamin D supplementation [2, 7–9].

Major RCTs that impacted our practice and the management of patients with DKD will be reviewed in this chapter with emphasis on a critical appraisal of their value, strengths, and shortcomings. We hope that such analysis will give a balanced view of the background for current clinical practice and draw attention to potential new interventions.

RCTs Based on Glycemia Control

The optimization of glycemia control has been the cornerstone of the management of people with diabetes mellitus. A large number of studies have examined, over the last 30 years, the impact of glycemia control on DM complications including macro- and micro-vascular complications. They have also included analyses of the effect of intensive glycemia control on the development and progression of diabetic nephropathy. Discussed below are the UKPDS study in T2DM and the DCCT study in T1DM.

UKPDS Trial

Lancet. 1998 Sep 12;352(9131):837–53.

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).

UK Prospective Diabetes Study (UKPDS) Group.
[No authors listed]

Abstract

Background: Improved blood-glucose control decreases the progression of diabetic microvascular disease, but the effect

M. El Kossi, A. Khwaja, and M. El Nahas (eds.), *Informing Clinical Practice in Nephrology: The Role of RCTs*,
DOI 10.1007/978-3-319-10292-4_9, © Springer International Publishing Switzerland 2015

on macrovascular complications is unknown. There is concern that sulphonylureas may increase cardiovascular mortality in patients with type 2 diabetes and that high insulin concentrations may enhance atheroma formation. We compared the effects of intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with type 2 diabetes in a randomized controlled trial.

Methods: Three thousand eight hundred and sixty-seven newly diagnosed patients with type 2 diabetes, median age 54 years (IQR 48–60 years), who after 3 months' diet treatment had a mean of two fasting plasma glucose (FPG) concentrations of 6.1–15.0 mmol/L were randomly assigned intensive policy with a sulphonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin, or conventional policy with diet. The aim in the intensive group was FPG less than 6 mmol/L. In the conventional group, the aim was the best achievable FPG with diet alone; drugs were added only if there were hyperglycemic symptoms or FPG greater than 15 mmol/L. Three aggregate endpoints were used to assess differences between conventional and intensive treatment: any diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, and sudden death); and all-cause mortality. Single clinical endpoints and surrogate subclinical endpoints were also assessed. All analyses were by intention to treat and frequency of hypoglycemia was also analyzed by actual therapy.

Findings: Over 10 years, hemoglobin A1c (HbA1c) was 7.0 % (6.2–8.2) in the intensive group compared with 7.9 % (6.9–8.8) in the conventional group – an 11 % reduction. There was no difference in HbA1c among agents in the intensive group. Compared with the conventional group, the risk in the intensive group was 12 % lower (95 % CI 1–21, $p=0.029$) for any diabetes-related endpoint; 10 % lower (−11 to 27, $p=0.34$) for any diabetes-related death; and 6 % lower (−10 to 20, $p=0.44$) for all-cause mortality. Most of the risk reduction in the any diabetes-related aggregate endpoint was due to a 25 % risk reduction (7–40, $p=0.0099$) in microvascular endpoints, including the need for retinal photocoagulation. There was no difference for any of the three aggregate endpoints between the three intensive agents (chlorpropamide, glibenclamide, or insulin). Patients in the intensive group had more hypoglycemic episodes than those in the conventional group on both types of analysis (both $p<0.0001$). The rates of major hypoglycemic episodes per year were 0.7 % with conventional treatment, 1.0 % with chlorpropamide, 1.4 % with glibenclamide, and 1.8 % with insulin. Weight gain was significantly higher in the intensive group (mean 2.9 kg) than in the conventional group ($p<0.001$), and patients assigned insulin had a greater gain in weight (4.0 kg) than those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg).

Interpretation: Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Randomization was by means of centrally produced, computer-generated therapy allocations in sealed, opaque envelopes which were opened in sequence
Double **blinded**?		−2	Open study
Is the **sample size** calculation described/adequate?	+3		Sample size and power calculation modified as the study went on, with changes implemented in 1987. The study was extended to include randomization of 3,867 patients with a median time from randomization of 11 years to the end of the study in 1997. In 1992, at the 1 % level of significance, the power for any diabetes-related endpoint and for diabetes-related death was calculated as 81 and 23 %, respectively 1138: Conventional DM control 2729: Intensive DM control
Does it have a hard primary **endpoint**?		−1	21 endpoints including: ESRD or serum creatinine reaching 250 umol/l
Is the endpoint surrogate?	−2		
Is the follow-up appropriate?	+1		Median follow-up was 10 year Parameters checked every 1–3 years
Was there a **Bias**?		+2	
Is the dropout >25 %?		+1	
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T2DM aged 25–65, normal serum creatinine, normoalbuminuric
Was the NNT <100?	+1		The number needed to treat to prevent one patient developing any of the single endpoints over 10 years was 19.6 patients (95 % CI 10–500)
Score	**50 %**		

Comments and Discussion

This is one of the most quoted studies in DM relating to the quality of glycemia control on outcomes. It also has the merit to be one of the largest and longest follow-up studies. It has the merit to have maintained a difference in glycemia control between the standard (HbA1c ~7 %) and the intensive control (HbA1c ~7.9 %) groups throughout the study duration averaging 10 years. The study showed a 25 % reduction in risk of developing microvascular complications, mostly retinal.

The development of microalbuminuria was reduced on intensive therapy (−34 %) but overt proteinuria did not significantly differ between the groups. There was a 67 % reduction in the number of patients who had a doubling of serum creatinine in the intensive therapy arm. Too few patients developed ESRD.

There was no significant effect on the macrovascular endpoints; major adverse cardiovascular events. This has been confirmed by more recent trials on intensive glycemia control in T2DM, such as ACCORD, ADVANCE, and VADT, that also failed to show benefit of cardiovascular outcomes (reviewed in [10]).

UKPDS has a number of limitations including:

1. Reliance of changes in microalbuminuria as a surrogate marker for kidney disease, when nowadays serious reservations exist regarding the specificity of this surrogate endpoint for renal disease [11]. It is more likely to reflect the potential beneficial effect of more intensive glycemia control on microvascular disease in general.
2. The reduction in the number of patients whose creatinine doubled on intensive therapy was large, but it was not statistically significant over the 10–15 years' observation time.
3. Serum creatinine and its changes can be confounded by numerous factors in T2DM including changes in weight/muscle mass or appetite.
4. The study was not powered to investigate progression of diabetic nephropathy to ESRD, in view of the fact that the cohort started with normal renal function. Consequently, it is impossible to evaluate whether the observed numerical reduction in doubling of serum creatinine translated into a reduction in the incidence of ESRD in this cohort in the long term.
5. The age range of the cohort study 25–65 years raises concern over the heterogeneity of the population studied. A more focused approach on a more homogeneous patients' group may have yielded different outcomes. Age, duration of diabetes, and presence of underlying cardiovascular disease at baseline may influence response to glycemia control [10]. Also, the impact of strict glycemia control on cardiovascular outcomes may be confounded by the impact of hypoglycemia itself as well as that of some oral hypoglycemic agents on cardiovascular events [10].

Conclusion

UKPDS showed some benefit of tighter glycemia control on microvascular complications and more specifically diabetic proliferative retinopathy. It showed little significant impact on other variables and endpoints, including proteinuria, doubling of serum creatinine, or ESRD.

DCCT Trial

Kidney Int. 1995 Jun;47(6):1703–20.

Effect of intensive therapy on the development and progression of diabetic nephropathy in the diabetes control and complications trial. The Diabetes Control and Complications (DCCT) Research Group

Abstract

The Diabetes Control and Complications Trial (DCCT) has demonstrated that intensive diabetes treatment delays the onset and slows the progression of retinopathy, nephropathy, and neuropathy in patients with IDDM. A detailed description of the effects of this treatment on diabetic nephropathy is presented here. In the primary prevention cohort, intensive treatment reduced the mean adjusted risk of the cumulative incidence of microalbuminuria (≥28 μg/min) by 34 % (95 % CI 2, 56 %; $P=0.04$). Furthermore, intensive treatment decreased the albumin excretion rate (AER) by 15 % after the first year of therapy (6.5 vs. 7.7 μg/min, $P<0.001$). Thereafter the rates of change for AER within each treatment group were no different from zero, retaining a constant difference in AER between groups in the trial. In the secondary intervention cohort with baseline AER <28 μg/min, intensive therapy reduced the mean adjusted risk of microalbuminuria (≥28 μg/min) by 43 % (95 % CI 21, 58 %; $P<0.0001$); the risk of a more advanced level of microalbuminuria (≥70 μg/min) by 56 % (95 % CI 26, 74 %; $P=0.002$); and the risk of clinical albuminuria (≥208 μg/min) by 56 % (95 % CI 18, 76 %; $P<0.01$). In the secondary intervention cohort, values for AER at year 1 were identical at 9 μg/min, but the 6.5 % change per year in the conventional group greatly exceeded the rate of change of −0.3 % in the intensive group ($P<0.001$). Among the 73 secondary cohort subjects with AER levels ≥28 μg/min but ≤139 μg/min at baseline, the reduction of progression to clinical albuminuria with intensive therapy was not statistically significant. The longitudinal treatment effect of conventional versus intensive therapy (11.0 % vs. 2.5 % per year, respectively, $P=0.087$) was similar in magnitude to that among patients with AER <28 μg/min at baseline. For the primary, secondary, and combined cohorts, there were no significant differences in the rates of change in creatinine clearance (CCr) between treatment groups during the study. Only seven subjects in the entire study (2 intensive, 5 conventional) developed urinary AER ≥208 μg/min coupled with a CCr<70 ml/min/1.73 m^2. Neither the rate of

change of blood pressure nor the appearance of hypertension (BP > 140/90 mmHg) differed significantly between treatment groups in the primary, secondary, or combined cohorts.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Primary prevention cohort Secondary prevention cohort with microalbuminuria
Double **blinded**?		−2	
Is the **sample size** calculation described/ adequate?	+3		1441 T1DM randomized
Does it have a hard primary **endpoint**?		−1	Albuminuria changes
Is the endpoint surrogate?	−2		Albuminuria
Is the follow-up appropriate?	+1		6.5 years
Was there a **Bias**?		+2	
Is the dropout >25 %?		+1	
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T1DM with normal renal function and normoalbuminuria
Was the NNT <100?	+1		
Score	**50 %**		

Comments and Discussion

The DCCT trial had previously demonstrated a beneficial effect of intensive glycemia control on diabetic complications including retinopathy and neuropathy [12]. In this study, it focused on renal outcomes, both prevention and development/progression of albuminuria.

It showed that intensive and sustained glycemia control, with an HbA1c around 7 % compared to 9 % in standard therapy group, reduced the incidence of microalbuminuria and its progression by 34 and 43 %, respectively.

Limitations of the DCCT study:

1. It was not powered to study changes in renal function with age and thus failed to detect any difference between the groups in the renal functional parameters including the measurement of GFR (iothalamate clearance).
2. It assumed that low-level albuminuria (microalbuminuria) was a valid surrogate for diabetic nephropathy; a commonly held view then that has been challenged since [13].
3. It also assumed that changes in albuminuria would imply subsequent changes in renal function, an assumption since challenged by a number of observations including the RASS study showing a dissociation between changes in microalbuminuria and renal function or histology [14]. However, the subsequent DCCT EDIC 22-year follow-up study in terms of renal functional decline supported the association of better functional (eGFR) outcomes in those initially on intensive glycemia control and lower levels of albuminuria as well as putting forward the notion of metabolic memory [15].

Conclusion

The DCCT study has been the key study underlying the importance of tight glycemia control in minimizing the complications of T1DM. It was supported by the long-term DCCT EDIC follow-up (22 years) observations of persistent benefit [15]. It was also supported by the STENO multi-intervention study that showed a protective effect on T2DM vascular and renal complications with intensive multi-targeted therapy [15]. The primary endpoint of the STENO study was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization, and amputation.

However, other studies in T2DM such as ACCORD, ADVANCE, and VADT failed to show an impact of strict glycemia control on cardiovascular outcomes (reviewed in [16]). It has been argued that the potential beneficial effect of strict glycemia control may largely depend on patients' characteristics, including age, diabetes duration, previous glucose control, presence of cardiovascular disease, and risk of hypoglycemia. Other confounders include the extent and frequency of hypoglycemic events and the impact of glucose-lowering medication itself on the cardiovascular system [16].

RCTs Based on RAAS Inhibition

Since Brenner and colleagues put forward their hypothesis related to the role of glomerular hyperperfusion-hyperfiltration, glomerular hypertension, and the related role of angiotensin II on the pathogenesis of diabetic nephropathy (DN), a very large number of clinical trials addressed the question of whether ACE inhibition slowed the development and progression of DN. More specifically, these trials aimed to show whether ACE inhibition or angiotensin receptor blockade (ARB) slowed DN progression independently of their anti-hypertensive effect. This started with the publication in 1993 of the seminal study of the collaborative study group in patients with T1DM. More recently, studies also examined the impact of renin blockade (AVOID and ALTITUDE studies) and dual ACE inhibition and ARB therapy on renal and cardiovascular outcomes (ONTARGET and VA-NEPHRON D).

The Collaborative Study Group (Lewis) Trial

N Engl J Med. 1993 Nov 11;329(20):1456–62.

The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group

Lewis EJ, Hunsicker LG, Bain RP, Rohde RD.

Abstract

Background: Renal function declines progressively in patients who have diabetic nephropathy, and the decline may be slowed by antihypertensive drugs. The purpose of this study was to determine whether captopril has kidney-protecting properties independent of its effect on blood pressure in diabetic nephropathy.

Methods: We performed a randomized, controlled trial comparing captopril with placebo in patients with insulin-dependent diabetes mellitus in whom urinary protein excretion was ≥500 mg/day and the serum creatinine concentration was ≤2.5 mg/dl (221 μmol/l). Blood-pressure goals were defined to achieve control during a median follow-up of 3 years. The primary endpoint was a doubling of the baseline serum creatinine concentration.

Results: Two hundred and seven patients received captopril and 202 placebo. Serum creatinine concentrations doubled in 25 patients in the captopril group, as compared with 43 patients in the placebo group ($P=0.007$). The associated reductions in risk of a doubling of the serum creatinine concentration were 48 % in the captopril group as a whole, 76 % in the subgroup with a baseline serum creatinine concentration of 2.0 mg/dl (177 μmol/l), 55 % in the subgroup with a concentration of 1.5 mg/dl (133 μmol/l), and 17 % in the subgroup with a concentration of 1.0 mg/dl (88.4 μmol/l). The mean (±SD) rate of decline in creatinine clearance was 11 ± 21 % per year in the captopril group and 17 ± 20 % per year in the placebo group ($P=0.03$). Among the patients whose baseline serum creatinine concentration was ≥1.5 mg/dl, creatinine clearance declined at a rate of 23 ± 25 % per year in the captopril group and at a rate of 37 ± 25 % per year in the placebo group ($P=0.01$). Captopril treatment was associated with a 50 % reduction in the risk of the combined endpoints of death, dialysis, and transplantation that was independent of the small disparity in blood pressure between the groups.

Conclusions: Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood-pressure control alone.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Standard urn design
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?		−3	Sample size calculation assumption not given: Captopril group: 207 patients Placebo: 202 patients
Does it have a hard primary **endpoint**?		−1	Doubling of serum creatinine
Is the endpoint surrogate?	−2		GFR was not measured
Is the follow-up appropriate?	+1		36 months
Was there a **Bias**?	−2		The placebo group had more severe DN at baseline based on a higher urine albumin excretion rate
Is the dropout >25 %?	−1		301/409 completed the study
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T1DM with proteinuria and serum creatinine <2.5 mg/dl
Was the NNT <100?	+1		Risk reduction of 48 % for doubling of serum creatinine in the captopril group
Score	**0 %**		

Comments and Discussion

There is little doubt that this clinical trial changed the practice of nephrologists in terms of management of progressive diabetic nephropathy. It pioneered the universal use of RAAS inhibitors to slow the progression of DN. While the authors concluded that Captopril reduced the rate of doubling of serum creatinine by 48 %, they emphasized that the beneficial effect was predominantly due to a slowing of DN progression in patients with a baseline serum creatinine >1.5 mg/dl. Proteinuria was reduced significantly in the Captopril group.

The Lewis study has a number of shortcomings:

1. There was a patients' selection bias as baseline proteinuria was significantly higher in the placebo group (3 g/24 h versus 2.5 g/24 h). Also the percentage of those with heavy proteinuria was higher in the placebo group. In view of the known association of higher proteinuria and worse outcomes in CKD and DN, such a bias could have impacted the subsequent outcome of the two groups.
2. Reliance on doubling of serum creatinine as a primary endpoint has been challenged as it does not always translate into progression to ESRD [17].
3. Reliance of changes in serum creatinine, without measuring GFR and its changes, raises concern about confounders such as the impact of ACE inhibitors on tubular secretion of creatinine [18].
4. Secondary endpoints such as ESRD or transplantation were not protocolized in terms of prespecified cutoffs for interventions.
5. Blood pressure (diastolic) was lower in the captopril group (MAP=96 mmHg) compared to placebo (MAP=100 mmHg); however, the difference did not exceed 5 mmHg and adjustments were made in relation to its impact of the rate of doubling of serum creatinine. Of note, blood pressure was measured casually at the office at given intervals and did not rely on a more accurate recording such as day- and nighttime measurements or 24 h ABPM recording. Those may have shown a bigger difference in BP between the groups. They are also more relevant to DN complications than office BP readings [19, 20].

Conclusion

The Lewis trial remains a reference RCT in diabetic nephropathy and the impact of ACE inhibition. Its results are primarily confounded by the patients' selection bias of those with worse prognosis being allocated to the placebo group.

The RENAAL Trial

N Engl J Med. 2001;345(12):861–9.

Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy

Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators.

Abstract

Background: Diabetic nephropathy is the leading cause of end-stage renal disease. Interruption of the renin-angiotensin system slows the progression of renal disease in patients with type 1 diabetes, but similar data are not available for patients with type 2, the most common form of diabetes. We assessed the role of the angiotensin-II-receptor antagonist losartan in patients with type 2 diabetes and nephropathy.

Methods: A total of 1,513 patients were enrolled in this randomized, double-blind study comparing losartan (50–100 mg once daily) with placebo, both taken in addition to conventional antihypertensive treatment (calcium-channel antagonists, diuretics, alpha-blockers, beta-blockers, and centrally acting agents), for a mean of 3.4 years. The primary outcome was the composite of a doubling of the baseline serum creatinine concentration, end-stage renal disease, or death. Secondary endpoints included a composite of morbidity and mortality from cardiovascular causes, proteinuria, and the rate of progression of renal disease.

Results: A total of 327 patients in the losartan group reached the primary endpoint, as compared with 359 in the placebo group (risk reduction, 16 %; $P=0.02$). Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25 %; $P=0.006$) and end-stage renal disease (risk reduction, 28 %; $P=0.002$) but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction, 32 %; $P=0.005$). The level of proteinuria declined by 35 % with losartan ($P<0.001$ for the comparison with placebo).

Conclusions: Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and it was generally well tolerated.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Previously described [21]
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		751 T2DM patients in Losartan group 762 in placebo
Does it have a hard primary **endpoint**?		+1	The first event of the composite endpoint of a doubling of the serum creatinine concentration, end-stage renal disease, or death
Is the endpoint surrogate?	−2		GFR was not measured
Is the follow-up appropriate?		−1	Mean follow-up time = 3.4 years Discontinued early by unanimous decision of the steering committee in view of reported benefits of cardiovascular outcomes by ACE inhibitors (HOPE study) [22]
Was there a **Bias**?		+2	
Is the dropout >25 %?		+1	
Is the analysis **ITT**?	+3		Study terminated prematurely
Utility/usefulness			
Can the findings be generalized?	+1		T2DM and nephropathy; serum creatinine between 1.3 and 3 mg/dl with overt proteinuria
Was the NNT <100?	+1		Treatment with Losartan led to a 16 % reduction in primary composite endpoints
Score	**75 %**		

Comments and Discussion

The RENAAL study is the pivotal study on angiotensin receptor blockade (ARB) efficacy in slowing the progression of T2DM-associated nephropathy. It showed a significant (16 %) reduction in the rate of reaching the composite endpoints of doubling of serum creatinine, ESRD or death. It also showed a significant reduction in proteinuria. Of interest, there was no significant difference between the groups in secondary CVD outcomes, as anticipated by the premature termination of the study based on the reported data from HOPE [22].

Limitations of the RENAAL study:

1. The study was powered for a mean follow-up duration of 4.5 years and was prematurely terminated thus having a much shorter mean follow-up period of 3.4 years. This could have impacted the power of the study and the appropriateness of the sample size.

2. Reliance on serum creatinine-based co-primary endpoint (doubling of serum creatinine and ESRD) without measuring GFR and its changes, raises concern about confounders such as the impact of ACE inhibitors on tubular secretion of creatinine [23, 24].
3. The co-primary endpoint of ESRD was not protocolized in terms of prespecified cutoffs for intervention; renal replacement therapy.
4. Reliance on composite and interrelated endpoints has its limitations [25].
5. Blood pressure (diastolic) was lower in the Losartan group (MAP = 100 mmHg) compared to placebo (MAP = 103 mmHg); however, adjustments were made in relation to the impact of BP differences on the composite endpoints and hardly affected the study outcome.
6. Blood pressure was measured casually at the office at given intervals and did not rely on a more accurate recording such as day- and nighttime measurements or 24 h ABPM recording. Those may have shown a bigger difference in BP between the groups. They are also more relevant to DN complications than office BP readings [26]. In fact, this was noted in the HOPE study upon which the study premature termination was based, as casual BP recording did not show differences between the Ramipril and placebo groups, while more accurate BP monitoring showed a significant difference and lower BP in those treated with Ramipril [27] possibly explain the better cardioprotection.

Conclusion

RENAAL is a major study that claimed that ARB slows the progression of DN. Its conclusion is confounded by the premature termination of the study thus raising concerns over its power and the use of serum creatinine as a primary endpoint without measuring changes in GFR.

IDNT Trial

N Engl J Med. 2001;345(12):851–60.

Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; Collaborative Study Group.

Abstract

Background: It is unknown whether either the angiotensin-II-receptor blocker irbesartan or the calcium-channel blocker amlodipine slows the progression of nephropathy in patients with type 2 diabetes independently of its capacity to lower the systemic blood pressure.

Methods: We randomly assigned 1,715 hypertensive patients with nephropathy due to type 2 diabetes to treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. The target blood pressure was 135/85 mmHg or less in all groups. We compared the groups with regard to the time to the primary composite endpoint of a doubling of the baseline serum creatinine concentration, the development of end-stage renal disease, or death from any cause. We also compared them with regard to the time to a secondary, cardiovascular composite endpoint.

Results: The mean duration of follow-up was 2.6 years. Treatment with irbesartan was associated with a risk of the

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Protocol previously published [28] Randomization into three groups: Irbesartan, amlodipine, placebo
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		On the basis of the results of study in type 1 diabetes, in which the 3-year rate of a doubling of the baseline serum creatinine concentration, end-stage renal disease, or death was 36 %, authors estimated that 550 patients per treatment group were needed for an analysis of the primary outcome. The sample size was selected to achieve 90 % power to detect a 26 % difference in the primary endpoint between the irbesartan group and the placebo group at a 5 % alpha level
Does it have a hard primary **endpoint**?		−1	Composite endpoint of doubling of serum creatinine, ESRD or death
Is the endpoint surrogate?	−2		GFR was not measured
Is the follow-up appropriate?	+1		~mean 3 years
Was there a **Bias**?		+2	
Is the dropout >25 %?		+1	
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T2DM with hypertension and serum creatinine between 1 and 3 mg/dl and proteinuria >900 mg/24 h
Was the NNT <100?	+1		Risk reduction by Irbesartan 20 % compared to placebo and 23 % compared to amlodipine
Score	**75 %**		

primary composite endpoint that was 20 % lower than that in the placebo group ($P=0.02$) and 23 % lower than that in the amlodipine group ($P=0.006$). The risk of a doubling of the serum creatinine concentration was 33 % lower in the irbesartan group than in the placebo group ($P=0.003$) and 37 % lower in the irbesartan group than in the amlodipine group ($P<0.001$). Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23 % lower than that in both other groups ($P=0.07$ for both comparisons). These differences were not explained by differences in the blood pressures that were achieved. The serum creatinine concentration increased 24 % more slowly in the irbesartan group than in the placebo group ($P=0.008$) and 21 % more slowly than in the amlodipine group ($P=0.02$). There were no significant differences in the rates of death from any cause or in the cardiovascular composite endpoint.

Conclusions: The angiotensin-II-receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood pressure it causes.

Comments and Discussion

The IDNT study results are similar to those of RENAAL in that an ARB slowed the rate of changes in serum creatinine over a reasonably long observation period.

It has the same limitations as RENAAL:

1. Reliance of changes in serum creatinine to ascertain DN progression; Inhibition of RAS has been associated with increased tubular secretion of creatinine [29, 30], thus confounding the interpretation of this parameter in terms of changes in GFR.
2. GFR was not measured. This has to be considered the gold standard for RCTs evaluating the rate of progression of CKD or DKD.
3. The use of interrelated composite endpoints subject to limitations and criticism [31].
4. Blood pressure measured casually/office readings rather than the more accurate 24 h ABPM recording can give the misleading impression that BP was comparable between the Irbesartan and Amlodipine groups.
5. Sample size estimation was made on the assumption that the rate of progression of T2DM-associated nephropathy was similar to that of T1DM. This is unlikely to be the case as most would argue that T2DM-associated DKD progressed more slowly than DKD in younger patients with T1DM [32, 33].

Conclusion

IDNT along with RENAAL are often cited as the ultimate proof that ARBs are protective against the decline in kidney function in DN. While this may be the case, these studies have their limitations highlighted above that confound irrefutable evidence.

VA-Nephron D Trial

N Engl J Med. 2013 Nov 14;369(20):1892–903. doi: 10.1056/NEJMoa1303154. Epub 2013 Nov 9.

Combined angiotensin inhibition for the treatment of diabetic nephropathy

Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, Leehey DJ, McCullough PA, O'Connor T, Palevsky PM, Reilly RF, Seliger SL, Warren SR, Watnick S, Peduzzi P, Guarino P; VA NEPHRON-D Investigators. Collaborators (248)

Abstract

Background: Combination therapy with angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) decreases proteinuria; however, its safety and effect on the progression of kidney disease are uncertain.

Methods: We provided losartan (at a dose of 100 mg/day) to patients with type 2 diabetes, a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, and an estimated glomerular filtration rate (GFR) of 30.0–89.9 ml/min/1.73 m^2 of body-surface area and then randomly assigned them to receive lisinopril (at a dose of 10–40 mg/day) or placebo. The primary endpoint was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml/min/1.73 m^2 if the initial estimated GFR was ≥60 ml/min/1.73 m^2 or a decline of ≥50 % if the initial estimated GFR was <60 ml/min/1.73 m^2), end-stage renal disease (ESRD), or death. The secondary renal endpoint was the first occurrence of a decline in the estimated GFR or ESRD. Safety outcomes included mortality, hyperkalemia, and acute kidney injury.

Results: The study was stopped early owing to safety concerns. Among 1,448 randomly assigned patients with a median follow-up of 2.2 years, there were 152 primary end-point events in the monotherapy group and 132 in the combination-therapy group (hazard ratio with combination therapy, 0.88; 95 % confidence interval [CI], 0.70–1.12; $P=0.30$). A trend toward a benefit from combination therapy with respect to the secondary endpoint (hazard ratio, 0.78; 95 % CI, 0.58–1.05; $P=0.10$) decreased with time ($P=0.02$ for nonproportionality). There was no benefit with respect to mortality (hazard ratio for death, 1.04; 95 % CI, 0.73–1.49; $P=0.75$) or cardiovascular events. Combination therapy increased the risk of hyperkalemia (6.3 events per 100 person-years vs. 2.6 events per 100 person-years with monotherapy; $P<0.001$) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years, $P<0.001$).

Conclusions: Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of

adverse events among patients with diabetic nephropathy. (Funded by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; VA NEPHRON-D ClinicalTrials.gov number, NCT00555217.).

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Protocol previously described Randomization into Losartan alone versus Losartan + Lisinopril on outcomes in T2DM with eGFR from 30 to 89 ml/min and overt proteinuria (ACR >300 mg/g)
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		Assuming a 45 % cumulative event rate and a 10 % loss to follow-up, authors initially calculated that they would need to enroll 1,850 patients over a period of 3 years, with a minimum follow-up of 2 years, for the study to have 85 % power to detect an 18 % relative reduction in the primary endpoint at a two-sided alpha level of 0.05. 1448 underwent randomization
Does it have a hard primary **endpoint**?		−1	Decrease in eGFR
Is the endpoint surrogate?	−2		GFR not measured
Is the follow-up appropriate?		−1	Terminated prematurely (~2 years) due to high rate of side effects; hyperkalemia and AKI in the combination arm of the study
Was there a **Bias**?		+2	
Is the dropout >25 %?	−1		Terminated prematurely
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T2DM with eGFR from 30 to 89 ml/min
Was the NNT <100?			Negative study
Score	**50 %**		

Comments and Discussion

The VA NEPHRON-D study confirmed the observations made in previous studies on the negative impact of dual RAS blockade; ONTARGET in high cardiovascular risk patients including people with high risk diabetes mellitus [34] as well as the ALTITUDE study that investigated the combination of a renin antagonist with ACE inhibition in patients with diabetic nephropathy [35]. These studies had to be discontinued due to a high rate of side effects and morbidity. VA NEPHRON-D was also stopped prematurely due to the increased rate of side effects, hyperkalemia, and AKI. During the observation time, the study failed to show benefit on the primary endpoint of decline in eGFR or in other endpoints of cardiovascular complications or mortality. Of note the highest rate of albuminuria decline took place in the combination group.

Limitations of the VA NEPHRON-D trial:

1. Clearly the main limitation of the VA NEPHRON-D trial is its early termination that impacts the power of the study and the interpretation of its final results.
2. Like most studies, if not all studies, of DKD progression reliance on serum creatinine changes and the derived eGFR can be misleading.
3. GFR was not measured.
4. BP was casually assessed at office visits.

Conclusion

The VA NEPHRON-D study was the third major RCT that showed the risks associated with dual blockade of the RAS. Like previous studies such focus has been on older patients with DM (mean age 64 years) compared to 66 years in ONTARGET and 60 years in ALTITUDE. Whether dual RAS blockade is equally harmful in younger patients with lower cardiovascular risk is unknown.

AVOID Trial

N Engl J Med. 2008 Jun 5;358(23):2433–46. doi: 10.1056/NEJMoa0708379.

Aliskiren combined with losartan in type 2 diabetes and nephropathy

Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators.

Collaborators (351)

Abstract

Background: Diabetic nephropathy is the leading cause of end-stage renal disease in developed countries. We evaluated the renoprotective effects of dual blockade of the renin-angiotensin-aldosterone system by adding treatment with aliskiren, an oral direct renin inhibitor, to treatment with the maximal recommended dose of losartan (100 mg daily) and optimal antihypertensive therapy in patients who had hypertension and type 2 diabetes with nephropathy.

Methods: We enrolled 599 patients in this multinational, randomized, double-blind study. After a 3-month, open-label, run-in period during which patients received 100 mg of losartan daily, patients were randomly assigned to receive 6 months of treatment with aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3

months) or placebo, in addition to losartan. The primary outcome was a reduction in the ratio of albumin to creatinine, as measured in an early-morning urine sample, at 6 months.

Results: The baseline characteristics of the two groups were similar. Treatment with 300 mg of aliskiren daily, as compared with placebo, reduced the mean urinary albumin-to-creatinine ratio by 20 % (95 % confidence interval, 9–30; $P<0.001$), with a reduction of 50 % or more in 24.7 % of the patients who received aliskiren as compared with 12.5 % of those who received placebo ($P<0.001$). A small difference in blood pressure was seen between the treatment groups by the end of the study period (systolic, 2 mmHg lower [$P=0.07$] and diastolic, 1 mmHg lower [$P=0.08$] in the aliskiren group). The total numbers of adverse and serious adverse events were similar in the groups.

Conclusions: Aliskiren may have renoprotective effects that are independent of its blood-pressure-lowering effect in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended renoprotective treatment. (ClinicalTrials.gov number, NCT00097955 [ClinicalTrials.gov].).

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		599 patients enrolled Losartan versus Losartan + Aliskiren (301 patients) (298 patients)
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		Assuming a dropout rate of 20 %, authors planned to randomly assign 496 patients. This sample size would have provided 90 % power to detect, at a two-sided level of significance of 0.05, a treatment difference of 18 % in the primary endpoint
Does it have a hard primary **endpoint**?		−1	Changes in urine ACE from baseline to 24 weeks
Is the endpoint surrogate?	−2		Albuminuria
Is the follow-up appropriate?		−1	6 months
Was there a **Bias**?	−2		Aliskiren group younger and shorter duration of T2DM
Is the dropout >25 %?	−1		
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T2DM with nephropathy and ACR >300 mg/g. GFR >30 ml/min
Was the NNT <100?	+1		18 % reduction in ACR by Aliskiren compared to control
Score	**25 %**		

Comments and Discussion

The AVOID study opened the way to dual blockade of RAS combining an ARB with a renin inhibitor (Aliskiren). It showed a significant reduction in albuminuria over and above that achieved with an ARB (Losartan) alone. This effect was obtained independently of changes in eGFR or blood pressure control.

The AVOID trial limitations are:

1. The reliance of albuminuria as a surrogate endpoint for DN progression. Studies such as ACCOMPLISH (in nondiabetic kidney disease) [36] and ONTARGET (in high-risk people with diabetes) [37] showed that a reduction in albuminuria may take place regardless of a faster decline in eGFR, thus dissociating the reduction in albuminuria from a protective long-term effect of CKD and DKD progression. Albuminuria is a very soft and unpredictable endpoint.

Conclusion

It is imperative that studies relying on changes in albuminuria as the primary endpoint are conducted long enough to ascertain the impact of the intervention on renal function (measured GFR) as well as blood pressure control and side effects. The assumption that a reduction of albuminuria by a given intervention will inevitably lead to a slowing of CKD progression is no longer tenable in view of the results of ALTITUDE [38] but also ONTARGET [37] and ACCOMPLISH [36].

ALTITUDE Trial

N Engl J Med. 2012 Dec 6;367(23):2204–13. doi: 10.1056/NEJMoa1208799. Epub 2012 Nov 3.

Cardiorenal endpoints in a trial of aliskiren for type 2 diabetes

Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Persson F, Desai AS, Nicolaides M, Richard A, Xiang Z, Brunel P, Pfeffer MA; ALTITUDE Investigators.

Collaborators (817)

Abstract

Background: This study was undertaken to determine whether use of the direct renin inhibitor aliskiren would reduce cardiovascular and renal events in patients with type 2 diabetes and chronic kidney disease, cardiovascular disease, or both.

Methods: In a double-blind fashion, we randomly assigned 8,561 patients to aliskiren (300 mg daily) or

placebo as an adjunct to an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor blocker. The primary endpoint was a composite of the time to cardiovascular death or a first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalization for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or doubling of the baseline serum creatinine level.

Results: The trial was stopped prematurely after the second interim efficacy analysis. After a median follow-up of 32.9 months, the primary endpoint had occurred in 783 patients (18.3 %) assigned to aliskiren as compared with 732 (17.1 %) assigned to placebo (hazard ratio, 1.08; 95 % confidence interval [CI], 0.98–1.20; $P=0.12$). Effects on secondary renal endpoints were similar. Systolic and diastolic blood pressures were lower with aliskiren (between-group differences, 1.3 and 0.6 mmHg, respectively) and the mean reduction in the urinary albumin-to-creatinine ratio was greater (between-group difference, 14 percentage points; 95 % CI, 11–17). The proportion of patients with hyperkalemia (serum potassium level, ≥6 mmol/l) was significantly higher in the aliskiren group than in the placebo group (11.2 % vs. 7.2 %), as was the proportion with reported hypotension (12.1 % vs. 8.3 %) ($P<0.001$ for both comparisons).

Conclusions: The addition of aliskiren to standard therapy with renin-angiotensin system blockade in patients with type 2 diabetes who are at high risk for cardiovascular and renal events is not supported by these data and may even be harmful (Funded by Novartis; ALTITUDE ClinicalTrials.gov number, NCT00549757.).

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Protocol previously published [39] Standard care including RAS inhibitor versus standard care + Aliskiren >4,200 in each group
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		The trial was designed to enroll 8,600 patients and to continue until 1,620 patients reached the primary composite endpoint, with the assumption of an annual event rate of 8 % in the placebo group, in order to provide 90 % power to detect a reduction in risk of 15 % or more at a significance level of 5 %
Does it have a hard primary **endpoint**?		−1	The primary outcome was a composite of death from cardiovascular causes or the first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalization for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or a serum creatinine value that was at least double the baseline value and that exceeded the upper limit of the normal range (>80 µmol/l [0.9 mg/dl] in women and >106 µmol/l [1.2 mg/dl] in men), sustained for at least a month
Is the endpoint surrogate?		0	GFR not measured but MACE well defined
Is the follow-up appropriate?		−1	Early termination of the study due to adverse events Mean follow-up 32 months
Was there a **Bias**?	−2		Early termination
Is the dropout >25 %?		+1	
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T2DM with CKD and proteinuria
Was the NNT <100?			Negative study
Score	**43 %**		

Comments and Discussion

ALTITUDE showed that dual RAS blockade including a renin inhibitor (Aliskiren) was potentially harmful and poorly tolerated in older patients with T2DM and CKD (mean GFR = 57 ml/min). In spite of a more significant reduction in blood pressure and albuminuria, the dual blockade led to a faster rate of decline of eGFR and a higher rate of complications including hyperkalemia and hypotension. This has led to the premature termination of the study on safety grounds.

ALTITUDE's limitations included:

1. Early termination for adverse events, thus somewhat compromising the power of the study
2. Reliance on eGFR and not measured GFR to ascertain the rate of CKD progression
3. Casual/office BP recording, when using hypotensive agents to control CKD progression; these may underestimate the overall, 24 h, extent of BP reduction

Conclusion

Dual RAS blockade is potentially harmful in older patients at high cardiovascular risk, this in spite of a significant reduction in albuminuria. Such harmful effect may be due to excessive blood pressure lowering in older age groups with cardiovascular complications and potential renal underperfusion exacerbated by dual blockade-induced hypotension. The reduction of albuminuria may be the reflection of a marked reduction in intraglomerular pressure seriously compromising renal function. This was also noted in the ONTARGET study [39].

RASS Trial

N Engl J Med. 2009 Jul 2;361(1):40–51. doi: 10.1056/NEJMoa0808400.

Renal and retinal effects of enalapril and losartan in type 1 diabetes

Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, Drummond K, Donnelly S, Goodyer P, Gubler MC, Klein R.

Abstract

Background: Nephropathy and retinopathy remain important complications of type 1 diabetes. It is unclear whether their progression is slowed by early administration of drugs that block the renin-angiotensin system.

Methods: We conducted a multicenter, controlled trial involving 285 normotensive patients with type 1 diabetes and normoalbuminuria and who were randomly assigned to receive losartan (100 mg daily), enalapril (20 mg daily), or placebo and followed for 5 years. The primary endpoint was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. The retinopathy endpoint was a progression on a retinopathy severity scale of two steps or more. Intention-to-treat analysis was performed with the use of linear regression and logistic-regression models.

Results: A total of 90 and 82 % of patients had complete renal-biopsy and retinopathy data, respectively. Change in mesangial fractional volume per glomerulus over the 5-year period did not differ significantly between the placebo group (0.016 units) and the enalapril group (0.005, $P=0.38$) or the losartan group (0.026, $P=0.26$), nor were there significant treatment benefits for other biopsy-assessed renal structural variables. The 5-year cumulative incidence of microalbuminuria was 6 % in the placebo group; the incidence was higher with losartan (17 %, $P=0.01$ by the log-rank test) but not with enalapril (4 %, $P=0.96$ by the log-rank test). As compared with placebo, the odds of retinopathy progression by two steps or more was reduced by 65 % with enalapril (odds ratio, 0.35; 95 % confidence interval [CI], 0.14–0.85) and by 70 % with losartan (odds ratio, 0.30; 95 % CI, 0.12–0.73), independently of changes in blood pressure. There were three biopsy-related serious adverse events that completely resolved. Chronic cough occurred in 12 patients receiving enalapril, 6 receiving losartan, and 4 receiving placebo.

Conclusions: Early blockade of the renin-angiotensin system in patients with type 1 diabetes did not slow nephropathy progression but slowed the progression of retinopathy. (ClinicalTrials.gov number, NCT00143949.)

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Protocol described elsewhere [40] Enalapril v Losartan v Placebo
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		Investigators calculated that a sample size of 86 patients per group would be required for the study to have a statistical power of 80 % to detect a 50 % reduction in the change in mesangial fractional volume over the 5-year period, with a significance level of 5 % that was reduced to 2.5 % to allow for the two contrasts of the primary analysis (losartan vs. placebo and enalapril vs. placebo) 256 in renal biopsy study 223 in retinopathy study
Does it have a hard primary **endpoint**?		−1	Renal Histology; Mesangial volume expansion Secondary endpoints included measured GFR (Iohexol clearance) Also progression of diabetic retinopathy
Is the endpoint surrogate?		0	
Is the follow-up appropriate?	+1		5 years
Was there a **Bias**?		+2	
Is the dropout >25 %?		+1	
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T1DM with normal renal function (GFR >90 ml/min) and normoalbuminuric
Was the NNT <100?			Negative renal outcome
Score	**93 %**		

Comments and Discussion

The RASS study comparing an ACE inhibitor, an ARN, and placebo in patients with T1DM, normal function, and normoalbuminuria is worth including in this chapter for a number of reasons:

1. It shows that ACE inhibition did not differ from placebo in the prevention of microalbuminuria development. This is in contrast with a previous and less well-designed study in T2DM (BENEDICT) [40].
2. It showed that ARB increased the incidence of microalbuminuria, also in disagreement with ROADMAP that showed a protective effect in T2DM [41]. Of note in ROADMAP, Olmesartan had a detrimental effect on cardiovascular events rate.
3. The rate of decline of measured GFR was not different between the groups and generally fairly slow; around 6–8 ml/min/5 years; 1–1.5 ml/min/year, an unexpectedly slow rate of GFR decline in diabetic nephropathy, specially T1DM.
4. Neither ACE inhibition nor ARB changed the rate of progression of mesangial expansion over 5 years.
5. Blood pressure levels and the incidence of hypertension were favorably affected by RAS inhibitors.
6. Both ACE inhibition and ARB reduced the rate of progression of diabetic retinopathy.
7. Glycemia control was comparable between the groups.

Strength and limitations of RASS:

1. The strength of this study is that it shows that serial measurement of GFR is achievable in patients with DM.
2. It also showed that serial renal biopsy is achievable.
3. The limitation is the assumption that changes in mesangial volume fraction would inevitably translate in the long term to parallel changes in glomerulosclerosis and kidney function.

ABCD Trial

Kidney Int. 2002;61(3):1086–97.

Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy, and strokes

Schrier RW, Estacio RO, Esler A, Mehler P.

Abstract

Background: Although several important studies have been performed in hypertensive type 2 diabetic patients, it is not known whether lowering blood pressure in normotensive (BP <140/90 mmHg) patients offers any beneficial results on vascular complications. The current study evaluated the effect of intensive versus moderate diastolic blood pressure (DBP) control on diabetic vascular complications in 480 normotensive type 2 diabetic patients.

Methods: The current study was a prospective, randomized controlled trial in normotensive type 2 diabetic subjects. The subjects were randomized to intensive (10 mmHg below the baseline DBP) versus moderate (80–89 mmHg) DBP control. Patients in the moderate therapy group were given placebo, while the patients randomized to intensive therapy received either nisoldipine or enalapril in a blinded manner as the initial antihypertensive medication. The primary endpoint evaluated was the change in creatinine clearance with the secondary endpoints consisting of change in urinary albumin excretion, progression of retinopathy and neuropathy, and the incidence of cardiovascular disease.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Protocol previously described [42]. Premuted block randomization with strata Patients were randomized into two treatment arms consisting of an intensive treatment with a diastolic blood pressure goal of 10 mmHg below the randomization diastolic blood pressure and moderate (placebo) treatment with a diastolic blood pressure goal between 80 and 89 mmHg. Intensive arms nisoldipine or enalapril
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		Moderate BP control: $n=243$ Intensive BP therapy: $n=237$
Does it have a hard primary **endpoint**?		−1	Changes in serum creatinine clearance
Is the endpoint surrogate?	−2		GFR was not measured
Is the follow-up appropriate?	+1		5 years
Was there a **Bias**?		+2	
Is the dropout >25 %?	−1		
Is the analysis **ITT**?		−3	
Utility/usefulness			
Can the findings be generalized?	+1		T2DM, normotensive, normal renal function. Results may not be applicable to patients with diabetic nephropathy
Was the NNT <100?			Negative study
Score	**20 %**		

Results: The mean follow-up was 5.3 years. Mean BP in the intensive group was 128 ± 0.8/75 ± 0.3 mmHg versus 137 ± 0.7/81 ± 0.3 mmHg in the moderate group, $P < 0.0001$. Although no difference was demonstrated in creatinine clearance ($P = 0.43$), a lower percentage of patients in the intensive group progressed from normoalbuminuria to microalbuminuria ($P = 0.012$) and microalbuminuria to overt albuminuria ($P = 0.028$). The intensive BP control group also demonstrated less progression of diabetic retinopathy ($P = 0.019$) and a lower incidence of strokes ($P = 0.03$). The results were the same whether enalapril or nisoldipine was used as the initial antihypertensive agent.

Conclusion: Over a 5-year follow-up period, intensive (approximately 128/75 mmHg) BP control in normotensive type 2 diabetic patients: (1) slowed the progression to incipient and overt diabetic nephropathy; (2) decreased the progression of diabetic retinopathy; and (3) diminished the incidence of stroke.

Comments and Discussion

The ABCD study was one of the first to explore the impact on intensive BP control compared to standard control on the progression of diabetic complications in patients with T2DM. Its primary endpoint was the changes in creatinine clearance over the 5 year observation time.
Intensive BP control had no impact on renal function decline. Subgroup analysis suggested a benefit for intensive BP control in patients with over proteinuria.

On the other hand, intensive BP control reduced the progression of normoalbuminuria to microalbuminuria and that of microalbuminuria to macroalbuminuria.

In the intensive BP control, there was no difference on renal function or albuminuria between those treated with nisoldipine and enalapril. Blood pressure control was comparable in both arms. Also no difference between nisoldipine and enalapril was noted in relation to albuminuria.

Strength and limitations of ABCD:

This was a well-conducted study in patients with T2DM, mostly normoalbuminuria, normotensive and with normal renal function.

Blood pressure difference between the standard and intensive BP control groups was maintained throughout the study. Also an effort was made to measure BP at peak drug action rather than a randomly defined time.

A preliminary study established the agreement between creatinine clearance and iothalamate clearance measured GFR in this patients' group [43]. The authors rightly attributed that agreement to that limited contribution of tubular secretion of creatinine at that level of GFR.

Secondary endpoints showed a beneficial effect of intensive BP control on the progression of diabetic retinopathy but not neuropathy or cardiovascular complications.

Limitations include:

1. Absence of measured GFR, although, as outlined above, this may be less important at this early stage of T2DM complications.
2. Blood pressure not recorded over 24 h; this is all the more relevant in a study whose focal point is BP control.
3. The study is also limited to patients with T2DM who are normotensive and with essentially normal renal function, thus limited its applicability to those with overt diabetic nephropathy. The beneficial effect observed in those with overt nephropathy of intensive BP control is limited by the lack of power of this sub-study and the small sample size of those with overt nephropathy, precluding any meaningful conclusions.

Conclusions

The ABCD study showed that more intensive BP control in normoalbuminuric T2DM individuals had little impact on CKD progression. It suggested a dissociation between the impact of lower BP on the progression of albuminuria from that of renal dysfunction. It also suggested a dissociation between the progression of diabetic nephropathy and retinopathy; the latter being affected by lower blood pressure levels. Finally, ABCD showed no superiority of enalapril over nisoldipine in any aspect of the progression of early diabetic complications.

Endothelin Antagonists

A role has been put forward for endothelin 1 in the pathogenesis of hypertension, albuminuria, as well as the progression of CKD including DKD. It made therefore good sense to follow promising preclinical data, showing a protective effect on the progression of renal scarring by endothelin antagonists, with clinical trials. Emphasis has been, to a large extent, on the selective blockade of endothelin type A (ETA) receptor thought to activate potentially inflammatory and fibrogenic intracellular signaling pathways and mediators.

ASCEND Trial

J Am Soc Nephrol. 2010 Mar;21(3):527–35. doi: 10.1681/ASN.2009060593. Epub 2010 Feb 18.

Avosentan for overt diabetic nephropathy

Mann JF, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T, Viberti G; ASCEND Study Group.

Abstract

In the short term, the endothelin antagonist avosentan reduces proteinuria, but whether this translates to protection from progressive loss of renal function is unknown. We examined the effects of avosentan on progression of overt diabetic nephropathy in a multicenter, multinational, double-blind, placebo-controlled trial. We randomly assigned 1,392 participants with type 2 diabetes to oral avosentan (25 or 50 mg) or placebo in addition to continued angiotensin-converting-enzyme inhibition and/or angiotensin receptor blockade. The composite primary outcome was the time to doubling of serum creatinine, ESRD, or death. Secondary outcomes included changes in albumin-to-creatinine ratio (ACR) and cardiovascular outcomes. We terminated the trial prematurely after a median follow-up of 4 months (maximum 16 months) because of an excess of cardiovascular events with avosentan. We did not detect a difference in the frequency of the primary outcome between groups. Avosentan significantly reduced ACR: In patients who were treated with avosentan 25 mg/day, 50 mg/day, and placebo, the median reduction in ACR was 44.3, 49.3, and 9.7 %, respectively. Adverse events led to discontinuation of trial medication significantly more often for avosentan than for placebo (19.6 and 18.2 versus 11.5 % for placebo), dominated by fluid overload and congestive heart failure; death occurred in 21 (4.6 %; $P=0.225$), 17 (3.6 %; $P=0.194$), and 12 (2.6 %), respectively. In conclusion, avosentan reduces albuminuria when added to standard treatment in people with type 2 diabetes and overt nephropathy but induces significant fluid overload and congestive heart failure.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Randomization 1:1:1 Avosentan 25 mg: 50 mg: placebo On a background of standard therapy including RAS inhibitors
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		A sample size of 2,364 patients and 747 primary outcomes were calculated to provide a 90 % power at the 5 % level (two-sided) to detect a 7 % (25-mg dose) and 10 % (50-mg dose) absolute reduction of the primary outcome compared with the placebo group, assuming a placebo cumulative incidence of 40 % at 36 months for the primary outcome
Does it have a hard primary **endpoint**?		−1	The primary outcome was defined as the composite of time to doubling of serum creatinine, ESRD, or death ESRD prespecified in protocol
Is the endpoint surrogate?	−2		GFR was not measured
Is the follow-up appropriate?		−1	Study terminated prematurely after 4 months
Was there a **Bias**?		+2	
Is the dropout >25 %?			Not applicable in view of early termination of the study due to serious adverse events
Is the analysis **ITT**?			Same as above
Utility/usefulness			
Can the findings be generalized?	−1		Inconclusive study
Was the NNT <100?			Inconclusive study
Score	**20 %**		Inconclusive trial due to premature termination

Comments and Discussion

ASCEND was the first major study investigating the impact of an endothelin type A (ETA) receptor on the progression of diabetic nephropathy. It had to be terminated early on safety grounds.

Avosentan reduced blood pressure, accelerated the decline in eGFR, and reduced albuminuria (ACR). The reduction in albuminuria was not entirely attributable to the decline in GFR most notable at 6 months on Avosentan 50 mg/daily.

While Avosentan significantly reduced albuminuria, the study had to be prematurely terminated due to serious adverse events related to fluid retention, congestive heart failure, and related death. Consequently, any meaningful conclusions cannot be drawn from this study on the value of endothelin ETAR antagonists on the progression of diabetic nephropathy.

Fluid retention may have been attributable to the dose of Avosentan used but also the study design and inappropriate usage of diuretics in patients with advanced renal insufficiency.

The results of the ASCEND study were reproduced with another ETA receptor antagonist, Atrasentan, that also reduced albuminuria and blood pressure along with an increased rate of side effects including weight gain, fluid retention, and heart failure [44]. Anemia was also noted with Atrasentan and attributed to the fluid retention and hemodilution effect of this class of compounds.

Conclusions

The addition of ETA receptor antagonists to RAS inhibitors for the management of progressive and proteinuric diabetic nephropathy further reduce blood pressure and proteinuria but appears to be unsafe.

Antioxidant Therapy

A role has been postulated for chronic inflammation and reactive oxygen species (ROS) in the pathogenesis of the complications of DM. ROS have the capacity to cause direct tissue and renal injury as well as activate a range of intracellular inflammatory as well as fibrogenic mediators implicated in renal scarring and the progression of CKD. It makes therefore good sense to attempt to inhibit some of the ROS-mediated signaling pathways in order to minimize renal injury and the progression of CKD.

BEACON Trial

N Engl J Med. 2013 Dec 26;369(26):2492–503. doi: 10.1056/NEJMoa1306033. Epub 2013 Nov 9.

Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease

de Zeeuw D, Akizawa T, Audhya P, Bakris GL, Chin M, Christ-Schmidt H, Goldsberry A, Houser M, Krauth M, Lambers Heerspink HJ, McMurray JJ, Meyer CJ, Parving HH, Remuzzi G, Toto RD, Vaziri ND, Wanner C, Wittes J, Wrolstad D, Chertow GM; BEACON Trial Investigators.

Collaborators (347)

Abstract

Background: Although inhibitors of the renin-angiotensin-aldosterone system can slow the progression of diabetic kidney disease, the residual risk is high. Whether nuclear 1 factor (erythroid-derived 2)-related factor 2 activators further reduce this risk is unknown.

Methods: We randomly assigned 2,185 patients with type 2 diabetes mellitus and stage 4 chronic kidney disease (estimated glomerular filtration rate [GFR], 15 to <30 ml/min/1.73 m^2 of body-surface area) to bardoxolone methyl, at a daily dose of 20 mg, or placebo. The primary composite outcome was end-stage renal disease (ESRD) or death from cardiovascular causes.

Results: The sponsor and the steering committee terminated the trial on the recommendation of the independent data and safety monitoring committee; the median follow-up was 9 months. A total of 69 of 1,088 patients (6 %) randomly assigned to bardoxolone methyl and 69 of 1,097 (6 %) randomly assigned to placebo had a primary composite outcome (hazard ratio in the bardoxolone methyl group vs. the placebo group, 0.98; 95 % confidence interval [CI], 0.70–1.37; $P=0.92$). In the bardoxolone methyl group, ESRD developed in 43 patients, and 27 patients died from cardiovascular causes; in the placebo group, ESRD developed in 51 patients, and 19 patients died from cardiovascular causes. A total of 96 patients in the bardoxolone methyl group were hospitalized for heart failure or died from heart failure, as compared with 55 in the placebo group (hazard ratio, 1.83; 95 % CI, 1.32–2.55; $P<0.001$). Estimated GFR, blood pressure, and the urinary albumin-to-creatinine ratio increased significantly and body weight decreased significantly in the bardoxolone methyl group, as compared with the placebo group.

Conclusions: Among patients with type 2 diabetes mellitus and stage 4 chronic kidney disease, bardoxolone methyl did not reduce the risk of ESRD or death from cardiovascular causes. A higher rate of cardiovascular events with bardoxolone methyl than with placebo prompted termination of the trial. (Funded by Reata Pharmaceuticals; BEACON ClinicalTrials.gov number, NCT01351675.).

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Bardoxolone methyl on a background of RAS inhibition Placebo = 1,097 Bardoxolone = 1,088
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		It was calculated that we needed to enroll 2,000 patients on the basis of the following assumptions: a two-sided type I error rate of 5 %, an event rate of 24 % for the primary composite outcome in the placebo group during the first 2 years of the study
Does it have a hard primary **endpoint**?	+1		ESRD or death from cardiovascular causes
Is the endpoint surrogate?	−2		
Is the follow-up appropriate?		−1	Median follow-up = 9 months due to the premature termination of the study due to serious adverse events
Was there a **Bias**?	−2		Control group was not progressive
Is the dropout >25 %?			
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?		−1	Inconclusive study prematurely terminated
Was the NNT <100?			Inconclusive study prematurely terminated
Score	**27 %**		Inconclusive trial due to premature termination

Comments and Discussion

It has long been assumed that oxidant stress plays an important role in the initiation and progression of diabetic nephropathy. A number of interventions aimed at reducing oxidant-induced renal injury have been tested in RCTs aimed at reducing renal injury and slowing the progression of diabetic kidney disease

[45, 46]. This has included Bardoxolone methyl, a nuclear 1 factor (erythroid-derived 2)–related factor 2 activator, that showed promise in experimental models [47].

Following the BEAM proof of concept study of the efficacy of Bardoxolone methyl, a nuclear 1 factor (erythroid-derived 2)–related factor 2 activator, on renal function in T2DM nephropathy that showed an acute and sustained increase in eGFR [48], BEACON was designed to confirm such potential benefit and its impact on the incidence of ESRD and cardiovascular events in T2DM.

BEACON, like BEAM [48] before it, showed that Bardoxolone methyl reduced serum creatinine and increased eGFR over the observation period. But the two studies also showed that patients suffered significant weight loss.

Of note, BEACON also showed a significant increase in blood pressure and albuminuria on Bardoxolone.

BEACON was terminated prematurely due to increased morbidity and mortality attributed to Bardoxolone.

Limitations and lessons from the BEAM/BEACON trials:

1. Changes in eGFR do not equate to measured GFR.
2. Changes in serum creatinine and eGFR are confounded by variables such as weight and muscle loss as observed with a toxic compound such as Bardoxolone.
3. Changes in serum creatinine and eGFR can also be affected by tubular effects of drugs such as Bardoxolone that may also have affected the urinary excretion of magnesium, uric acid, and phosphate with consequent lower blood levels compared to placebo.
4. GFR has to be measured to evaluate CKD and DKD progression.
5. ESRD incidence based on changes in serum creatinine and eGFR has the same limitations outlined above.
6. In the BEAM study, the nature of progressive DKD was not established prior to randomization, hence the non-progressive nature of eGFR in the placebo group.

Conclusions

The BEAM/BEACON tragedy highlights the serious and potentially dangerous practice of relying on changes in serum creatinine and its derived eGFR to measure renal function decline in RCTs [48–50]. This reflects that dangerous oversight that serum creatinine changes can be confounded by a number of factors including diet, metabolism, and muscle mass as well as tubular secretion.

The BEAM-BEACON "improved GFR" myth was also noted in a study of another potential antioxidant pirfenidone that showed an increase in eGFR in diabetic nephropathy along with serious gastrointestinal side effects that would have undoubtedly impacted protein intake, weight and serum creatinine levels, without necessarily affecting measured GFR [49].

It is high time nephrologists realize that eGFR does not always reflect measured GFR and that RCTs have to rely on the latter to avoid confounders affecting the former.

Miscellaneous Interventions

Pirfenidone

Pirfenidone has been at the forefront of anti-fibrotic agents for more than a decade. It has proved effective in minimizing a number of experimental fibrosis models. While the precise anti-fibrotic effect of pirfenidone is not fully understood, it has shown great promise for the management of patients with lung fibrosis. Translational studies based on the treatment of patients with CKD and DKD with Pirfenidone have tested whether such agent is capable of slowing the progression of the underlying nephropathy.

J Am Soc Nephrol. 2011;22(6):1144–51. doi: 10.1681/ASN.2010101049. Epub 2011 Apr 21.

Pirfenidone for diabetic nephropathy

Sharma K, Ix JH, Mathew AV, Cho M, Pflueger A, Dunn SR, Francos B, Sharma S, Falkner B, McGowan TA, Donohue M, Ramachandrarao S, Xu R, Fervenza FC, Kopp JB.

Abstract

Pirfenidone is an oral antifibrotic agent that benefits diabetic nephropathy in animal models, but whether it is effective for human diabetic nephropathy is unknown. We conducted a randomized, double-blind, placebo-controlled study in 77 subjects with diabetic nephropathy who had elevated albuminuria and reduced estimated GFR (eGFR) (20–75 ml/min/1.73 m^2). The prespecified primary outcome was a change in eGFR after 1 year of therapy. We randomly assigned 26 subjects to placebo, 26 to pirfenidone at 1,200 mg/day, and 25 to pirfenidone at 2,400 mg/day. Among the 52 subjects who completed the study, the mean eGFR increased in the pirfenidone 1,200-mg/day group (+3.3 ± 8.5 ml/min/1.73 m^2) whereas the mean eGFR decreased in the placebo group (−2.2 ± 4.8 ml/min/1.73 m^2; $P = 0.026$ versus pirfenidone at 1,200 mg/day). The dropout rate was high (11 of 25) in the pirfenidone 2,400-mg/day group, and the change in eGFR was not significantly different from placebo (−1.9 ± 6.7 ml/min/1.73 m^2). Of the 77 subjects, 4 initiated hemodialysis in the placebo group, 1 in the pirfenidone 2,400-mg/day group, and none in the pirfenidone 1,200-mg/day group during the study ($P = 0.25$). Baseline levels of plasma biomarkers of inflammation and fibrosis significantly correlated with baseline eGFR but did not predict response to therapy. In conclusion, these results suggest that pirfenidone is a promising agent for individuals with overt diabetic nephropathy.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		Randomly assigned 26 subjects to placebo, 26 to pirfenidone at 1,200 mg/day, and 25 to pirfenidone at 2,400 mg/day
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?		−3	
Does it have a hard primary **endpoint**?		−1	Changes in eGFR after 1 year follow-up
Is the endpoint surrogate?	−2		
Is the follow-up appropriate?		−1	1 year
Was there a **Bias**?		+2	
Is the dropout >25 %?	−1		52 of 77 completed the study and were analyzed. Biggest dropout in the 2,400 mg/day pirfenidone group due to gastrointestinal side effects
Is the analysis **ITT**?		−3	52 of 77 analyzed
Utility/usefulness			
Can the findings be generalized?		−1	T2DM with eGFR 20–75 ml/min and albuminuria
Was the NNT <100?			Negative study
Score	**0 %**		

Comments and Discussion

The Pirfenidone in diabetic nephropathy study is another example of a badly conducted and interpreted study [51]. In view of large dropout rate and missing data for the final analysis, it required statistical assistance, permutation tests, and ANCOVA with iterated re-weighted least squares, controlling for baseline values and their inter- action with treatment, to conclude that there was an improvement in eGFR between the Pirfenidone 1,200 mg/day group and placebo. This conclusion is confounded by the serious study limitations, mostly the likely misinterpretation of changes in serum creatinine (and eGFR) levels due to the side effects of the compound. It bears similarities to the BEAM/BEACON studies [52] where claims of improved eGFR sadly reflected the investigators' choice of wrong primary endpoint (serum creatinine/eGFR) when using a compound/pirfenidone that affects gastric emptying and may therefore impact food/protein intake [53].

Limitations:

1. This is not an intention to treat analysis and in view of the large dropout rate (>30 %), the study is clearly underpowered and therefore inconclusive.
2. Pirfinedone at 2,400 mg/day had so many gastrointestinal side effects that few patients completed the study in this arm, thus excluding it from any meaningful analysis.
3. The known gastrointestinal side effects of Pirfenidone, abdominal discomfort, nausea, vomiting, and decreased appetite make the use of serum creatinine unacceptable at best and misleading at worst. Changes reported in serum creatinine (fall) and in eGFR(rise +3 ml/min) in the Pirfenidone 1,200 mg/day group are most likely related to decreased food intake and consequent fall in serum creatinine; little to do with renal function and/or its improvement.
4. GFR was not measured.

Conclusions

The Pirfenidone study is fraught by its numerous limitations including its inadequate power and inappropriate use of serum creatinine as the primary endpoint and, therefore, is inconclusive. Pirfenidone may be a compound with too many side effects to be safely administered to patients with CKD, never mind those with diabetes mellitus who are often already suffering from underlying autonomic neuropathy and impaired gastric emptying [53].

AGE Inhibition

Advanced glycation end products (AGE) have been implicated in the pathogenesis of a number of degenerative diseases including diabetes mellitus. In diabetes, sustained glycation of endogenous proteins through the Amadori nonenzymatic reaction has been linked to all the micro- and macro- vascular complications of the disease including DN. Inhibitors of AGE formation have shown promise in experimental models of diabetic nephropathy in rodents, hence their translation into the treatment of patients with DKD.

J Am Soc Nephrol. 2012 Jan;23(1):131–6. doi: 10.1681/ASN.2011030272. Epub 2011 Oct 27.

Pyridorin in type 2 diabetic nephropathy

Lewis EJ, Greene T, Spitalewiz S, Blumenthal S, Berl T, Hunsicker LG, Pohl MA, Rohde RD, Raz I, Yerushalmy Y, Yagil Y, Herskovits T, Atkins RC, Reutens AT, Packham DK, Lewis JB; Collaborative Study Group.

Abstract

Pyridoxamine dihydrochloride (Pyridorin, NephroGenex) inhibits formation of advanced glycation end products and scavenges reactive oxygen species and toxic carbonyls, but whether these actions translate into renoprotective effects is unknown. In this double-blind, randomized, placebo-controlled trial, we randomly assigned 317 patients with proteinuric type 2 diabetic nephropathy to twice-daily placebo; Pyridorin, 150 mg twice daily; or Pyridorin, 300 mg twice daily, for 52 weeks. At baseline, the mean age ± SD was 63.9 ± 9.5 years, and the mean duration of diabetes was 17.6 ± 8.5 years; the mean serum creatinine level was 2.2 ± 0.6 mg/dl, and the mean protein-to-creatinine ratio was

2,973 ± 1,932 mg/g. Regarding the primary endpoint, a statistically significant change in serum creatinine from baseline to 52 weeks was not evident in either Pyridorin group compared with placebo. However, analysis of covariance suggested that the magnitude of the treatment effect differed by baseline renal function. Among patients in the lowest tertile of baseline serum creatinine concentration, treatment with Pyridorin associated with a lower average change in serum creatinine concentration at 52 weeks (0.28, 0.07, and 0.14 mg/dl for placebo, Pyridorin 150 mg, and Pyridorin 300 mg, respectively; $P = 0.05$ for either Pyridorin dose versus placebo); there was no evidence of a significant treatment effect in the middle or upper tertiles. In conclusion, this trial failed to detect an effect of Pyridorin on the progression of serum creatinine at 1 year, although it suggests that patients with less renal impairment might benefit.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?		−1	
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		The sample size estimate for this study was determined using data from previous Pyridorin studies (PYR 206, PYR 205/207) and the IDNT. The study was powered to detect a 40 % difference between the Pyridorin groups and placebo Placebo: 106, Pyridorin 150 mg/bid = 105, pyridorin 300 mg/bid = 106
Does it have a hard primary **endpoint**?		−1	Changes in serum creatinine over 12 months
Is the endpoint surrogate?	−2		GFR not measured, prespecified ESRD not considered
Is the follow-up appropriate?		−1	12 months too short for progression study
Was there a **Bias**?		+2	
Is the dropout >25 %?		+1	
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T2DM with serum creatinine between 1.3 and 3 mg/dl and overt albuminuria >1,200 mg/g
Was the NNT <100?			Negative study
Score	**47 %**		

Comments and Discussion

One of the main hypotheses related to the pathogenesis of the complications of DM focuses on the role of advanced glycation endproducts (AGE) and their deposition in tissues [54]. The kidney is no exception as it has been argued that the glomerular as well as tubular accumulation of AGE initiate and contribute to the progression of glomerulosclerosis and tubulointerstitial fibrosis, respectively [55]. Consequently, experimental and clinical attempts at the prevention of AGE formation and deposition have become one of the main therapeutic targets and strategy for the management of DM and its complications [55].

Earlier experimental [56] and clinical [57] studies suggested that an inhibitor of advanced glycation endproducts (pyridoxine/pyridorin) may slow the rate of increase in serum creatinine. However, the proof of concept (POC) study under discussion above failed to confirm such findings as serum creatinine changes were not affected by treatment with pyridorin. Pyridorin had no effect on albuminuria. Diabetes control was comparable between groups.

This study has a number of limitations:

1. Relatively small sample size.
2. Short duration of follow-up; 12 months' follow-up period does not allow for a comprehensive evaluation of an intervention aimed to inhibit the ongoing deposition of AGE on the progression of DN.
3. The study relied on the soft endpoint of changes in serum creatinine rather than the hard endpoint of measured GFR.
4. Changes in Cystatin C were measured, although these may be affected in obesity and inflammation associated with T2DM.
5. Proof of compound efficacy was not ascertained by measurement of AGE in circulation.

Conclusions

A study with a flawed design and short follow-up period that does not allow the drawing of any meaningful conclusions.

Suledoxide

Suledoxide and other naturally occurring glycosaminoglycans as well as heparinoids have shown in a number of experimental renal models a capacity to reduce albuminuria and decrease renal fibrosis. Pilot studies have also shown an anti-proteinuric effect in patients with diabetic nephropathy.

The Sun-MACRO Trial

J Am Soc Nephrol. 2012;23(1):123–30. doi: 10.1681/ASN.2011040378. Epub 2011 Oct 27.

Sulodexide fails to demonstrate renoprotection in overt type 2 diabetic nephropathy

Packham DK, Wolfe R, Reutens AT, Berl T, Heerspink HL, Rohde R, Ivory S, Lewis J, Raz I, Wiegmann TB, Chan JC, de Zeeuw D, Lewis EJ, Atkins RC; Collaborative Study Group.

Abstract

Sulodexide, a mixture of naturally occurring glycosaminoglycan polysaccharide components, has been reported to reduce albuminuria in patients with diabetes, but it is unknown whether it is renoprotective. This study reports the results from the randomized, double-blind, placebo-controlled sulodexide macroalbuminuria (Sun-MACRO) trial, which evaluated the renoprotective effects of sulodexide in patients with type 2 diabetes, renal impairment, and significant proteinuria (>900 mg/day) already receiving maximal therapy with angiotensin II receptor blockers. The primary endpoint was a composite of a doubling of baseline serum creatinine, development of ESRD, or serum creatinine ≥6.0 mg/dl. We planned to enroll 2,240 patients over approximately 24 months but terminated the study after enrolling 1,248 patients. After 1,029 person-years of follow-up, we did not detect any significant differences between sulodexide and placebo; the primary composite endpoint occurred in 26 and 30 patients in the sulodexide and placebo groups, respectively. Side effect profiles were similar for both groups. In conclusion, these data do not suggest a renoprotective benefit of sulodexide in patients with type 2 diabetes, renal impairment, and macroalbuminuria.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		1,248 studied instead of the anticipated 2,240: sulodexide = 619 patients
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?		−3	
Does it have a hard primary **endpoint**?		−1	The primary endpoint was a composite of a doubling of baseline serum creatinine, development of ESRD, or serum creatinine >6.0 mg/dl
Is the endpoint surrogate?	−2		GFR not measured
Is the follow-up appropriate?		−1	Premature termination of the study for futility; follow-up <12 months
Was there a **Bias**?		+2	
Is the dropout >25 %?			Premature termination
Is the analysis **ITT**?		−3	Premature termination
Utility/usefulness			
Can the findings be generalized?	+1		T2DM, with renal impairment (serum creatinine: 1.5–3 mg/dl) and significant proteinuria (>900 mg/day)
Was the NNT <100?			Inconclusive study
Score	**0 %**		Inconclusive study

Comments and Discussion

Sulodexide is a mixture of naturally occurring glycosaminoglycan polysaccharide. It has heparin-like effects. It has shown anti-proteinuric properties in preclinical studies [58]. Early experimental [59] and clinical [60, 61] evidence confirmed such impression in patients with early and advanced diabetic nephropathy.

The Sun-MACRO study aimed to test this hypothesis in T2DM patients with a median GFR of 30 ml/min and macro-proteinuria (>900 mg/day). While the study was meant to run for 3 years and recruit >2,200 patients, it was terminated early (<12 months) with <1,500 patients recruited.

Limitations of the Sun-MACRO trial

The study has many of the limitations of other RCTs in patients with DN.

1. GFR was not measured and it relied on the soft endpoint of changes in serum creatinine.
2. A decision to terminate prematurely is difficult to explain as the study neither reached its power or had a long enough follow-up to determine renal functional outcome. To some extent the lack of the early and anticipated (within 4 months) effect on the secondary endpoint of proteinuria, for which the authors claim that the study was powered to detect, seems to have been the decisive factor in the study termination.
3. The advanced stage of DN (CKD3b-4) may have confounded the likelihood of response to a compound that may have otherwise altered early changes in glomerular basement membrane structure and charge.
4. As with many experimental compounds, investigators have failed to show that the oral administration of sulodexide effected some anticipated actions, for instance, Factor Xa inhibition.

Conclusions

The premature termination of this study precludes any meaningful conclusions regarding the efficacy of sulodexide in diabetic nephropathy. As only one tenth of endpoints were reached during the short follow-up of a small number of patients, a type 2 statistical error cannot be excluded.

Vitamin D

Increasingly, vitamin D deficiency has been implicated in the pathogenesis of a range of chronic diseases including CKD. Vitamin D deficiency has also been associated with increased cardiovascular morbidity and all-cause mortality. Patients with CKD and ESRD with vitamin D deficiency are at increased risk of mortality. While initially thought to act primarily on calcium absorption and bone mineralization, it is becoming apparent that vitamin D is a pleomorphic

hormone that modulates the physiology of a number of organs as well as the immune system. This has prompted the administration of vitamin D and its analogues to patients with DN in an attempt to improve outcomes.

VITAL Trial

Lancet. 2010 Nov 6;376(9752):1543–51. doi: 10.1016/S0140-6736(10)61032-X.

Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): A Randomized Controlled Trial

de Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T, Parving HH, Pritchett Y, Remuzzi G, Ritz E, Andress D.

Abstract

Background: Despite treatment with renin–angiotensin–aldosterone system (RAAS) inhibitors, patients with diabetes have increased risk of progressive renal failure that correlates with albuminuria. We aimed to assess whether paricalcitol could be used to reduce albuminuria in patients with diabetic nephropathy.

Methods: In this multinational, placebo-controlled, double-blind trial, we enrolled patients with type 2 diabetes and albuminuria who were receiving angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers. Patients were assigned (1:1:1) by computer-generated randomization sequence to receive 24 weeks' treatment with placebo, 1 μg/day paricalcitol, or 2 μg/day paricalcitol. The primary endpoint was the percentage change in geometric mean urinary albumin-to-creatinine ratio (UACR) from baseline to last measurement during treatment for the combined paricalcitol groups versus the placebo group. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00421733.

Findings: Between February 2007 and October 2008, 281 patients were enrolled and assigned to receive placebo ($n=93$), 1 μg paricalcitol ($n=93$), or 2 μg paricalcitol ($n=95$); 88 patients on placebo, 92 on 1 μg paricalcitol, and 92 on 2 μg paricalcitol received at least one dose of study drug, and had UACR data at baseline and at least one time-point during treatment, and so were included in the primary analysis. Change in UACR was: −3 % (from 61 to 60 mg/mmol; 95 % CI −16 to 13) in the placebo group; −16 % (from 62 to 51 mg/mmol; −24 to −9) in the combined paricalcitol groups, with a between-group difference versus placebo of −15 % (95 % CI −28 to 1; $p=0.071$); −14 % (from 63 to 54 mg/mmol; −24 to −1) in the 1 μg paricalcitol group, with a between-group difference versus placebo of −11 % (95 % CI −27 to 8; $p=0.23$); and −20 % (from 61 to 49 mg/mmol; −30 to −8) in the 2 μg paricalcitol group, with a between-group difference versus placebo of −18 % (95 % CI −32 to 0; $p=0.053$). Patients on 2 μg paricalcitol showed a nearly, sustained reduction in UACR, ranging from −18 to −28 % ($p=0.014$ vs placebo). Incidence of hypercalcemia, adverse events, and serious adverse events was similar between groups receiving paricalcitol versus placebo.

Interpretation: Addition of 2 μg/day paricalcitol to RAAS inhibition safely lowers residual albuminuria in patients with diabetic nephropathy and could be a novel approach to lower residual renal risk in diabetes.

Funding: Abbott.

Critical Appraisal

Parameters	Yes	No	Comment
Validity			
Is the **Randomization** Procedure well described?	+1		1:1:1 Paricalcitol 1 ug/day: 2 ug/day: Placebo Patients continued on standard therapy including RAAS inhibition
Double **blinded**?	+2		
Is the **sample size** calculation described/adequate?	+3		We calculated that a total sample size of 258 patients was needed for at least 82 % power to detect an absolute difference in log-transformed UACR of 0.034 mg/mmol (SD 0.088) from baseline to last measurement during treatment between the combined paricalcitol group and placebo at a two-sided significance level of 0.05 Paricalcitol 1: 93 patients, Paricalcitol 2: 95 patients and Placebo: 93 patients
Does it have a hard primary **endpoint**?	+1		Percentage change in geometric mean of urinary ACR (UACR)
Is the endpoint surrogate?	−2	0	
Is the follow-up appropriate?	+1		24 weeks
Was there a **Bias**?		+2	
Is the dropout >25 %?		+1	
Is the analysis **ITT**?	+3		
Utility/usefulness			
Can the findings be generalized?	+1		T2DM (eGFR 15–90 ml/min) and albuminuria (11–339 mg/mmol)
Was the NNT <100?			Negative study
Score	**73 %**		

Comments and Discussion

The interest in the potential benefit of vitamin D and its analogues in CKD has stemmed from a number of observations including the correlations between low circulating calcitriol

levels and raised albuminuria [62], as well as observations made in preclinical studies, showing that the selective vitamin D receptor activator, paricalcitol, reduced albuminuria and reduced the renal scarring process [63].

The VITAL study tested the hypothesis that activation of the Vitamin D receptor reduces albuminuria in T2DM. The study was negative overall as no statistically significant difference was detected between placebo and those treated with paricalcitol. Subgroup analysis suggested that the higher dose (2 ug/day) of paricalcitol reduced albuminuria compared to placebo.

Paricalcitol was also associated with a reduction in blood pressure that considerably attenuated the putative beneficial effect on albuminuria reduction.

Of note, paricalcitol (2 ug/day) also reduced eGFR.

L**imitations of the VITAL study**:

1. This is at best a proof-of-concept (POC) study of a small number of patients with T2DM followed up for 24 weeks.
2. The population studied was quite heterogeneous with eGFR from 15 to 90 ml/min and UACR from 11 to 339 mg/mmol. Such heterogeneity would affect the expected response to a given intervention.
3. As with many studies pertaining to the effect of vitamin D on UACR, it somewhat underestimated the known effect of vitamin D supplementation on serum creatinine and its excretion [64]. Increased urinary excretion of creatinine may explain to some extent the fall in UACR. However, there was also a fall in the geometric mean of 24 h urine albumin excretion.
4. Changes in serum creatinine due to vitamin D administration may also explain the "fall" in GFR; eGFR is entirely a reflection of serum creatinine levels and its changes that could be confounded in this study by the impact of vitamin D on creatinine metabolism.
5. Subgroup analysis showing differences compared to placebo is at best hypothesis generating and should not be considered conclusive evidence.
6. Finally, studies based on changes in albuminuria assume a surrogate value for that parameter for progression of DN; a number of studies have now shown that this is not the case; ONTARGET [65] and VA NEPHRON-D [66] as well as ASCEND [67] show the two parameters to be dissociated.

Conclusions

Hypothesis-generating study on the potential of vitamin D and its analogues at reducing albuminuria.

General Discussion

The history and critical appraisal of RCTs on the progression of DN are most informative.

Studies focusing on strict and intensive glycemia control on diabetes micro- and macro-vascular outcomes, including progression of DKD, have shown conflicting results. This is most likely due to a large number of confounders including the heterogeneity of the populations studied as well as the complexity of DM and its complications as well as treatment modalities [68].

Regarding hypertension control, there remains little evidence to support recommendations that patients with DM and DKD warrant tighter blood pressure control; <130/80 mmHg [69], although blood pressure levels <140/90 mmHg seem protective and therapeutic inertia unjustifiable [70].

As to the choice of anti-hypertensive agents, while a stream of RCTs supports the suggestion that RAAS inhibition slows the progression of type 1 and 2 DN, most of these studies have their limitations. Meta-analyses have been conflicting with some being unable to separate the anti-hypertensive advantage of RAAS inhibition from its impact on DN progression [71], while others suggesting an undeniable benefit on DN progression [72]. This is also the case of meta-analyses analyzing the impact of RAAS inhibition of cardiovascular events [73, 74]. The critical appraisal of RAAS inhibition studies in DN reveals that not a single study (other than RASS that investigated people with DM and normal renal function) on progressive DN evaluated progression by measuring GFR. They invariably rely on serum creatinine and eGFR that have proved unreliable measures of renal function in intervention studies where the intervention may impact appetite and protein intake, muscle metabolism (BEAM-BEACON as well as Pirfenidone), as well as the potential confounder of changes in tubular secretion of creatinine that seems underestimated and seldom considered in RCTs of RAAS inhibition [75, 76].

Many studies have relied on the short-term surrogate endpoint of changes in albuminuria as a surrogate for the longer term outcome of decline in renal function. Such assumption is no longer tenable in view of the increasing number of studies showing a dissociation between albuminuria and renal function decline; ACCOMPLISH [77] and in people with diabetes ASCEND (Endothelin receptor blockade), ONTARGET (dual RAS blockade), and VA NEPHRON-D (dual RAS blockade), among others, are all discussed above.

A large number of interventions have not been reviewed in this chapter as they had no impact on clinical practice and are unlikely to do so in the future. They have been outlined in a number of recent publications [78, 79]. They are mostly proof-of-concept studies that have no advanced to large Phase 3 RCTs to date.

Recommendations for RCTs on DKD

1. GFR has to be measured if the aim of the RCT is the evaluation of the impact on an intervention of DKD progression. Too many compounds with gastrointestinal side

effects and/or inducing weight loss (low protein diets, Pirfenidone, Bardoxolone) have been inappropriately tested by using serum creatinine/eGFR as primary endpoint to claim improved renal function when in reality these changes in these parameters reflected serious adverse effects and harm to patients.

2. Serum creatinine /eGFR are soft and unpredictable surrogate endpoints that should not be used as primary endpoint in RCTs testing new therapeutic compounds.
3. Microalbuminuria/albuminuria is no longer acceptable as a surrogate marker for DKD progression in view of the numerous disconnect between changes in its excretion rate and the harder endpoint/outcome of disease progression [80].
4. Interventions impacting blood pressure levels should be supported by accurate BP recordings and not occasional office BP measurements. 24 h ABPM would be recommended in studies focusing on the impact of BP control or using agents that affect blood pressure.
5. A well-defined and mostly homogeneous and progressive population would increase the likelihood of positive outcomes with smaller sample size. To include patients with type 1 and 2 DM and GFR ranging from 90 to 15 ml/min or albuminuria from normal to macroalbuminuria reflect poor RCT design that seriously compromises the likelihood of a meaningful outcome.
6. RCTs should also focus on progressive DN, as studies where the control/placebo group is not progressive (as in BEAM) raise questions regarding the whole premise of the clinical trial.
7. Focus on DM patients with detectablerenal/cardiovascular disease (secondary prevention) may yield more results than those aimed at primary prevention warranting much larger sample size and longer follow-up.
8. A better understanding of the changing nature of DM [81] and DKD with slower CKD progression and less albuminuria in older T2DM [82] has to be taken into consideration. Many have primarily a hypertensive and ischemic nephropathy rather than the putative hyperperfused and hyperfiltering kidneys upon which many interventions have been based over the recent decades.

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