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ORIGINAL RESEARCH

Clinical Trials on Diabetic Nephropathy: A Cross-Sectional Analysis

Sergio Modafferi · Markus Ries · Vittorio Calabrese · Claus. P. Schmitt · Peter Nawroth · Stefan Kopf · Verena Peters

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ABSTRACT

Introduction: Treatment options and decisions are often based on the results of clinical trials. We have evaluated the public availability of results from completed, registered phase III clinical trials on diabetic nephropathy and current treatment options.

Methods: This was a cross-sectional analysis in which STrengthening the Reporting of OBservational studies in Epidemiology criteria were applied for design and analysis. In June 2017, 34 completed phase III clinical trials on diabetic nephropathy in the ClinicalTrials. gov registry were identified and matched to publications in the ClinicalTrials.gov registry and to those in the PubMed and Google Scholar databases. If no publication was identified, the principal investigator was contacted. The ratio of published and non-published studies was calculated. Various parameters, including study design, drugs, and comparators provided, were analyzed.

Results: Drugs/supplements belonged to 26 different categories of medications, with the main ones being angiotensin-converting enzyme inhibitors, angiotensin-II receptors blockers, and dipeptidyl-peptidase-4-inhibitors. Among the trials completed before 2016 (n = 32), 22 (69%) were published, and ten (31%) remained unpublished. Thus, data on 11 different interventions and more than 1000 patients remained undisclosed. Mean time to publication was 26.5 months, which is longer than the time constrictions imposed by the U.S. Food and Drug Administration Amendments Act. Most trials only showed weak effects on micro- and macroalbuminuria, with an absolute risk reduction of 1.0 and 0.3%, respectively, and the number needed to treat varied between 91 and 333, without any relevant effect on end-stage-renal disease by intensive glucose-lowering treatment. Comparison of the results,

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S. Modafferi · M. Ries · Claus. P. Schmitt · V. Peters (✉)
Center for Pediatric and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany
e-mail: Verena.Peters@med.uni-heidelberg.de

S. Modafferi · V. Calabrese
Department of Biomedical and Biotechnological Sciences, School of Medicine, University of Catania, Catania, Italy

P. Nawroth · S. Kopf
Department of Endocrinology, Diabetology and Clinical Chemistry, University Hospital Heidelberg, University Heidelberg, Heidelberg, Germany

P. Nawroth · S. Kopf
Deutsches Zentrum für Diabetesforschung e.V. (DZD), Neuherberg, Germany

P. Nawroth
Joint Heidelberg-IDC Translational Diabetes Program, Institute for Diabetes and Cancer, Helmholtz Zentrum, Neuherberg, Germany

however, was difficult since study design, interventions, and the renal outcome parameters vary greatly between the studies.
Conclusion: Despite the financial and human resources involved and the relevance for therapeutic guidelines and clinical decisions, about one-third of phase III clinical trials on diabetic nephropathy remain unpublished. Interventions used in published trials showed a low efficacy on renal outcome.
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Keywords: ACE inhibitors; Angiotensin-II receptors; ClinicalTrials.gov; Diabetes mellitus; Diabetic nephropathy; Dipeptidyl-peptidase-4-inhibitors; Phase III clinical trials

INTRODUCTION

The ever-increasing global prevalence of diabetes mellitus, which was estimated to affect over 415 million people worldwide in 2017 [1], is giving rise to serious concern among healthcare providers. Diabetic nephropathy (DN) is a major complication associated with both type 1 and type 2 diabetes (T1DM and T2DM, respectively) and is the leading cause of end-stage renal disease (ESRD) [2]. DN follows distinct phases, wherein glomerular hyperfiltration is followed by a relentless decline in renal function, typically occurring over a 15- to 20-year period [3]. The development of ESRD requires the patient to receive dialysis or undergo renal transplantation, two procedures which are associated with excess morbidity and mortality [4]. The current standard treatment regimen for patients with T2DM involves lifestyle modifications and medical treatment targeted against the fundamental dysregulation of glucose and hypertension [3, 5], but this strategy is unable to affect the underlying pathophysiology of the DN. Although the results of many studies indicate a correlation between the degree of hyperglycemia and progression of DN, diabetic patients receiving intensive glycemic control therapy continue to develop DN. Hyperglycemia can in fact induce modifications in gene expressions which persist even after normoglycemia is restored through a process known as metabolic memory [6]. In a recent study, the risk of development of kidney complications was correlated with a specific cluster of diabetic patients with insulin-resistance, leading the authors to suggest that glucose-lowering therapy is not the optimum management strategy for preventing this complication. Hence, there is a need to focus on new therapeutic targets and initiate treatments at an early stage in order to prevent complications [7]. Treatment options and decisions are often based on the results of clinical trials that meet the highest standards of scientific rigor and ethical oversight [8]. The specific aim of phase III clinical trials is to confirm results obtained in previous experimental trials; as such, phase III clinical trials must test experimental study drugs or treatment in larger populations in order to confirm the effectiveness and safety of use of the drug(s) under study (https://www.fda.gov/). To realize the benefits of a clinical trial, the results must be shared quickly after the study has concluded [9]. However, timely dissemination of clinical trial results continues to be a serious issue. Since favorable results of intervention by drugs are twofold more likely to be published than negative or unfavorable results [10], the efficacy of a drug may be overestimated by the medical community, and trials may be unnecessarily repeated. Beyond the impact on treatment decisions, however, there is an explicit ethical obligation to publish towards study participants, as mandated by the Declaration of Helsinki. Therefore, the non-publication of trial outcome data is against ethical obligations that investigators have towards study participants. In this context, the aim of our study was to assess the public availability of results of phase III clinical trials on DN. Since treatment options and decisions are often based on clinical trials, knowledge on current therapies and their outcome is of utmost importance.

METHODS

The analysis was performed according to STROBE (STrengthening the Reporting of

Observational studies in Epidemiology) criteria. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Clinical Trials Search

For the cross-sectional analysis, we searched the Clinical Trials.gov registry of clinical trials in June 2017 for clinical trials on DN, with the added restriction of only completed phase III trials. The search was performed by entering the keywords "diabetic nephropathy" and "diabetic renal disease" in the ClinicalTrials.gov search engine. Data on studies obtained from the database were organized in a spreadsheet for analysis. The data available on ClinicalTrials.gov included National Clinical Trial (NCT) number, study title, study description, study design, eligibility criteria, enrollment, arm and interventions, outcome measures, primary completion date, and availability of study results. Following the evaluation of these parameters, we excluded studies that did not meet the following exclusion criteria: no diabetic patients investigated and/or intervention not relevant for diabetic kidney disease (DKD).

Publication Search

A trial was considered to have been published when the results were present in the ClinicalTrials.gov registry or when a journal had published a peer-reviewed manuscript online or in print that included primary or secondary outcome data from the trial in question. When the ClinicalTrials.gov registry did not provide results or links to publications in peer-reviewed journals, we searched the PubMed or/and Google Scholar databases for articles using the study identification number (NCT), the study title, and other study identification numbers. When no published results were found on these latter two databases, the principal investigators (PIs) or sponsors were contacted by email and asked to provide either an article with the study results, which we might have missed, or the reason for the failure to publish the results. Feedback on the missing publications and available data on unpublished clinical trials were analyzed. Clinical trial results that could not be obtained by the preceding described procedure were assessed as unpublished.

Time to Publication

Time to publication refers to the period of time between the primary completion date of the clinical trial and the date of publication of the results either on the ClinicalTrials.gov registry or in peer-reviewed journals. The calculation of the time to publication was performed in accordance with the Food and Drug Administration Amendments Act of 2007 (FDAAA) which requires the publication of results within 1 year after completion of the trial [11] and, therefore, our analysis regarded only studies completed before 2016.

Absolute Risk Reduction Analysis and Patient Number Needed to Treat

The absolute risk reduction (AAR) is the change in the risk of an outcome of a given treatment or activity in relation to a comparison treatment or activity. The number needed to treat (NNT) corresponds to the inverse of the absolute risk reduction.

Statistical Analysis

The following continuous or categorical variables were analyzed: NCT number, study title, gender, age, study phase, study type, study design, condition, intervention, recruitment status, primary completion date and completion date, availability of study results, publication date, time to publication, sponsor, and funding source. Standard methods of descriptive statistics were applied. Two-sided p values 0.05 were considered to be statistically significant.

RESULTS

Publication of Clinical Trials

A total of 49 completed phase III clinical trials were identified from the search of the ClinicalTrials.gov registry in June 2017. Of these studies, 15 were excluded from subsequent analysis since they did not include diabetic patients or any intervention for DKD (Fig. 1). Of the remaining 34 studies, 22 were published and 12 were unpublished. The results of seven studies were recorded in the ClinicalTrials.gov registry, with a direct link provided between these studies and publications in peer-reviewed journals of 11 other studies. Publications on two studies were identified by searching the PubMed/Google Scholar databases, and in two cases, published manuscripts were sent directly to the authors by the PIs. Regarding the unpublished studies, we received answers from six of the 12 PIs or sponsors contacted. Of these, three asserted they were in the process of finalizing the paper or submitting it to journals; two stated that the reasons for failure to publish were "adverse effect" of the testing drug (one case) and "no funds" (one case); and one declared that the results were only available on the sponsor's website. The FDAAA requires the results of clinical trials to be published within 1 year after the completion of the study; thus, in accordance with the FDAAA, in our analysis of publications we considered only those trials completed before 2016 ($n = 32$). Of these, 22 studies (69%) had been published, with a mean time to publication of 26.5 (median 23.5, standard deviation [SD] 16.5) months for published studies completed before 2016 and for which the primarly dates were available (n = 18). Thus, only 33% of the studies analyzed met all FDAAA criteria (Fig. 2).

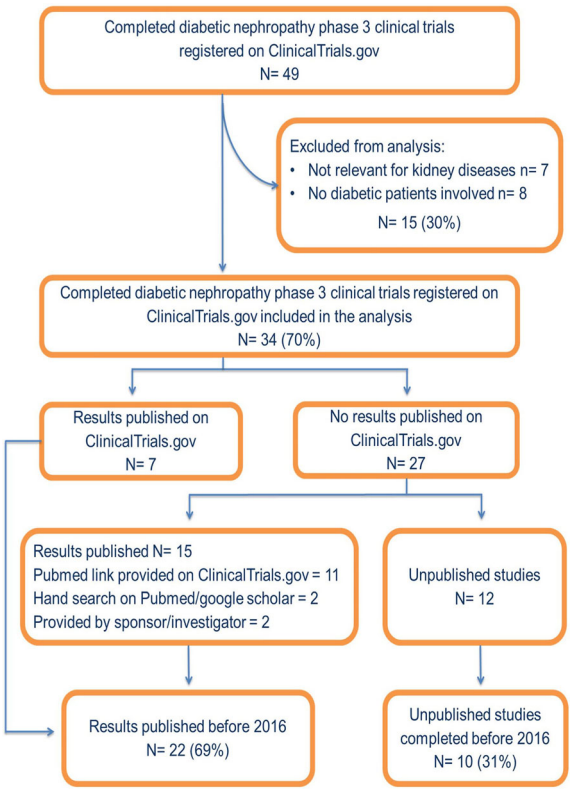

Fig. 1 Study flow diagram of the identification of published and unpublished phase III clinical trials on diabetic nephropathy in the ClinicalTrials.gov registry

Characteristics of Clinical Trials

The interventions tested were either compared to a placebo control group (20 studies; 59%), to another intervention or to standard care (11 studies; 32%), or to no intervention (3 studies; 9%). Most of the studies (30/34) included renal parameters as primary or secondary outcomes. Overall, 16 different renal parameters were measured to study the effect of interventions on the renal system. Of these, proteinuria and glomerular filtration rate (GFR) were main renal parameters analyzed—in 23 and 14 clinical trials, respectively; progression to ESRD was tested in only three studies (Fig. 3). None of the 34 studies performed a gender-specific analysis; allocation of participants in groups was predominantly randomized (88%). The interventions tested included 26 different categories, with the most represented drug classes being angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-II receptor blockers (ARBs). Data on 11 different interventions, 19 renal outcomes, and more than 1000 patients remained undisclosed (Table 1).

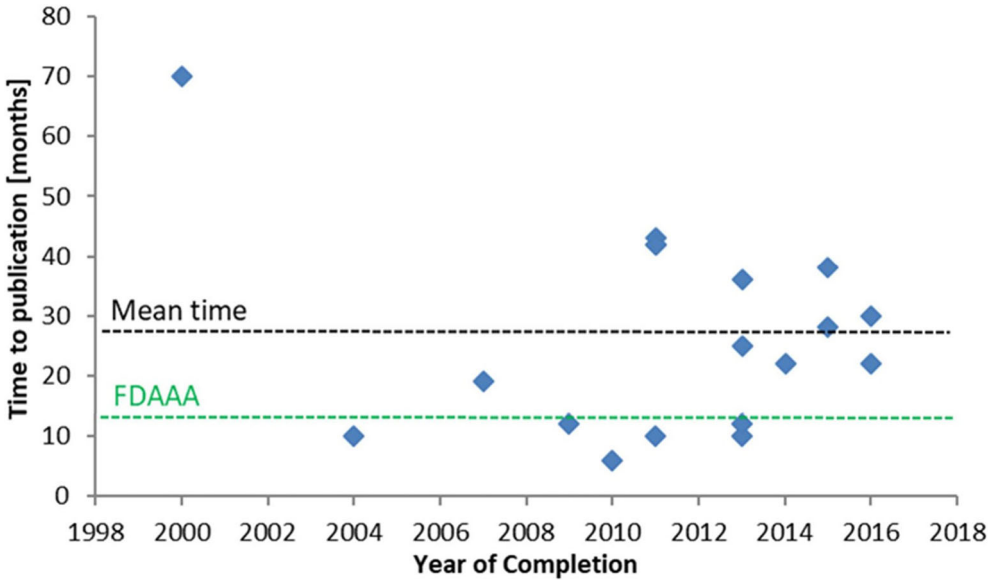

Fig. 2 Time to publication of completed phase III clinical trials on diabetic nephropathy (completed before 2016) for which the primary completion dates were available on on ClinicalTrials.gov. Time to publication indicates the number of months between the primary completion date of the clinical trial and the date of publication of the results. *FDAAA* Timeline mandated by the U.S. Food and Drug Administration Amendments Act of 2007

Interventions Efficacy on Renal Outcomes

The effects of interventions on the renal outcomes described in the 22 published studies are summarized in Table 2 [12–32]. Two-thirds (77%) of the published studies versus 25% of the non-published studies compared the interventions to a placebo control group. The most common interventions were ARBs (7 studies) and/or ACEi (5 studies). The cohort size in these studies varied between 22 and 11,140 patients. Whereas most studies included solely patients with T2DM, two studies included patients solely with T1DM [17, 18], and two studies included patients with either T1DM or T2DM [24, 33]. No improvement on renal outcome parameters, such as proteinuria/albuminuria and/or GFR, was reported for most medications [12, 14, 16, 19, 20, 24, 26–30, 32]. Proteinuria/albuminuria was improved only by the addition of ARB treatment to the standard therapeutic regimen [13, 17] or by the addition of vitamin D_3 to the standard therapy (study NCT00552409). The addition of sodium–glucose cotransporter 2 inhibitors reduced the urine albumin-to-creatinine ratio (UACR) but not the GFR, but only when added to the standard therapy [31]. Medication with ACEi and a diuretic in addition to standard therapy [25] reduced the risk of DN.

Relative and Absolute Risk Reduction

Two published clinical trials obtained significant risk reduction of renal events. Patel et al. described a relative risk reduction of 21% for a combined endpoint (total renal events) [25], and Haller et al. described a relative risk reduction of 16% for new onset of microalbuminuria [26]. For these two trials, absolute risk reduction (ARR) and number needed to treat (NNT) were calculated (Table 3). Combined intervention with perindopril + indapamide in addition to current therapy [25] reduced the relative risk of nephropathy and of new microalbuminuria by 18 and 21%, respectively. This means that 159 patients need to be treated to prevent new onset or worsening nephropathy in one patient (ARR 0.6%), and 25 patients need to be treated to prevent new onset of microalbuminuria in one

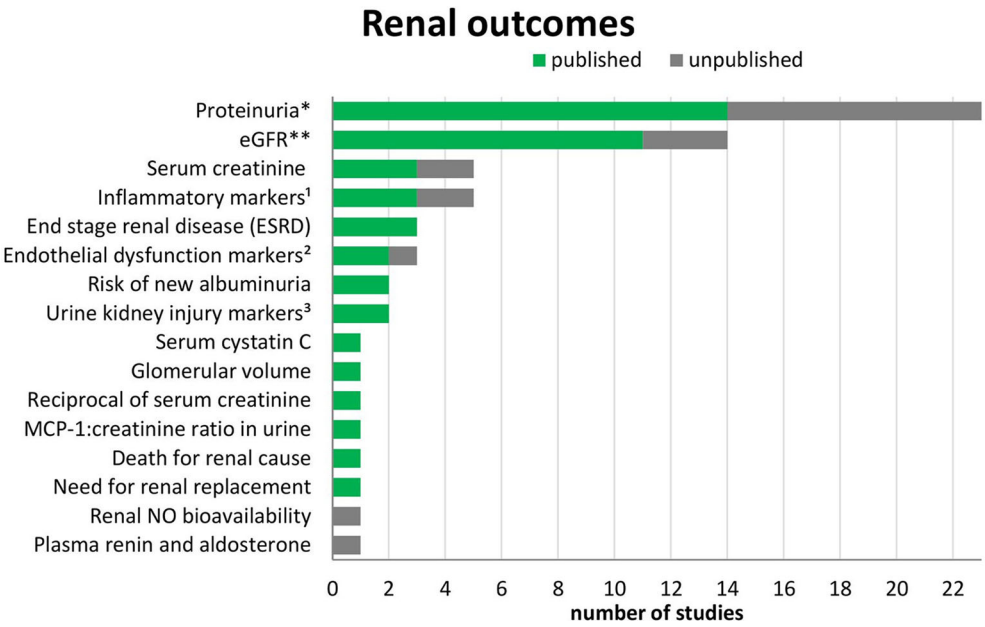

Fig. 3 Renal parameters measured as the primary or secondary outcomes in the 34 completed phase II clinical trials on diabetic nephropathy included in our analysis. Bars indicate the number of published (green) and unpublished (grey) studies which measured the outcomes (*Y-axis*). Four studies did not measure any renal outcome. Proteinuria (single asterisk) was measured by the following different methods: urine-albumin concentration ratio (n = 9 studies); urine protein excretion/24 h (n = 5 studies, urine albumin excretion rate (n = 5 studies), not specified (n = 4 studies). Estimated glomerular filtration rate (*eGFR*; double asterisk) was measured by the following different methods: creatinine clearance (modification of diet in renal disease [MDRD] study equation or Cockcroft and Gault equation) (n = 9 studies); clearance of iohexol (n = 2 studies); clearance of iothalamate (n = 1 study) ; not specified (n = 2 studies). Inflammatory markers (superscript 1) were: high-sensitivity C-reactive protein; monocyte chemoattractant protein-1 (*MCP-1*); tumor necrosis factor alpha; interleukin-6; fibrinogen. Endothelial dysfunction markers (superscript 2) were: von Willebrand factor; soluble vascular cell adhesion molecule-1; soluble intercellular adhesion molecule-1; soluble E-selectin. Urine kidney injury markers (superscript 3) were: kidney injury molecule 1; *N*-acetyl-β-D-glucosaminidase; neutrophil gelatinase-associated lipocalin; liver fatty acid-binding protein. *NO* Nitric oxide

patient (ARR 4%). In Patel et al.'s study [26], the absolute risk for new microalbuminuria was reduced by 2% with olmesartan; thus, 63 patients need to be treated to avoid the development of new microalbuminuria in one patient. An effect on ESRD was not found in either of these studies.

DISCUSSION

Since treatment options and decisions are often based on the results of clinical trials, knowledge of the outcome of these studies is of great importance. In our analysis, 31% of the completed phase III clinical trials on DN remained unpublished, which is in line with previous findings on phase III clinical trials on other diseases [34–36]. The high number of undisclosed clinical trials may lead to an underestimation of the relevance of DN in the medical literature and thereby hinder a correct risk–benefit assessment of a certain intervention. It is well known that trials showing a benefit of a drug or device have a much greater chance of full publication than trials showing no benefit [37] due to commercial interest and publication strategy of papers since Editors prefer articles that guarantee citations [10]. In addition to publication bias, adverse events are

Table 1 Characteristics of the completed phase III clinical trials on diabetic nephropathy that were not published (n = 12)

NCT	Intervention	Intervention category	Question/aim	Cohort	Completion date
NCT00362960	Olmesartan	ARB	Effect of olmesartan vs. losartan on proteinuria, renal function, and inflammatory markers	300 diabetic patients with DN	09-2004
NCT00782847	DiaNeal: behavior-modifying support program	Behavioral	Effect on deterioration of kidney function and on glycemic control	125 diabetic patients with DN	01-2007
NCT00556465	*N*-Acetylcysteine	Antioxidant	Effect on proteinuria, blood pressure, serum creatinine, glomerular filtration rate, C-reactive protein	60 diabetic patients with DN	06-2007
NCT00297401	Ruboxis-taurine	PKCi	Effects of PKC inhibition on renal and peripheral hemodynamic function	20 T1DM patients with evidence of early DN	11-2007
NCT00663949	Captopril + pentoxifylline	ACEi + TNFa blocker	Effect of captopril vs. combination of captopril and pentoxifylline on reducing proteinuria	70 diabetic patients with DN	01-2008
NCT00507494	Pioglitazone	TZD	Effect on proteinuria and renal function of kidney transplant recipients with T2DM	Not provided	09-2009
NCT00765830	Vildagliptin	DPP-4i	Safety and tolerability of vildagliptin and effect on renal insufficiency	349 diabetic patients with renal insufficiency	04-2011
NCT01219959	Dianeal, extraneal, nutrineal (D–E–N)	Peritoneal dialysis solution	Effect of D-E-N vs. DiaNe only on glycosylated hemoglobin, glycemic control medication usage, hypoglycemic events, nutritional status, quality of life	71 diabetic CAPD patients	07-2011
NCT01875341	NCPAP	Respiratory device	Effect of NCPAP vs. NCPAP sub-therapeutic treatment on blood pressure, renin, and aldosterone, sympathetic activity	16 diabetic patients with DN	02-2015
NCT01847313	Liraglutide	GLP-1	Effect on DN by reducing inflammation in the kidney	20 diabetic patients with diabetic kidney disease	11-2015

Table 1 continued

NCT	Intervention	Intervention category	Question/aim	Cohort	Completion date
NCT00503152	Benazepril + valsartan	ACEi + ARB	Effect of benazepril + valsartan combination vs. benazepril or valsartan alone on microalbuminuria and cardiovascular events	613 diabetic patients	09-2016
NCT02807974	CS 3150 + ARB or ACEi	Mineralocorticoid receptor antagonists	Safety of administration and effect on blood pressure and albuminuria	51 diabetic patients with albuminuria	03-2017

ACEi Angiotensin-converting enzyme inhibitor, *ARB* angiotensin-II receptor blocker, *DN* diabetic nephropathy, *DPP-4i* dipeptidyl peptidase 4 inhibitor, *GLP-1* glucagon-like peptide 1, *NCPAP* nasal continuous positive airway pressure *NCT* ClinicalTrials.gov registry number, *PkCi* protein kinase C iota type; *T2DM* type 2 diabetes mellitus, *TNFa* tumor necrosis factor alpha, *TZD* thiazolidinediones

often poorly described. Some studies fail to report the incidences of severe, serious, and fatal adverse events, such as in cancer drug trials [38]. The failure to publish negative results and the underestimation of adverse events lead to an accumulation of literature favoring the benefits of treatments [10].

Further, we found that the time to publication of results was longer than that recommended by FDAAA, with a mean time to publication of 26.5 months compared to the 12 months required by the FDAAA. The effect is a delay in reporting therapeutic strategies. A comparison of results from the various studies, however, remains difficult since study design and the renal outcome parameters vary greatly between the studies.

Overall, the interventions reported in each study, which were aimed at improving renal outcomes, showed low efficacy. The initial clinical evidence of renal involvement in patients with T2DM is usually the appearance of microalbuminuria, which has been defined as a urine albumin excretion rate (UACR) of 30–299 mg/24 h [39]. Patients with diabetes mellitus and microalbuminuria are at high risk of developing overt progressive DN [12]. Urinary albumin concentrations in the upper normal range have been reported to predict both cardiovascular and renal events in both high- and low-risk populations. For these and other reasons, some authors suggest the treatment of urinary albumin excretion as a continuous variable [40]. Proteinuria was measured in many of the clinical trials analyzed (14/34 published trials), indicating that it is used as an important predictor of renal outcome when evaluating DN (Fig. 3). A decline in eGFR was also broadly used to assess the effectiveness of interventions, but only a few studies investigated the risk of ESRD because it requires long-term trials. The measurement of urine protein excretion and eGFR varied greatly among the studies, complicating a reliable comparison of the outcomes [41]. This comparison is further complicated by the fact that current clinical recommendations for the treatment of DN are based on results that in the initial study investigated another primary endpoint (usually glucose therapy), with renal outcome evaluated only secondarily. The

Table 2 Characteristics of the completed phase III clinical trials on diabetic nephropathy that were published (n = 22): effects on renal outcomes

NCT	Intervention	Cohort	Effect	Publication
NCT00130208	Sulodexide (glycosaminoglycan) vs. Placebo	1056 DM2 patients with DN	Sulodexide failed to decrease urine albumin excretion	*Lewis EJ et al. Am J Kidney Dis. (2011)*
NCT00141453	Olmertasan (ARB) in addition to standard therapy (ACEi) vs. Placebo	577 Asian DM2 patients with DN	Olmesartan reduced blood pressure and proteinuria but had no effect on primary composite outcome of doubling of serum creatinine, end stage renal disease and death	*Imai E, Chan JCN et al. Diabetologia (2011)*
NCT00340678	Losartan (ARB) vs. Placebo	169 American Indians DM2 with normoalbuminuria or microalbuminuria	No effect on GFR (primary outcome) Effect on some structural features of kidney only in the microabuminuric group	*Weil EJ et al. Diabetes (2013)*
NCT00354341	Epoetin beta vs. Placebo	172 DM patients with CDK	No effect on GFR and no change in urine protein excretion	*Ritz E et al. Am J Kidney Dis. (2007)*
NCT00136188	NG-monomethyl-L-arginine (L-NMMA) (blockade of NO synthases)	84 DM2 patients with normal renal function	NOS inhibition with L-NMMA provoked an increase in UACR This finding was evident in patient groups prone to endothelial dysfunction and albuminuria, therefore cannot be extrapolated to the general population	*Ott C et al. Diabetes (2011)*
NCT00274118	Telmisartan (ARB) vs. Enalapril (ACEi)	250 DM2 patients with early nephropathy	Telmisartan was not inferior to Enalapril in preventing the progression of renal dysfunction, measured as the decline in the GFR. No differences in change of GFR, serum creatinine, urinary albumin excretion and rates of ESRD between the two drugs	*Barnett AH et al. N Engl J Med (2004)*
NCT00738660	Telmisartan (ARB) + Ramipril (ACEi) (crossover)	30 DM1 patients with micro or macroalbuminuria	The dual blockade with Telmisartan and Ramipril had complimentary significant effect on lowering of the BP, but similar beneficial effect on the nocturnal dipping was not observed possibly due to inappropriate chronotherapy. Reduction in albumin excretion rate	*Anantharaman R et al. Indian J Med Res (2011)*
NCT00552409	Vitamin D3 in addition to standard therapy (ACEi or ARB) vs. Placebo	22 DM patients with early kidney disease.	Mean UACR on treatment was 17% lower among participants assigned to Vit D3 compared to participants assigned to placebo	*ClinicalTrials.gov*
NCT00594152	Pulsatile intravenous insulin therapy (PIVIT) in addition to Diabetes Control and Complications Trial (DCCT) intensive therapy (IT) regimen.	90 type DM 1 patients with nephropathy	PIVIT added to IT slowed the decline of creatinine clearance showing to reduce the progression of diabetic nephropathy. The effect appears independent of ACE inhibitor therapy, blood pressure, or glycemic control. No decrease in urine protein excretion	*Dailey GE et al. Metabolism (2000)*
NCT01092390	Long-chain n-3 polyunsaturated fatty acid (n-3 PUFA) vs. Placebo	29 DM2 patients	n-3 PUFA had significant effects on urine NGAL excretion compared to placebo. No significant effect on urine albumin excretion, on serum markers of kidney function and on GFR. In subgroup analyses, there were significant decreases in 24-h urinary excretion of albumin, NGAL, LFABP, and NAG among participants taking medications that block the renin-angiotensin-aldosterone system (RAAS)	*Miller III ER et al. Diabetes Care (2013)*
NCT01204528	Paracalcitol vs. Placebo	Two groups of patients (n=72) 1) CKD 2)CKD+DM.	No renal outcomes	*Lundwall K et al. Am J Nephrol (2015)*

Table 2 continued

NCT01419912	Soy milk vs. cow milk	25 DM2 patients with DN	Soy milk had no significant effects on inflammatory markers (tumor necrosis factor-a, interleukin-6, high-sensitivity C-reactive protein)	*Miraghajani MS et al.* *Diabetes Care (2012)*
NCT01835678	Linagliptin (DPP-4i) vs. Placebo	62 DM2 patients	Linagliptin prevented upregulation of basal NO activity; UACR increased in the placebo group but not in the linagliptin group. No significant effect on renal plasma flow, GFR and intrarenal hemodynamics; no change in tubular markers; linagliptin reduced hs-CRP but not MCP-1	*Ott C et al.* *Diabetologia (2016)*
NCT00317915	Irbesartan (ARB) vs. Placebo	590 DM2 patients with microalbuminuria	Endothelial dysfunction and inflammation markers (vWf Plasma sVCAM-1 sICAM-1 Interleukin-6) are novel predictors of progression to DN in DM2 and persistent microalbuminuria, independently of traditional risk factor	*Persson F et al.* *Scandinavian Journal of Clinical and Laboratory Investigation (2008)*
NCT01831193	Curcumin vs. Placebo	101 Mexican patients with nondiabetic or diabetic proteinuric CKD (51% diabetic)	Curcumin did not improve proteinuria and eGFR; in plasma enhanced antioxidant capacity in subjects with diabetic proteinuric CKD. No effect was observed on the antioxidant enzymes activities or Nrf2 activation	*Jiménez-Osorio AS et al.* *Journal of Renal Nutrition (2016)*
NCT00145925	Perindopril (ACEi) + Indapamide (Diuretic) in addition to current therapy vs. Placebo	11140 DM2 patients	Intervention did reduce the risk of nephropathy (development of macroalbuminuria, doubling of serum creatinine, need for renal replacement therapy, or death due to renal disease). Reduction of systolic and diastolic blood pressure	*Patel A et al.* *Lancet (2007)*
NCT00185159	Olmesartan (ARB) vs. Placebo	4447 DM2 normoalbuminuric patients	Olmesartan was associated with a delayed onset of microalbuminuria. No change in eGFR and serum creatinine. ESRD did not develop in any patient	*Haller H et al.* *N Engl J Med (2011)*
NCT00157586	Manidipine (CCB)/Delapril (ACEi) vs. Delapril alone vs. Placebo	380 hypertensive type 2 diabetics with albuminuria	Combined treatment failed to slow GFR decline and progression to micro/macroalbuminuria or regression to normoalbuminuria	*Ruggenenti P et al.* *Hypertension (2011)*
NCT00800683	Linagliptin (DPP-4i) added to preexisting therapy vs. Placebo	133 DM2 patients with severe chronic renal impairment	Average eGFR values did not decrease by a clinically meaningful degree with either linagliptin or placebo	*McGill JB et al.* *Diabetes Care (2013)*
NCT01316094	Ipragliflozin (SGLT2i) vs. Placebo	165 DM2 patients, Japanese with mild or moderate renal impairment (RI)	No renal outcomes	*Kashiwagi A et al.* *Diabetes, Obesity and Metabolism (2014)*
NCT01087502	Linagliptin (DPP-4i) + Glimepiride (sulfonylurea) vs. Placebo	235 DM2 patients with moderate or severe renal impairment	eGFR remained stable throughout the 52 weeks in both groups	*Laakso M et al.* *Diabetes Care (2015)*
NCT01164501	Empagliflozin (SGLT2i) in addition to standard therapy vs. Placebo	741 DM2patients with micro/macroalbuminuria	Empagliflozin reduced UACR by a clinically meaningful amount; this effect was largely independent of the known metabolic or systemic haemodynamic effects of this drug class; no significant change in eGFR	*Cherney D et al.* *Diabetologia (2016)*

CCB Calcium channel blocker, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESRD* end stage renal disease, *hs-CRP* high-sensitive C-reactive protein, *LFABP* liver fatty acid–binding protein, *MCP-1* monocyte chemoattractant protein-1, *NAG* *N*-acetyl b-D-glucosaminidase, *NGAL* neutrophil gelatinase-associated lipocalin, *NOS* NO synthase, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *slCAM-1* soluble intercellular adhesion molecule-1, *sVCAM* soluble vascular cell adhesion molecule-1, *T1DM* type 1 diabetes mellitus *UACR* urine albumin-to-creatinine ratio, *vWF* von Willebrand factor

Table 3 Risk reduction of renal events in two completed phase III clinical trials on diabetic nephropathy

Studies	Relative risk reduction (%)	NNT[a]	ARR[a] (%)
Perindopril + indapamide (Patel et al. 2007) [25]			
Total renal events[b]	21	22	5
New or worsening nephropathy[c]	18	159	0.6
New microalbuminuria	21	25	4
All deaths	14	89	1
Olmesartan (Haller H et al. 2011) [26]			
New microalbuminuria	16[a]	63	2

[a] Values of NNT (needed to treat) and ARR (absolute risk reduction) were calculated from data in publications

[b] New or worsening nephropathy + new microalbuminuria

[c] Development of macroalbuminuria; doubling of serum creatinine to a level of at least 200 μmol/L; need for renal replacement therapy; or death due to renal disease

DCCT/EDIC study showed that only 24 of 1441 patients developed ESRD after more than 25 years of observation. The ARR was only 1.7% with a NNT of 74 patients due to intensive glucose therapy in patients with T1DM [42]; in patients with T2DM similar results were shown. The mega-trials (ACCORD, ADVANCED, VADT, and UKPDS) only showed weak effects on micro- and macroalbuminuria, with an ARR of 1.0 and 0.3%, respectively, and an NNT of between 91 and 333 patients, without any relevant effect on ESRD by intensive glucose-lowering treatment [43]. In addition, empagliflozin seems to be a new treatment option for DN, but the main effects shown to date are on surrogate parameters, such as creatinine doubling (ARR 1%, NNT 20) and worsening of albuminuria (ARR 5%, NNT 20), while ESRD occurred with an ARR of 0.3% and NNT of 310 [44]. Almost two-thirds of all trials were placebo-controlled, with a higher percentage of placebo-controlled trials in published studies than in unpublished trials (77 vs. 25%, respectively). Placebo-controlled trials produce strong evidence of the effectiveness of a new intervention, limited only by the statistical uncertainty of the outcome [45]. However, knowledge about the relative efficacies between various drugs is also needed for decision-making in clinical practice. In our analysis, only one study [27] compared an intervention to both placebo and another drug(s).

The most represented drug classes in all trials were ACEi and ARBs. Angiotensin-II receptor blockers are renoprotective in hypertensive azotemic patients with T2DM, but their efficacy in early DKD is uncertain. Findings support the current recommendation that inhibitors of the renin–angiotensin–aldosterone system should not be used for primary prevention of DN in normotensive normoalbuminuric persons with diabetes. However, these medications seem to mitigate the progression of DKD when used after the onset of microalbuminuria. ACEi has demonstrated efficacy in reducing cardiovascular risk [27] and, in combination with diuretics, and also shown to correlate with a reduced risk of developing microalbuminuria [25]. However, their effects on preventing DN progression have been less clear, and they have failed to reduce the decline in GFR [21, 23]. A growing body of evidence indicates that the decline in GFR might occur irrespectively of the progression of albuminuria in non-proteinuric DN phenotypes [46]. Altogether, these data call for an early intervention that targets potential mediators of renal dysfunction other than proteinuria to prevent or slow GFR decline already at the stage of normoalbuminuria. In this regard, the role of reactive metabolites [47] and inflammation in the progression to DN is gaining attention. The mechanisms involved are little understood, with evidence of increased inflammatory cytokines (monocyte chemoattractant protein 1 [MCP-1], human tumor necrosis factor alpha [TNF-α)], and mononuclear infiltrates in the glomeruli and tubulointerstitium that would contribute to the progression of DN [45]. Endothelial dysfunction and inflammation markers (von Willebrand factor [vWf], plasma soluble vascular cell adhesion molecule-1 [sVCAM-1], soluble intercellular adhesion molecule-1 [sICAM-1] and interleukin-6 [IL-6])

have been found to be correlated to DN onset in patients with T2DM and microalbuminuria, independently of traditional risk factors [19]. Clinical trials included in our analysis showed poor effects on inflammatory markers. Soy milk showed no significant effect on inflammation [TNF-α, IL-6 and C-reactive protein [CRP]) compared to cow milk [21], while linagliptin, a dipeptidyl peptidase-4 inhibitor, reduced CRP but not MCP-1 [22]. Further, two studies testing the effect of ARBs and liraglutide on kidney inflammation, remained unpublished (Table 2). Curcumin and long-chain –3 polyunsaturated fatty acids are examples of new interventions, as an alternative to RAAS blockade. Unfortunately, in two studies these supplements were not able to reduce proteinuria and to affect GFR [15, 20]. Conversely, vitamin D and its analogs, which activate the vitamin D receptor, were able to reduce proteinuria, inflammation, and glomerulosclerosis in animal models of DKD [48]. One small trial investigating the effect of vitamin D_3 in addition to standard therapy in 22 DM patients with early kidney disease, obtained a 17% reduction of mean UACR (ClinicalTrials.gov; NCT00552409). Pentoxifylline (phosphodiesterase inhibitor), ruboxistaurine (protein kinase C inhibitor), and *N*-acetylcysteine (antioxidant) are promising molecules that showed renoprotective effect in a mouse model and in small trials on humans [48]. The data and outcomes from patients treated with these experimental drugs are as yet not available for assessment due to a delay or failure to publish (Table 1).

This analysis has some limitations. Since ClinicalTrials.gov is considered the most relevant clinical trial registry, we did not investigate other databases. In addition, the investigation of a clinical trial registry implies that only registered trials were included in our analysis. In order to prevent classifying a trial as unpublished, we conducted an exhaustive literature search in two major databases (i.e., PubMed and Google Scholar) with multiple search terms and contacted investigators or sponsors. This analysis assumes that the entries provided in the ClinicalTrials.gov registry are accurate and complete as mandated by the FDAAA. Our data define the current publication bias in phase III clinical trials investigating DN. We hope that the publication efforts will increase over time.

CONCLUSION

The need for a better publication discipline of clinical trials is obvious based on our study which found that data on 11 different interventions and more than 1000 patients remained undisclosed. Transparency in clinical research has the potential to improve patient care and prevent patients from being exposed to redundant research. The outcome of the phase III clinical trials included in our study was quite limited, and the need for new approaches to prevent or slow the progression of DN is obvious. Several mechanisms underlying DN pathophysiology have been elucidated, which opens new frontiers for the development of specific DKD therapies. Experimental therapies targeting inflammatory, oxidant, or pro-fibrotic pathways activated during DKD are currently under investigation in phase II and III clinical trials [48].

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Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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