Should We Still Believe in Randomized Controlled Trials in Nephrology?

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Abstract

The randomized controlled trial (RCT) is the cornerstone upon which clinical decision-making is based. Pivotal RCTs in the nephrology area efficiently demonstrated the renoprotective effects of treatment with renin-angiotensin system inhibitors in patients with diabetic and non-diabetic proteinuric nephropathies. However, there is concern about the increasing cost, complexity and duration of clinical studies. Moreover, recent large RCTs addressing key issues for patients with renal disease failed to achieve definitive conclusions mainly due to critical flaws in the investigational strategies, including the adoption of excessive/fixed doses of the study medications, inappropriate use of the placebo-controlled design, enrollment of low-risk individuals, poor reporting of adverse events or unreliable evaluation of renal function. The information now available on the biases that characterize the current RCTs should serve as a tool to rethink the design, patient selection and implementation of future RCTs in nephrology.

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Chronic kidney disease (CKD) is increasingly recognized as a major public health problem worldwide. In the past 20 years, age-standardized death rates from CKD increased by 15%, whereas rates for other non-communicable diseases declined, including major vascular diseases, pulmonary disorders, most forms of cancer and liver cirrhosis [1]. Despite this, it has been claimed that in the past 20 years, kidney research has been associated with a lower number of randomized controlled trials (RCTs) as compared to other medical specialties [2]. This is not true, however, if one corrects for the number of patients affected and the dedicated investigators. Nevertheless, the reputation of randomized trials has suffered owing to concern about increasing complexity, study design, expense, time required to recruit study participants, as well as inadequate representativeness of enrollees for the general patient population [3]. Clearly, this dismal state of affairs has created a challenge for nephrologists to improve clinical decision-making upon the basis of high-quality RCTs.

Successful RCTs in Nephrology

Pioneering large, simple RCTs were designed to address straightforward questions about the value of novel therapeutic strategies on important health outcomes, such as renal disease progression to end-stage renal dis-

ease (ESRD) and mortality. Studies of this kind were useful to demonstrate the renoprotective effects of renin-angiotensin system (RAS) inhibition in patients with diabetic nephropathy. Indeed, Bjorck et al. [4] reported that, at comparable blood pressure, the angiotensin-converting enzyme inhibitor (ACEi) enalapril reduced the rate of glomerular filtration rate (GFR) decline more than the treatment with a beta blocker in type 1 diabetic patients with overt nephropathy. In 1993, the seminal Collaborative Study [5] found less progression to the combined endpoint of doubling serum creatinine, ESRD or death while on the ACEi captopril compared to placebo in 409 patients with type 1 diabetes and overt nephropathy. Almost 10 years later, the Reduction of Endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial [6] and the Irbesartan in Diabetic Nephropathy Trial [7] showed that angiotensin-receptor blocker (ARB) treatment, as compared with placebo, reduced the incidence of a composite endpoint of doubling of serum creatinine concentrations, ESRD, or death by 16 and 19%, respectively, in 2 large cohorts of patients with type 2 diabetes and overt nephropathy. Renoprotection was associated with a significant reduction in urinary protein excretion; this finding remained significant after adjustment for the small differences in blood pressure control between treatment groups. Independent of treatment allocation, both trials showed that an early reduction in urinary protein excretion was associated with slower renal function loss and reduced cardiovascular mortality in the long-term [8]. The first observation that RAS inhibition can prevent the development of overt proteinuria was provided by the Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients (IRMA)-2 study, an RCT involving 590 hypertensive patients with type 2 diabetes and microalbuminuria [9]. A median of 2-year treatment with full dose (300 mg/day) irbesartan was associated with a threefold reduction in the incidence of macroalbuminuria compared with placebo [9]. Similar studies have also efficiently demonstrated the renoprotective effects of ACEi therapy in patients with non-diabetic progressive chronic nephropathies. Indeed, prior to 1995, several small, randomized trials tested ACEi treatment in patients with non-diabetic renal disease, but they did not report uniform results. Possible sources of variability included different methods to measure renal function, different causes and severity of renal disease, use of different ACEi, and small sample sizes. Then, the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency study showed that the ACEi benazepril reduced the risk

of serum creatinine doubling compared to placebo in patients with non-diabetic CKD, but a difference in blood pressure between the 2 treatments left open the question of whether the renoprotective effect of the active drug was related to its antiproteinuric property or to better pressure control [10]. Convincing evidence of the renoprotective potential of ACEi therapy was first provided by the triad of *Lancet* publications generated by the Ramipril Efficacy in Nephropathy study from 1997 to 1999 [11]. At equivalent blood pressure control, the ACEi ramipril reduced the rate of GFR decline and halved the risk of progression to ESRD compared to placebo in patients with non-diabetic proteinuric nephropathies [11]. Ramipril-treated patients also enjoyed a greater decrease in proteinuria that inversely correlated with the rate of GFR decline, indicating that nephroprotection was eventually linked to the reduction of protein traffic through the glomerular capillary barrier [11]. As large-scale trials became an accepted way to evaluate new therapies, the original intent of simplicity was lost while large sizes were maintained, leading to increasingly complex trials. Indeed, between 2002 and 2012, the average number of eligibility criteria in a typical phase 3 protocol dramatically jumped from 31 to 50 and the mean number of study procedures increased from 106 to 167 [12]. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuing costs.

Failure of Recent RCTs in Nephrology

A number of recent RCTs addressing core issues for patients with renal diseases failed to draw firm conclusions because of crucial flaws in the investigational strategies, such as adoption of too high and/or fixed doses of study drugs, inappropriate use of the placebo-controlled design, enrollment of low-risk patients, poor reporting of adverse events or unreliable assessment of renal function.

Inappropriate Selection of Drug Dose

The adoption of too high and/or fixed doses of investigational compounds can inflate the incidence of adverse events and can lead to the early closure of an RCT for safety reasons, eventually precluding the opportunity to demonstrate clinically relevant treatment effects. This issue has been illustrated by the Veteran Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial that compared double RAS blockade with the ACEi lisinopril plus ARB losartan versus losartan monotherapy on a primary com-

posite endpoint of changes in estimated GFR (eGFR), ESRD and death in 1,448 patients with type 2 diabetes and overt nephropathy [13]. The study was prematurely terminated because of concerns about a high prevalence of hypotension, hyperkalaemia and acute kidney injury with dual RAS therapy. In fact, these adverse events could have been prevented by avoiding forced ACEi up-titration (up to 40 mg lisinopril daily, in patients with an eGFR as low as 30 ml/min/1.73 m²) on top of full-dose losartan. Of note, at study closure dual versus single RAS inhibition had already reduced ESRD events by 34%, a treatment effect never reported before in type 2 diabetes. Risk reduction was associated with a significantly greater decline in proteinuria and approached nominal significance ($p = 0.07$) over just 2.2 years of follow-up. In the RENAAL study, in a similar cohort of patients with type 2 diabetes, the larger antiproteinuric effect of losartan was associated with a similar (28%) ESRD reduction compared to placebo. The treatment effect was, however, not still appreciable at 2.2 years, but became statistically significant over the planned 3.2 years of follow-up [6]. These data strongly suggest that even in the VA NEPHRON-D trial, ESRD events could have been significantly reduced over the initially scheduled 5-year study period. Of course, dual blockade therapy requires diligence by clinicians to ensure that RAS inhibition is held during acute illness, but the benefits are clearly worth the extra effort.

Inappropriate Use of the Placebo-Controlled Design

Clinical trials of novel medications should not use a placebo control group when proven effective therapies already exist for the condition, preferring active controls. Indeed, superiority trials over placebo may allow drugs into the market that are in fact less effective or safe than those already available, and do not help define the clinical value of new medications with respect to treatments currently in use. In this regard, the Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) was the first large-scale trial designed to assess whether an ACEi could prevent the onset of microalbuminuria in hypertensive but normoalbuminuric patients with type 2 diabetes [14]. Overall, 1,204 patients were randomized to the ACEi trandolapril alone, the calcium-channel blocker verapamil alone, trandolapril plus verapamil or placebo. After 3.6 years of follow-up, trandolapril alone or in combination with verapamil reduced the risk of progression to microalbuminuria from 10.9 to 5.8% compared to non-ACEi therapy, an effect that was observed at comparable blood pressure control [14]. A virtually identical study, the Randomised Olmesartan and Diabetes Microalbu-

minuria Prevention (ROADMAP) trial, was published 7 years later with an ARB instead of an ACEi in 4,447 patients with type 2 diabetes and normoalbuminuria. After 3.2 years of follow-up, olmesartan therapy reduced the incidence of microalbuminuria compared to placebo from 9.8 to 8.2%, an effect that was no longer significant when adjusting for blood pressure in the 2 treatment arms [15]. The use of a placebo-controlled design for ROADMAP appeared questionable considering that BENEDICT had already demonstrated a clear benefit of trandolapril in preventing microalbuminuria in a similar patient population. The inclusion of an ACEi arm in ROADMAP could have informed about the renoprotective effects of olmesartan in relation to those of trandolapril. A comparative study would have provided data as well on the adverse event rates associated with these treatments, since indirect comparison of hard outcomes from ROADMAP and BENEDICT indicated a higher risk of cardiovascular mortality with olmesartan than with trandolapril [16].

Post-Treatment Assessment in RCT Design

RAS blockade has been almost universally considered the key approach for renoprotection in proteinuric diabetic and non-diabetic kidney diseases, mainly via its ability to prevent the development of proteinuria or lowering urinary protein excretion rate in patients already with overt nephropathy. However, at least for the prevention target, most studies do not provide formal evidence that indeed RAS blockade is capable, for example, to prevent the appearance of microalbuminuria in type 2 diabetes [14, 15], since post-treatment assessment is not usually included in the RCT design. Instead, if microalbuminuria becomes apparent after stopping RAS blockade, then the conclusion would be that these drugs are anti-proteinuric. Therefore, a critical issue in RCT design would be to always include a short post-treatment assessment period that could help to get insights on the mechanism(s) of the potential renoprotection of drugs under investigation, as shown by the sub-study of the IRMA-2 [17] and the Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 diabetes (BEAM) study [18].

Enrollment of Low-Risk Patients

Trial enrollment of patients with low risk for outcome events may dilute or even mask any real treatment effect. As an example, a post-hoc analysis of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) suggested that

combined therapy with the ACEi ramipril and ARB telmisartan increased the risk of the pre-specified composite endpoint of any dialysis, serum creatinine doubling or death compared with either agent alone in 25,620 patients with atherosclerotic disease and/or diabetes with end-organ damage [19]. However, the excess of adverse renal outcomes on combination therapy was mainly driven by the more frequent need for short-term dialysis, conceivably a treatment-related acute effect on renal hemodynamics that is reversible upon treatment withdrawal [20]. Conversely, the incidence of ESRD was similarly rare in the 3 groups, reflecting the slow rate of renal function loss that, independent of treatment allocation, was close to that observed in the general population as a result of aging and also similar to that reported in patients who have diabetes or hypertension, without proteinuria [21]. Indeed, the slow rate of GFR decline and the lack of any appreciable improvement in renal outcomes following RAS inhibitors therapy can be largely explained by the fact that only 4% of the study participants had overt proteinuria [20]. This observation highlights that the ONTARGET renal sub-study was actually off target, due to the selective bias of patients with low-risk renal disease progression, given the lack of proteinuria in most of them [20]. In proteinuric nephropathies, proteinuria reduction is one important treatment target [22], and dual RAS blockade is the most efficient way of achieving this target [23]. Thus, the ONTARGET sub-study findings should not be extended to patients with chronic proteinuric nephropathies, in whom proteinuria reduction can delay or even prevent the progression of renal disease towards ESRD.

Poor Reporting of Adverse Events

Excessive optimism that stemmed from positive preliminary results can cause the importance of troublesome adverse reactions to be overlooked. A paradigmatic example is represented by bardoxolone methyl, an anti-inflammatory agent that was tested as a treatment for diabetic nephropathy in the BEAM study, a phase 2, double-blind RCT [18]. Bardoxolone methyl significantly increased eGFR compared to placebo, but the trial report tended to underestimate the adverse event profile of the drug, which included worsening proteinuria, massive weight loss, hypomagnesemia, liver function disarray and gastrointestinal effects. These adverse reactions to bardoxolone methyl were not analyzed in detail and the phase 3 Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (BEACON) trial was ini-

tiated in patients with advanced diabetic nephropathy. Enrollment was completed, but after only 9 months of follow-up, the trial was stopped on the recommendation of its independent data-monitoring committee, which reported a safety imbalance between the bardoxolone and the placebo arms [24]. Adverse events associated with study closure included unintended weight loss, increased proteinuria, and more gastrointestinal symptoms in the bardoxolone group (all already noted in the BEAM study), in addition to higher rates of heart failure and cardiovascular events versus placebo. Of note, later studies conducted in diabetic Zucker rats given the bardoxolone methyl analog RTA 405 reproduced most of the side effects observed in the BEAM and BEACON trials [25], which were, however, attributed to meaningful levels of impurities and/or degradation products in the compound preparation, which could have contributed to the toxicity. Nevertheless, some diabetic rats treated with another bardoxolone methyl analog dh404 (that was free of any potential toxic impurities) but not with vehicle, showed the presence in the kidney of granulomatous and inflammatory process that was suspicious of a pseudotumor [25]. These results were at variance with subsequent study in a similar rat model by investigators from the drug company sponsoring the BEACON trial, who did not find adverse effects of both synthetic bardoxolone analogues [26]. However, it should be pointed out that activation of the nuclear factor erythroid 2-related factor, as it occurs with bardoxolone methyl, in a knockdown model of leptin-deficient mice increased insulin resistance and caused anorexia and hepatic steatosis [27], possibly providing an additional warning sign that this drug may be harmful in particular conditions. Nevertheless, besides the adverse events, the major design pitfall in BEACON was the failure to carefully consider what worked well in terms of patient selection in the phase 2 BEAM trial and the use of a fixed maximal dose of bardoxolone methyl instead of a dose up-titration approach. Thus, the valuable lesson is that a meticulous examination of available clinical data and an unbiased analysis of experimental findings would avert the failure of large-scale RCTs.

Unreliable Assessment of Renal Function

CKD is often characterized by a slow, progressive loss of renal function that may eventually lead to ESRD. GFR estimating equations are widely used in randomized clinical trials testing treatment effects on renal disease progression. These formulas, however, do not allow a rigorous assessment of renal function, and their use may generate misleading information. The importance of this

point can be appreciated analyzing the results of the A Long-Acting somatostatin on DIsease progression in Nephropathy trial due to autosomal dominant polycystic kidney disease (ALADIN); this trial compared the effects of 3-year treatment with Octreotide-LAR or placebo on kidney and cyst growth and renal function decline in patients with autosomal dominant polycystic kidney disease (ADPKD) [28]. At 1 year follow-up, reduction of GFR measured by the plasma clearance of unlabeled iothexol was similar between groups, but subsequent chronic GFR decline from years 1 to 3 was significantly slower with Octreotide-LAR compared to placebo. Intriguingly, when renal function was estimated by the abbreviated Modification of Diet and Renal Disease (aMDRD) equation, no difference in chronic eGFR changes (from years 1 to 3) was observed between the Octreotide-LAR and the placebo groups (Piero Ruggenti, Personal communication). Thus, in the ALADIN trial, the clinically relevant renoprotective effect of Octreotide-LAR would have been missed if GFR had not been measured, but just estimated with equations. In the same vein, the prediction formulas CKD Epidemiology Collaboration and aMDRD unreliably estimated actual GFR values, and failed to predict GFR changes over time in a cohort of adult patients with ADPKD, independent of their kidney function [29]. Similarly, evidence is available that questions the use of any GFR estimation formula to monitor renal disease progression and response to treatment in type 2 diabetics with normo- or microalbuminuria [30]. Therefore, direct measurements of GFR by gold-standard techniques based on the use of suitable exogenous compounds (i.e., inulin, iothexol, iohalamate) would allow a more accurate assess-

ment of the potential renoprotective effects of novel drugs, and should be strongly advised to monitor renal function change in RCTs.

Conclusions

RCTs have become a cornerstone of evidence-based medicine, and therefore have an important impact on clinical decision-making. However, recent trials in the nephrology field achieved inconclusive findings as a result of the inappropriate choice of investigational strategies. Enough information is now available on the biases present in the current RCTs, and should serve as tool to rethink the design, patient selection, implementation and reporting of future RCTs. It should also be appreciated that very large studies do not always represent the best option since they often detect very small, statistically significant differences in outcomes that, however, have little or no clinical relevance. The use of the gold-standard tools, such as measured GFR, to assess treatment effects on renal disease progression would increase the power of statistical analyses, and eventually allow the execution of RCTs with affordable sample size and follow-up duration. Better interactions between academia, pharmaceutical industry and regulatory authorities would be of paramount importance for ensuring the quality, efficacy and safety of drugs in RCTs.

Disclosure Statement

The authors declare no conflicts of interest.

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