Innovations in randomized clinical trials in Nephrology: from study design to patient's activism

In depth review

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ABSTRACT
Current clinical practice is guided by novel robust evidence from randomized clinical trials (RCT). These studies usually follow a rigorous prospective design with pre-defined visits and planned exams during follow-up. In the context of Nephrology, RCTs have been mainly designed to test the efficacy of new therapies in reducing the risk for kidney failure, estimated Glomerular Filtration Rate decline and mortality or cardiovascular events. However, the progress of informatics is reflected in an improvement and expansion of technologies and innovations in present and future RCTs. We here present some innovations and future directions of RCTs in Chronic Kidney Disease patients.

KEYWORDS: Randomized Clinical Trials, Chronic Kidney Disease, Informatics Innovation, Medical Devices, Albuminuria

Introduction

Randomized clinical trials (RCTs) represent, to date, the most robust research tools for generating evidence on the efficacy and safety of new therapies for a given clinical condition [1]. The reliability of randomized studies lies in their prospective, *ad hoc* design, in which one group of subjects (controls) is assigned to the standard of care for the condition under investigation, while another group (active treatment arm) receives the standard of care plus the experimental treatment. The assignment to the control or active arm is random and occurs through randomization, which aims to create two groups of patients with similar characteristics (e.g. age, sex, prevalence of patients with type 2 diabetes, or those treated with diuretics), with the only difference being their assignment to either the active treatment or the control group. This randomization tool therefore allows for the optimal isolation and estimation of the effect of the "new" treatment compared to the standard of care in reducing the incidence of a specific clinical outcome (e.g., reduction in proteinuria or admission to dialysis) or in improving the symptoms of a disease (e.g., improving blood pressure or reducing fatigue).

In the field of kidney diseases, numerous randomized studies have been conducted over the past two decades. They have proven the effectiveness of drugs targeting different mechanisms, such as antihypertensives, erythropoiesis-stimulating drugs, and mineralocorticoid receptor antagonists, in terms of nephroprotection, as well as in reducing mortality and cardiovascular (CV) events, across different patient groups (e.g., diabetic, non-diabetic chronic kidney disease, glomerulonephritis) [2].

Recently, there has been an explosive and rapid increase in drugs available to treat kidney diseases, which has simultaneously led to a rise in the number of randomized studies in Nephrology [3]. In this scenario, with the progress and refinement of research tools in association with digital technologies, the design of randomized studies is undergoing innovations that involve the type of patients included, the methods of their inclusion, the monitoring or choice of treatment, the randomization sequence, and the study outcomes (endpoints). In this article, we describe the essential points of randomized studies in Nephrology and the innovations to consider for their accurate and timely interpretation.

Principal aspects of a randomized trial in Nephrology

Inclusion criteria

One starting point when designing a randomized study is to establish which type of patients should be included. This leads to the definition of inclusion criteria. The first inclusion criterion should define the disease setting, for example patients with Chronic Kidney Disease (CKD) with or without diabetes, or both. Such a decision may lead to the estimation of a treatment effect in both types of CKD conditions rather than restrict to one of them. For example, canagliflozin, a SGLT2 inhibitor that protects the kidneys from chronic failure, was tested in patients with CKD and diabetes in the CREDENCE trial, whereas similar agents, empagliflozin and dapagliflozin, were tested in both diabetic and non-diabetic CKD in the EMPA-KIDNEY and DAPA-CKD trials [4–7]. The extremely positive results from these studies influenced the guidelines and clinical practice, leading to changes in drug reimbursement [8].

The other major inclusion criteria in CKD trials are the so called "kidney measures" namely estimated Glomerular Filtration Rate (eGFR) and albuminuria levels. Such a biomarkers-based enrichment in clinical trials is due to the fact that eGFR and albuminuria represent two main predictors of clinical outcomes in patients suffering from CKD [9, 10]. Moreover, the presence of abnormal levels of eGFR and albuminuria allows to reach a significant number of clinical endpoints throughout the study. In

previous trials, such as the first studies testing the efficacy of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), including the RENAAL and IDNT studies, serum creatinine was used instead of eGFR [11, 12]. For instance, in the RENAAL study, patients with a serum creatinine level of 1.3 to 3.0 mg/dL were included. Later on, serum creatinine was replaced by eGFR, that is considered a more accurate prognostic biomarker [13]. Another lesson from previous trials was the "flexibility" of inclusion criteria. In the DERIVE study, a phase 3 trial designed to test the efficacy and safety of dapagliflozin in early CKD, only patients with CKD stage 3A (eGFR between 45 and 60 mL/min/1.73 m^2) on at least two visits were included. Such restriction, albeit of clinical relevance, was associated with a high percentage of screening failure and slowed the study completion. Similarly, the ALTITUDE study (Aliskiren in patients with CKD and diabetes) included patients with albuminuria > 200 mg/g in at least two out three first morning voids or eGFR between 30 and 60 mL/min [14]. A recent post-hoc analysis of the ALTITUDE database highlighted how adopting more flexible criteria, such as lowering thresholds for albuminuria (e.g. >160 mg/g at the second collection) and relaxing thresholds for eGFR (e.g. 25-75 mL/min), can significantly reduce screening failure rates. This approach not only increases the number of eligible patients participating in the study, but also maintains the integrity of the clinical endpoints, without compromising the statistical power of the study. In particular, the intrapatient variability of albuminuria and eGFR values, which can be influenced by factors such as diet, hydration and therapy adherence, suggests that more stringent screening criteria may not be necessary to predict clinical outcomes [15].

Owing to this evidence, recent RCTs have been designed by including CKD patients with lower levels of albuminuria and larger range of eGFR. For example, in the ROTATE-3 study, a 100 mg of 24h-albuminuria, stable on two visits, was considered sufficient to screen and randomize patients. The stability in this case was not interpreted as a value of at least 100 mg/day also on the second measurement, but rather as a difference in albuminuria from the first visit: less than 40 mg/24hr for subjects with albuminuria between 100 and 300 mg/24hr, and less than 20% difference for subjects with albuminuria between 300 and 3500 mg/24hr [16]. Such an implementation was used to warrant a reliable and appreciable evaluation of the treatment effect (eplerenone or dapagliflozin or the combination of both them) in reducing albuminuria after 4 weeks. A further element to take into consideration to enroll patients is the trajectory of the eGFR decline over time. A steeper decline means that patients are at increased risk for future kidney failure and thus are exactly those patients who need a more urgent treatment. A post-hoc analysis of the SONAR trial, a phase 3 trial showing the nephroprotection of atrasentan in CKD and diabetes, demonstrated that treatment effect of atrasentan in terms of kidney failure risk reduction was greater in patients with higher eGFR decline before the trial initiation [17]. Recent trials used the eGFR decline criterion (i.e. eGFR decline > 1 mL/min/year during the 2 years prior to entry in the study based on at least 3 eGFR measurements) to select patients [18].

Outcomes of clinical trials

The outcome or endpoint is defined as the event of interest on which a specific therapeutic intervention should act. In reference to the aforementioned RCTs, the randomization process creates two patient groups that are homogeneous with respect to factors such as gender, age, demographics and blood chemistry characteristics. Each group is assigned a therapeutic protocol to compare the effects of the experimental treatment with those of the standard of care or placebo. In some cases, depending on the study design, the same patient may receive different treatments over time, generally separated by washout periods (the so-called crossover design). What is observed at the end of the study period represents the primary outcome. The primary outcome is crucial in clinical trials because the entire study is designed around its incidence rate (in terms of sample size, duration). Other outcomes that can however be tested as pre-specified or post hoc

analyses are the secondary outcomes. The difference in the incidence of the outcome between the treated group and the control group is generally expressed in the form of Relative Risk (RR), defined as the probability that a subject belonging to the group exposed to certain factors (i.e. experimental intervention) develops the outcome compared to the probability that a subject in the unexposed group (i.e. standard of care/placebo) develops the same outcome.

For years, the main hard endpoint evaluated in Nephrology trials was End Stage Kidney Disease (ESKD, that nowadays is also called Kidney Failure or KF), then differentiated into subgroups of persistence of CKD stage 5 (defined by the finding of eGFR < 15 ml/min confirmed on at least two occasions 15-30 days apart), entry into dialysis or arrival at kidney transplantation. The main trials in Nephrology, including the studies that demonstrated the effectiveness of ACEi and ARBs on slowing the progression of kidney damage, have adopted this primary endpoint.

However, it is known that the onset of ESKD may require a long observation period (even over 10 years), generally longer than the duration proposed in the study design [19]. This limit is added to the high rate of failures in the patient screening process, which is far higher than that of trials conducted in other areas of medicine and which, together, account for the important delay recorded in the panorama of scientific research in Nephrology.

To counter this trend, the identification of secondary endpoints or surrogate endpoints that could faithfully anticipate entry into dialysis was proposed as a workaround. Among these, we remember the main ones of reduction of eGFR and albuminuria. While on the first endpoint an eGFR decline of 57-40-30-20% within 3 years was tested, on proteinuria there is still no certain data on the expected reduction necessary to be able to speak of a good response to the treatment.

Despite the attempt by some authors to reduce the threshold of albuminuria among the inclusion criteria of a trial with the aim of increasing the sample of patients enrolled and reducing the study time, there was only a modest reduction in renal and cardiovascular events, contrary to what was expected.

This data was interpreted as a consequence of the variability in the measurement of albuminuria, confirming the importance of extending the inclusion criteria during the screening process to improve feasibility and efficiency of the study [20].

The use of eGFR and albuminuria as secondary outcomes could, on the other hand, reduce the generalizability of the trial results. One could, for example, incur the bias of excluding a given nosological entity such as non-albuminuric CKD, which is known to have an increased prevalence and a high risk of progression towards ESKD [21]. Regarding the reduction in eGFR, historically the main secondary endpoint identified has been an eGFR slope of -57%, generally represented in the form of a doubling of creatininemia. Also in this case, some authors have attempted to identify alternative endpoints with the aim of obtaining greater precision in estimating therapeutic efficacy at the cost, however, of recording a reduction thereof in the absence of a substantial increase in the statistical significance of the study [22]. In any case, the percentage reduction in filtration appears to be the best unit of measurement to estimate the temporal trend of renal function compared to the changes in eGFR in absolute value [19].

Furthermore, it was observed that reducing the percentage slope threshold of the eGFR from 57% to 40% increases the number of patients who develop the outcome, and this data also correlates with a high risk of evolution towards ESKD and mortality [23]. In light of what has been observed, the use of new potential surrogate outcomes such as an eGFR slope equal to – 30/40% on a sample of patients with baseline eGFR < 30 ml/min and a linear filtrate loss recorded in the run period equal to – 5 ml/min/year, could allow the achievement of the outcome and at the same time a reduction in study times.

Among the limitations identified, however, it should not be forgotten that some categories of patients, mainly elderly, non-proteinuric patients, with higher baseline eGFR, observe a non-linear trajectory of renal function which may reduce the predictability of the surrogate endpoints analyzed on the hard endpoints. Furthermore, the various formulas for estimating glomerular filtration take into account factors that can be modified over time, requiring optimization of the precision of the study with the integration of directly measured glomerular filtration values [19].

Innovations in the nephrology field of clinical trials

Role of the patient in treatment decisions

In recent decades, the role of the patient has undergone a significant transformation in decision-making processes within randomized clinical trials. In this context, a new doctor-patient relational model has gradually emerged, known as "Shared-Decision Making" (SDM), which involves the sharing of information and decisions between healthcare professionals and enrolled patients, empowering the latter with an increasingly active, informed, and autonomous role [24].

This model has found space since the end of the 1990s in the field of oncology, when various therapeutic options with uncertain outcomes emerged for terminally ill patients.

Thus, an increasingly broad exchange of communication began between the doctor and the patient, in order to involve them in decision-making and increase their awareness in the clinical field (Figure 1).

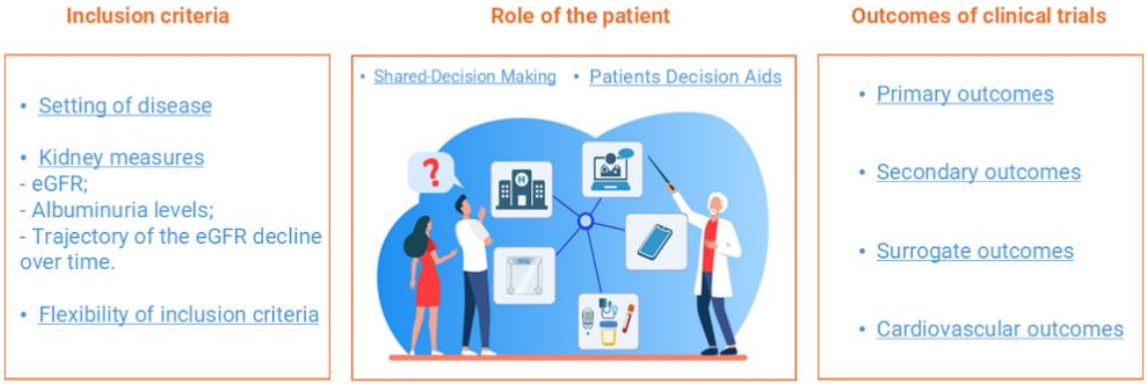

Figure 1. Innovations in the nephrology field of clinical trials and patients' role.

The SDM model is based on four fundamental pillars, as illustrated by some of its pioneers such as Charles and colleagues: 1) equal involvement of medical staff and patients; 2) sharing of information by both; 3) shared participation in drawing up consent to treatment; 4) reaching an agreement on the therapeutic path to follow [25].

The adoption of this model has allowed an ever-increasing participation of patients in trials, with better quality of the trials and construction of more solid evidence.

Greater therapeutic adherence and a reduction in losses during follow-up were also progressively documented, probably as a result of a greater degree of satistaction and psycho-physical well-being on the part of the patients enrolled in these types of trials.

The evidence shows that the use of SDM strategies also allows us to achieve better clinical, behavioral and psychological outcomes compared to those observed in trials with different strategies [26].

If the adoption of this model presents numerous positive implications on a scientific level, those on an ethical level are intuitive, as the priority of these trials is to place the will and needs of the patient at the centre.

However, guaranteeing greater information, awareness and decision-making autonomy implies a greater expenditure of energy and resources such as time and workload, giving more complexity to the decision-making process.

Conflicting circumstances can sometimes arise when the possibility of randomization in the control group or the blinding procedures do not reflect the patient's wishes [27].

Patients with dementia, or any other type of cognitive dysfunction, also represent a real barrier [28].

Instead, in various circumstances, informing the patient about possible side effects and risks can lead to agitation and confusion, and it is easy to run into misunderstandings [29].

For these reasons, healthcare personnel have made use of Patients Decision Aids (PtDA), i.e. decision-making aids to support patients, consisting of educational materials or easy-to-consult media assistance. These come in the form of smartphone apps, web sources, videos or written documentation such as brochures. In some circumstances, healthcare personnel undergo professional training courses with the aim of acquiring greater communication skills [24].

An international cooperation, the International Patient Decision Aid Standards (IPDAS) Collaboration, was launched specifically to establish the criteria, on the basis of scientific evidence, according to which PtDAs should be drawn up and evaluated, guaranteeing the best possible information and supporting the sharing of decision-making processes [30].

Additionally, the use of questionnaires to assess patients' preferences for different treatments in a crossover clinical trial is becoming more widespread, and collecting this information will assist clinicians in making personalized treatment decisions. An example is the upcoming FINESSE trial (EU trial number 2023-506434-69-00), in which digital questionnaires will be used to assess patients' preferences of finerenone or semaglutide, as well as their perspectives on the feasibility of participation in a home-based trial.

New outcomes in current and future RCTs

In addition to monitoring treatment effect with eGFR and albuminuria changes over time (after treatment initiation), novel outcomes are gaining momentum in Nephrology nowadays. To this aim, the International Society of Nephrology is publishing a bi-monthly volume called Global Trial Focus (GTF) reporting the new RCTs related to kidney diseases (herein the link: https://www.theisn.org/in-action/research/clinical-trials-isn-act/). In the GTF, a number of studies tested the effect of treatment on new endpoints, such as quality of life, chronic pain, glycemic control, change in pruritus in different stages of CKD, and others. The combination of an increasing number of RCTs (mirroring a more feasibility of these studies compared to the past) and more comprehensive endpoints may allow for deeper insights and improve the care of kidney diseases in the future.

Apps that remotely monitor blood pressure

Hypertension affects over a billion people in the world and constitutes a preponderant risk factor for the onset of various diseases, including cardiovascular and renal diseases [31].

It is estimated that approximately 12.8% of global deaths are attributable to this pathology, the treatment of which is based on lifestyle changes and medication. However, despite the initiation of therapeutic and behavioral measures, hypertension control rates remain suboptimal, with only about half of patients achieving adequate blood pressure control [31–33].

Self-monitoring has allowed us to obtain some clinical benefits over time, favoring greater therapeutic adherence and the reduction of some problems such as masked hypertension or “white coat” hypertension [33].

However, further measures are necessary. The demand for health tools to support the problem has grown considerably, due to the significant impact it has on public health and economic resources. In recent years, there has been an ever-increasing interest in digital innovations, as an inexpensive method within everyone’s reach [31, 34].

The Health App market is constantly growing, and thousands of new ones are produced every year. The main fields of interest are, in fact, represented by chronic diseases such as arterial hypertension and diabetes [33]. The invention of sensors and wearable devices, such as Bluetooth bracelets or smartwatches, has made it possible to detect vital parameters such as heart rate, blood pressure, sleep quality and physical activity [35].

Apps that detect blood pressure also offer various additional functions, such as maintaining a daily blood pressure log, organizing records, and providing reminders for measurements and medication. They also provide the patient with basic information on disease, treatment, lifestyle management and how to self-monitor.

There are available also analysis tools that offer an overview of the trend in blood pressure over time, using graphs or tables. Readings and other recorded data can be exported, allowing healthcare professionals to view and analyze them remotely. Most of these apps are available for free [33, 36].

However, sufficient data is not yet available to evaluate the quality and accuracy of these applications. The results obtained so far must be interpreted with caution due to the variance between the sizes of the samples on which the studies were conducted (very often too small and with subjects coming from different populations), due to the heterogeneity of the studies themselves and the use of self-reported scales to measure adherence to treatments. Therefore, research should establish standardized protocols for measuring parameters and reporting adherence. But it is important not to overlook the potential of this type of intervention to implement knowledge of patients’ health status and support self-management towards a healthy lifestyle and adherence to therapy, especially given the ever-increasing role that artificial intelligence is acquiring, which could guarantee significant support [37].

Remote collection of blood and urine samples

One of the challenges in patient participation in clinical trials is the frequency of visits required for monitoring the progress of the study and for collecting biological samples (blood and urine) for analysis. The introduction of new technologies that allow patients to collect blood and urine samples without needing to visit the study center opens up new possibilities for remote protocol monitoring. Examples of validated devices for at-home blood and urine sampling are Hem-Col® and PeeSpot®, respectively. The Hem-Col® tool is an innovative blood collection microtube designed to facilitate capillary blood sampling through a finger prick; the presence of an anticoagulant and a preservation buffer enhances analyte stability in whole blood, allowing the device to be sent to the laboratory for analysis via regular post. The PeeSpot® is a validated tool for collecting small amounts of urine (about 1.2 mL) through absorption onto a pad, which is held inside a tube. By adding various preservatives, the urine in the PeeSpot® can be preserved for up to 4 days in the refrigerator before being sent to the laboratory for the measurement of urinary albumin and creatinine. These devices represent a practical and efficient solution for both patients and healthcare professionals involved in clinical trials, lowering costs associated with frequent in-patient visits and optimizing the workflow. The FINESSE study (EU trial number 2023-506434-69-00), which will soon be launched, will use both devices for the remote monitoring of enrolled patients.

Conclusions

Many randomized studies have been published around kidney disease in the past few years. Taken together, results of randomized studies have allowed to improve guidelines and, at the end, to improve patients' survival, time free from dialysis and to reduce the number of CV events. Significant progresses have also been made over the past decades in terms of inclusion criteria, outcomes, and patients'role, which will aid the future conduction of randomized studies worldwide.

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