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Guidelines at a crossroads Listening to the evidence – what trials on blood pressure targets in CKD say about current guidelines

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This review summarises the available evidence on this topic and evaluates the role of proteinuria as an effect modifier.

INTRODUCTION

Chronic kidney disease (CKD) tends to progress to end-stage renal disease, which is a major problem associated with high morbidity and mortality and low quality of life[1]. Both high blood pressure and increased proteinuria are predictors of progression of renal disease in patients with chronic kidney disease[2]. Effective blood pressure control delays the progression of renal disease, and antihypertensive agents that inhibit the renin-angiotensin system seem to provide additional renoprotection as compared with drugs of different pharmacological groups, although there is a lack of sufficient evidence as to this[3,4].

Recent clinical practice guidelines have recommended intensified blood pressure control in delaying the progression of renal disease, aiming at a blood pressure target of 130/80 mm Hg or less, based on the assumption that available evidence shows lower blood pressure further reduces CKD progression[5].

HYPERTENSION TRIALS THAT EVALUATED THE CONCEPT THAT LOWER BLOOD PRESSURE FURTHER SLOWS CKD PROGRESSION

There are five published trials designed to evaluate whether reduction of blood pressure to lower than usual targets can achieve further renoprotection: the MDRD (Modification of Diet in Renal Disease) study[6], the Collaborative Study Group trial[7], the ABCD (Appropriate Blood Pressure Control in Diabetes) trial[8], the AASK (African-American Study of Kidney Disease) trial[9] and the REIN-2 (Ramipril Efficacy In Nephropathy 2) trial[10].

The Modification of Diet in Renal Disease (MDRD) study[6] was composed of two studies (study 1 included 585 patients with glomerular filtration rates of 25 to 55 mL/min/1.73 m^2 and study 2 included 255 patients with glomerular filtration rates of 13 to 24 mL/min/1.73 m^2) in which patients were randomly assigned to a usual or a low blood pressure group (mean arterial pressure [MAP], 107 or 92 mm Hg). The mean follow-up was 2.2 years. The primary outcome measure was the rate of change in the glomerular filtration rate (the GFR slope). The glomerular filtration rate was measured on the basis of the renal clearance of iodine I 125 iothalamate. The difference in mean blood pressure between the usual-pressure and the low-pressure groups during the follow-up period was 4.7 mm Hg ($p < 0.001$). There was no difference in the rate of decline in the glomerular filtration rate between study groups.

A post-hoc analysis suggested that patients in the low blood pressure group who had more pronounced proteinuria (higher than 1g/day) at baseline had a significant slower rate of decline in the glomerular filtration rate.

The Collaborative Study Group[7] was a small trial comparing the effects of two levels of blood pressure control (mean arterial pressure, 100 to 107 mm Hg or 92 mm Hg or less) on the progression of diabetic nephropathy in patients with type 1 diabetes who had previously participated in the Angiotensin-Converting Enzyme Inhibition in Diabetic Nephropathy Study. All patients received ramipril as the primary antihypertensive agent. The primary outcome was GFR slope as measured by the renal clearance of iodine I 125 iothalamate. The study included 129 patients. All patients were followed up for a minimum of two years. The average difference in MAP between groups was 6 mm Hg over the 24-month follow-up. The mean GFR slope did not differ significantly between blood pressure groups: the median GFR in the lower and usual blood pressure groups at baseline was 62 and 64 mL/min/1.73 m^2, respectively, and at month 24 was 54 and 58 mL/min/1.73 m^2, respectively ($p = 0.62$)· However, given the relatively small loss of renal function during the two years of follow-up, this study did not have the power to detect significant differences between the two groups.

Although the baseline median urinary protein excretion of the two groups was similar (1.0 *vs.* 1.1 g/24 hour), there was a significant difference in total 24-hour urinary protein excretion at end of follow-up between patients assigned to the low blood pressure group as compared with the usual blood pressure group: 0.5 *vs.* 1.7 g/24 hour, respectively (95% CI, 27 to 1017; $p = 0.003$). During follow-up, 23% in the low blood pressure group and 11% in the normal blood pressure group had a remission in proteinuria, defined as a reduction in proteinuria to below 500 mg/day ($p = 0.059$). In a post-hoc analysis, patients with an achieved mean blood pressure ≤92 mm Hg (independent of assigned blood pressure group) had a lower proteinuria at end of follow-up and a slower rate of decline in GFR (-2.6 mL/min/year), than patients with higher achieved blood pressure ($p < 0.05$).

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial[8] compared the effect of intensive (diastolic blood pressure of 75 mm Hg) versus moderate blood pressure control (diastolic blood pressure of 80 to 89 mm Hg) on the incidence and progression of type 2 diabetic complications. The primary outcome measure was glomerular filtration rate as assessed by 24-hour creatinine clearance. The study included 470 non-insulin-dependent diabetes (NIDDM) patients with a diastolic blood pressure of 80 mm Hg or higher, but the presence of CKD was not required. Therefore, at baseline, CKD was present in an undefined number of participants, and patients who had a serum creatinine greater than 3.0 mg/dL were excluded. The mean blood pressure achieved was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate control group. During the five-year follow-up period, no difference was observed between intensive versus moderate blood pressure control with regard to the change in creatinine clearance.

In a post-hoc analysis, after the first year of antihypertensive treatment, creatinine clearance stabilised in both the intensive and moderate blood pressure control groups in those patients with baseline normo- or microalbuminuria. In contrast, patients starting with overt albuminuria demonstrated a steady decline in creatinine clearance of 5-6 mL/min/1.73 m^2 per year throughout the follow-up period whether they were on intensive or moderate therapy.

The African-American Study of Kidney Disease (AASK)[9] trial compared the effects of two levels of blood pressure control (mean arterial pressure, 102 to 107 mm Hg or 92 mm Hg or less) on the progression of hypertensive kidney disease. The primary outcome was GFR slope as measured by the renal clearance of iodine I 125 iothalamate. The GFR slope was determined separately during the first three months following randomisation (acute slope) and after 3 months (chronic slope). There were two coprimary outcomes: the chronic slope and the mean total slope from baseline (including both the acute and chronic slope). The analysis plan stipulated that a benefit of a treatment intervention would be inferred if it was shown to reduce the magnitude of both the chronic and total mean slopes. The study included 1094 African Americans with hypertensive CKD (GFR, 20 to 65 mL/min/1.73 m^2). Blood pressure decreased from 152/96 to an average of 128/78 (12/8) mm Hg in the lower blood pressure group, and from 149/95 to 141/85 (12/7) mm Hg in the usual blood pressure group. The mean GFR slope did not differ significantly between blood pressure groups either during the chronic phase or the total follow-up period.

In a post-hoc analysis, two thirds of the participants (n=733) had a baseline protein to creatinine ratio of 0.22 or less, and one third (n=357) had a baseline protein to creatinine ratio higher than 0.22. Baseline proteinuria was a strong predictor of GFR decline. Proteinuria increased by 7% in the usual blood pressure group and decreased by 17% in the lower blood pressure group. However, the comparison of GFR slopes between blood pressure groups was not significantly different within either lower (baseline urinary protein to creatinine ratio ≤0.22) or higher (baseline urinary protein to creatinine ratio >0.22) proteinuria strata.

The Ramipril Efficacy In Nephropathy 2 (REIN-2)[10] trial compared the effect of intensive (systolic/diastolic blood pressure <130/80 mm Hg) versus conventional blood pressure control (diastolic blood pressure <90 mm Hg) on CKD progression. The study included 338 patients with non-diabetic proteinuric nephropathies (urinary protein excretion exceeding 1 g/day), as defined by a proteinuria of 1 to 3 g/day and creatinine clearance of less than 45 mL/min/1.73 m2, or a proteinuria equal to or greater than 3 g/day and a creatinine clearance of less than 70 mL/min per 1.73 m2. The primary outcome was time to end-stage renal disease over 36 months' follow-up. Blood pressure decreased from 137/84 to an average of 130/80 mm Hg in the lower blood pressure group, and from 136/84 to 134/82 mm Hg in the usual blood pressure group. 38 (23%) of 167 patients in the intensified-control group and 34 (20%) of 168 in the conventional-control group progressed to end-stage renal disease (95% CI 0.61 to 1.64; p =0.99). Therefore, the study showed no additional benefit from further blood pressure reduction. Throughout the study, urinary protein excretion was similar in both arms.

INTERPRETING THE RESULTS OF CLINICAL STUDIES ON TREATMENT, USING DIFFERENT LEVELS OF EVIDENCE

Most guidelines in nephrology are based on expert opinion, observational data and post-hoc analysis. Therefore, it is critical to understand whether these levels of evidence give the same answers as randomised trials.

In a systematic review comparing the results of observational studies and randomised controlled trials of cardiologic treatments published in the year 2000 in the New England Journal of Medicine, Benson *et al.* found little evidence that estimates of treatment effects in observational studies reported after 1984 were either consistently larger than or qualitatively different from those obtained in randomised controlled trials[11].

This conclusion contradicts the widely accepted assumption that the impressive advances in cardiovascular treatment during the last several decades were largely due to randomised trials. In fact, the well-known fallibility of expert opinion and observational data in support of the therapeutic value of treatments, without evidence from well-designed randomised clinical trials, is reflected in multiple examples of widely used treatments that were subsequently proved to be ineffective or harmful.

In the non-nephrological area, these treatments include hormone replacement therapy in postmenopausal women that showed a 40 to 50% decrease in coronary heart disease on observational studies, but was shown to be associated with multiple serious adverse outcomes[12,13]; antiarrhythmic drugs such as encainide and flecainide that were adopted on the basis of non-validated surrogate outcomes and proved to increase mortality as compared with placebo[14]; high-dose chemotherapy with bone marrow transplantation for metastatic breast cancer, which produced high rates of response in phase 2 trials but was found no more effective and more toxic than standard chemotherapy[15]; and arthroscopic surgery for osteoarthritis of the knee, which was proved to be no better than a sham intervention in relieving pain[16].

In the nephrological area, there are multiples examples of therapies that are widely used based on the beneficial effects suggested by observational studies, which were subsequently shown to be ineffective or harmful. These include anaemia therapy with epoetin that was shown to reduce mortality in observational studies, but was shown not to be associated with improved outcomes[17,18], dialysis with high-flux membranes that were adopted on the basis of observational data suggesting a beneficial effect on mortality and which proved to have no effect on survival[19,20], and early initiation of dialysis that showed a decrease in mortality on observational studies, but was subsequently shown to be ineffective[21].

Medical research relies on clinical trials to assess therapeutic benefits. Clinical trials include patients with a particular disorder and estimate the effect of the intervention under study. The likely benefits and risks for an individual patient are thus estimated.

Frequently, clinical trials include several end points and/or subgroup analysis, trying to extract additional information. A subgroup analysis is sometimes undertaken to assess treatment effects among different subpopulations. "Sub-group analysis" may be defined by any evaluation of treatment effects for a specific end point in subgroups of patients defined by baseline characteristics[22].

There are two types of subgroup analysis, the prespecified and the post-hoc analysis. A prespecified subgroup analysis is one that is planned and documented in the study protocol[22]. Post-hoc analyses refer to those in which the hypothesis being tested are not specified before any examination of the data, and these analyses are of particular concern because it is often unclear how many were undertaken and whether some were motivated by inspection of the data[22]. Furthermore, both prespecified and post-hoc subgroup analyses are subject to inflated false positive rates arising from multiple testing. Therefore, subgroup analysis can lead to overstated and misleading results. A major concern with conducting multiple tests of significance ("multiplicity") of different end points and/or subgroups in a clinical trial involves the so-called Type I error, the probability that a null hypothesis is rejected when the null hypothesis is actually true. When multiple tests of significance are performed, the probability of a (false) positive finding resulting from chance alone can be substantial. Although secondary end points and/or subgroup analysis can provide additional characterisation and understanding of treatment effects, they can be hard to interpret[22,23], and they by themselves are not sufficient to confirm that the treatment is efficacious.

When the primary end point is not significant, the results of subgroup analysis or secondary end points should be used only for generating hypothesis. Even when the primary end point is statistically significant, attention should be directed to whether secondary end points and subgroup analysis were specified in advance by the protocol, a priori power calculations were done for subgroups, and adjustments for multiplicity were performed[22,24]. There are several approaches for addressing multiplicity in clinical trials[24], and one of them should be included in the methods section of the study protocol.

INTERPRETING THE RESULTS OF PUBLISHED TRIALS

The MDRD (Modification of Diet in Renal Disease) study[6], the Collaborative Study Group trial[7], the ABCD (Appropriate Blood Pressure Control in Diabetes) trial[8], the AASK (African-American Study of Kidney Disease) trial[9], and the REIN-2 (Ramipril Efficacy In Nephropathy 2) trial[10] failed to support the concept that lower blood pressure further slows CKD progression. Therefore, all published hypertension trials that evaluated the concept that lower blood pressure further slows CKD progression failed to show any benefit for renal outcomes from the low to the usual blood pressure targets.

As far as the role of proteinuria as an effect modifier is concerned, the major limitation when evaluating this issue comes from the absence of large-scale clinical trials using clinically meaningful end points that

Table I

Quality assessment of subgroup analysis by proteinuria

	MDRD	CSG	ABCD	AASK	REIN 2
Was subgroup analysis prespecified?	No	No	No	No	Yes
Were proteinuria strata prespecified?	No	No	No	No	Yes
Were adjustments for multiplicity performed?	No	No	No	No	No
Were a priori power calculations done for subgroups?	No	No	No	No	No

have targeted different levels of proteinuria as the intervention. Therefore all the evidence derives from secondary analysis of interventions designed to influence a different pathway of disease, e.g. impact of different levels of blood pressure on CKD progression, while change in proteinuria was a secondary end point. Additionally, the cut-off points and measures for proteinuria assessment varied substantially across studies and were frequently defined in post-hoc analysis (Table I).

Although some of these studies have major limitations, such as the use of non-validated surrogate end points (GFR decline), insufficient duration of follow-up to observe clinical end points, and insufficient power to detect significant differences between groups, the treatment effect on progression was not predicted from the treatment effect on proteinuria in many of these trials, and therefore, available evidence does not support proteinuria as an effect modifier in this context. A recent report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration on "Proteinuria as a surrogate outcome in CKD" concluded that "at the present time, there appears to be sufficient evidence to recommend changes in proteinuria as a surrogate for kidney disease progression in only selected circumstances. Further research is needed to define additional contexts in which changes in proteinuria can be expected to predict treatment effect"[25].

SHOULD THE LEVEL OF EVIDENCE REQUIRED TO ISSUE A GUIDELINE BE LOWER THAN THAT REQUIRED FOR REGULATORY AND COVERAGE DECISIONS?

An individual patient faced with a serious condition may have only one opportunity to benefit from a potentially beneficial treatment. For the individual patient, the subgroup or secondary end point analysis may provide the best available estimate of treatment benefit, and therefore, in individual decision-making, it is acceptable that the individual doctor may use that information for the individual patient, informing the patient about the uncertainties of the proposed treatment.

Clinical practice guidelines were designed to support the decision-making processes in patient care. Therefore, they were defined as "systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances"[26]. However, over time, this definition has become fundamentally flawed as the purposes of guidelines have been widely broadened, and now include additional goals such as to reduce inappropriate variation in practice, to promote efficient use of resources, and to act as focus for quality control, including audit. Insensibly, guidelines became non-assumed performance measures.

However, the level of evidence required to issue a guideline did not change, being considered as acceptable to construct a guideline based on the best available evidence, including observational data, post-hoc analysis, and expert opinion. However, guidelines currently relate not just to the individual patient but to all patients, as can easily be found by looking at the number of published manuscripts on achievement of the NKF-K/DOQI targets on bone and mineral metabolism retrieved from a PubMed search. Although the level of evidence that supports each guideline may vary substantially, it is expected that they will all be equally adhered to.

Worldwide, there has been a special concern with the variability of practice patterns. However, from the perspective of the quality of care, the variation that is a cause for concern is that between actual practice and evidence-based best practice. When evidence-based best practice is unknown, to reduce the variability of practice may be a dangerous option, and a way of generalising the use of ineffective or harmful therapies. The inability for defining a new scope for guidelines, as well as to adapt the level of evidence to the new paradigm, has already had dramatic consequences in the nephrological area.

The decision to issue a guideline based on observational data, post-hoc analysis, and expert opinion rests on a flawed intuition that patients and doctors "should be aware" of the best available option, even if the best available option is unknown. This false sense of security induced by guidelines based on observational data, post-hoc analysis and expert opinion can be misleading and is a way of wronging patients and doctors, and represents a violation of the patient's right to evidence-based medicine. When experts recommend a given treatment that has not yet been adequately evaluated, they are recommending a drug of unknown value, and therefore, they may be recommending a treatment that may prove to be beneficial, but they may also be recommending a therapy that may subsequently prove to be useless or even harmful.

Therefore, guidelines, as well as regulatory and coverage decisions, should be protected from the risk of undue inference, by using data from relevant clinical trials, and only using the effect of the intervention on the predefined primary end point[23]. When the primary end point is statistically significant, the results of secondary end points and subgroup analysis may be considered when specified in advance by the study protocol, a priori power calculations were done for subgroups, and adjustments for multiplicity were performed[22,24].

GUIDELINES: BACK TO THE FUTURE

There is a widely accepted concept that "to inform regulatory and coverage decisions, rigorous evaluation of a new treatment before it is made available in clinical practice must be pursued beyond the point at which physicians and informed patients would choose it over the current standard treatment based on initial efficacy data"[27]. Therefore, it is generally accepted that the level of evidence required for individual clinical decision-making is lower than that required for regulatory and coverage decisions.

However, even when clinical practice guidelines were used exclusively for individual clinical decision-making, this concept of a differential requirement of the evidence level was probably inappropriate. Moreover, as clinical practice guidelines have progressively turned into performance measures, this differential requirement of evidence level became no longer acceptable. Clinical practice guidelines should be based upon the highest level of evidence, demonstrating that benefits outweigh harm. When such evidence is not available, no guideline should be issued, as unproven statements may be more harmful than the absence of recommendations**.** Whenever the current state of knowledge precludes the existence of clinical practice guidelines, decision-making should be performed on an individual basis, taking into account clinicians' own expertise and experience, availability of resources, and patients' preferences.

Issuing a guideline based on insufficient evidence may allocate patients to futile or harmful treatments, and may induce the use of limited healthcare resources in a futile or harmful way rather than allocating them to interventions able to achieve improvements in outcomes.

Now is the time for a paradigm shift.

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