Targets, trends, excesses, and deficiencies: refocusing clinical investigation to improve patient outcomes

Adeera Levin[1], William Lancashire[2,3] and Robert G. Fassett[4,5,6]

[1]Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada; [2]Critical Care Medicine, Port Macquarie Base Hospital, Port Macquarie, New South Wales, Australia; [3]Rural Clinical School, University of New South Wales, Sydney, New South Wales, Australia; [4]Chronic Kidney Disease Queensland, Renal Medicine, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [5]School of Human Movement Studies, The University of Queensland, Brisbane, Queensland, Australia and [6]School of Medicine, The University of Queensland, Brisbane, Queensland, Australia

Clinical trials in nephrology have focused on achieving targets, supplementing deficiencies, and correcting excesses in order to improve patient outcomes. The majority of interventions have failed to demonstrate benefit and some have caused harm. It may be that therapies aiming to 'normalize' parameters may actually disturb evolutionary adaptation, thus causing harm. By refocusing on the physiology of disease, and complexity of adaptation, we may design better trials. We review successful and unsuccessful trials in nephrology and other disciplines and suggest a set of principles by which to design future clinical trials: (1) acknowledge heterogeneity of chronic kidney disease populations and appropriately characterize populations for studies; (2) develop better validated biomarkers (through proteomics, genomics, and metabolomics) to identify responders and nonresponders to interventions; (3) design interventions that mimic physiological processes without collateral detrimental effects; (4) reconsider the status of the randomized-controlled trial as the only 'gold standard' and perform large-scale pragmatic trials comparing current care with the intervention(s) of interest, and (5) broaden nephrology research culture so that the majority of patients are enrolled into observational cohorts and intervention studies, which foster greater knowledge acquisition and dissemination. Improved understanding of pathophysiological mechanisms, in conjunction with more innovative but stringent clinical trial design, will ultimately lead to improved patient outcomes.

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Correspondence: *Adeera Levin, Division of Nephrology, University of British Columbia, 1081 Burrard Street, Room 6010A, Vancouver, British Columbia, Canada V6Z1Y8. E-mail: alevin@providencehealth.bc.ca*

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Chronic kidney disease (CKD) is a complex disorder characterized by altered endocrine, exocrine, and paracrine functions. Many of the biochemical and metabolic abnormalities are well known, but the interconnections and relationships remain incompletely understood. The rapid and ongoing discovery of new molecules and pathways, through proteomics, metabolomics, and genomics, may lead to insights that render ongoing studies redundant or erroneously conceived, before they are completed.

Observational studies have demonstrated associations between some of these parameters and adverse outcomes such as the onset of cardiovascular events, end stage kidney disease (ESKD), and death. However, when we have tested interventions to render these abnormalities within the normal range, the results have often been disappointing and sometimes harmful. This failure may be due to poor trial design such as inadequate sample size, trial duration, and too restrictive inclusion and exclusion criteria to name a few. Alternatively, in some instances the intervention altered other parameters in an unfavorable way resulting in a negative or harmful result. In some instances, trials have produced positive outcomes but these have not been translated because of expressed concerns with trial design, validation did not occur or perhaps the interventional agent did not have potential marketing profitability[1–5]

Logically, an improved understanding of the adaptive pathophysiology in CKD might allow for more precision to test using the current gold standard, the randomized-controlled trial (RCT). It is important that before embarking on such trials, we appreciate the mechanism of action of interventional agents, acting on well-delineated pathways, with minimal chance of altering other unfavorable ones. For example, two recent large RCT's, BEACON, and EVOLVE have had disappointing outcomes.[6,7] These were designed with the best intentions, integrating clinical observation, physiology, cell biology, and molecular mechanisms but failed to impact patient outcomes. Many other RCT's have failed. This may be because studies are truly negative, but may also be because the hypothesis was incorrect, the intervention was ineffective,

the primary outcome (target) was selected based on incorrect assumptions derived from observational studies or surrogate outcome studies, the study was conducted in the wrong population and not generalizable, there was an inadequate sample size, or the trial design was flawed.

This review will highlight some key negative, successful, and early-terminated clinical trials in nephrology and general medicine and examine some of the reasons for the results. We will suggest the need to understand and address pathophysiological processes and approach these with balanced strategies, and avoid targeting laboratory values to perceived thresholds or normal ranges. We will suggest a framework for the design of clinical trials in nephrology.

HOMEOSTASIS REVISITED

Conditions such as CKD are associated with multiple abnormal parameters measured clinically and biochemically. Many of these have been measured longitudinally and are associated with adverse patient outcomes. This does not prove causation but provides the basis for hypothesis generation to test in RCT's. Clinical trials design has focused on restoring these parameters to a normal range but this has often not improved patient outcomes and sometimes the interventions have caused harm. There are several potential reasons for this.

Firstly, 'static' measures of a variable or set of variables, existing in a nonlinear dynamic system, may not be clinically relevant. Kavanagh states: 'Abnormal physiological variables always suggest an abnormal milieu or disease state, this does not mean all abnormal variables are directly causing harm.'[8] We extend that argument and suggest that in acute kidney injury and CKD an abnormal parameter may be 'normal' for that patient with that disease state, and may not require restitution to normal to improve outcomes.

Secondly, the parameters measured may have unrecognized variability that is often neglected. Clinical studies should have stringent preanalytical requirements.[9]

Thirdly, the use of surrogate outcome measures in clinical trials is fraught with risk. There are many examples where an improvement of a surrogate outcome measure in a clinical trial has not been translated into improved hard outcomes such as mortality.[10]

Finally, the heterogeneity of populations with and without CKD makes targeting surrogate endpoints, or discrete physiological deficiencies or excesses, problematic. We are only just coming to terms with CKD classification, accurate measurment of estimated glomerular filtration rate (eGFR) upon which the former is based, initiating longitudinal epidemiological studies in CKD and discovering, testing, and validating biomarkers. Layering clinical trials on unstable foundations risks finding investigational agents ineffective, when in fact, they may have been tested on the wrong population.

HETEROGENEITY OF PATIENT CHARACTERISTICS AND OUTCOMES

CKD patients may progress towards ESKD with inherent complications and comorbidities such as cardiovascular disease (CVD), others remain stable long term and some may improve if they have a treatable primary disease. This heterogeneity may represent the different underlying aetiologies, genetic factors, or environmental exposures such as medication.[11,12] Many outcome measures have been used in CKD clinical trials to assess disease progression including serum creatinine, doubling of serum creatinine, reciprocal of serum creatinine, rate of change in eGFR or composites of these. However, the main outcomes of interest are the need for dialysis and/or transplantation, CVD, total mortality and quality of life. If a clinical trial assessing CKD progression is composed of many patients that are stable or improving then this will potentially dilute or mask the benefits in those that are progressing. Hence, it would be beneficial to allocate patients into trials according to preintervention rate of change of kidney function to minimize bias and sample size. Although this would increase trial duration it would improve validity.[13]

In addition, there may be heterogeneity within individual CKD patients. The balance between altered excretory and endocrine function may be quite different between individuals. This may relate to the underlying etiology. Each abnormality may contribute to adverse CKD outcomes, but targeting one without reference to other ongoing unaddressed ones, may be problematic, as the interactions are complex. For example, in the EVOLVE study those taking cinacalcet required more calcium containing phosphate binders to balance the fall in serum calcium.[7] This may have increased the risk of vascular calcification, with its inherent adverse impact on outcomes. Thus, correction of the pathological pathway may be more complex than simply restoring abnormal blood values to normal.

CLINICAL STUDIES: OBSERVATIONAL DATA AND RANDOMIZED-CONTROLLED TRIALS

Recent availability of large nephrology observational databases has revealed many associations between clinical abnormalities, biomarkers, and adverse outcomes ripe for hypothesis generation and testing in RCT's. Biological plausibility is an essential prerequisite before validating observed associations, but with large databases this may be sought after the fact without appreciating the physiological relevance of the association. In nephrology, robust associations demonstrated in observational studies have been tested with interventions in clinical trials, with limited success. Where 'success' has been achieved it has not been validated in larger studies.[2] Failure may have been due to poor trial design, ineffective intervention, or unexpected negative effects of the intervention. Furthermore, irrespective of clinical trial findings, the nephrology community has been inconsistent in the uptake of clinical trial findings into practice.

Despite data from observational studies indicating poor outcomes associated with low dialysis dose, hyperphosphatemia, elevated parathyroid hormone (PTH), anemia, hyperlipidemia, oxidative stress, and hyperhomocystinemia,

intervention studies designed to correct these abnormalities have been of limited benefit and in some cases harmful.[14–19]

Observational data suggests patients receiving the lowest dialysis doses have the worst outcomes.[20] The HEMO study[14] using a 2 by 2 factorial design found longer dialysis time and higher flux membranes did not improve outcomes in the population studied. So, was it study design that failed to demonstrate a benefit from increased dose? Patients eligible for entry into the trial had to be able to achieve the desired Kt/V a priori, so that if the patients were randomized to the high Kt/V arm they would be able to sustain the targeted Kt/V. While the study design was sound, it may be that the selection of patients who were well enough at baseline to achieve the high Kt/V, were not the population of original interest. Thus, the negative study results are robust in the population studied. Targeting higher doses of dialysis in those with good vascular access, which were able to achieve the desired higher Kt/V before study entry, does not result in better outcomes. Those individuals in the original observational studies had lower Kt/V for a variety of reasons: poor access, hypotension, vascular instability, and symptoms on dialysis: these were not the people that were eligible for enrollment in the HEMO study. Alternative methods to study the question would be either to have a much larger sample size, including a more diverse group of patients, including those with low Kt/V, or to test a variety of strategies to improve clearances in those individuals (including longer and more frequent dialysis, or alternatively, addressing patient factors like vascular access, or hypotension, which limit clearance). The main point is that the HEMO study results answered a specific question in relatively well patients, but was not designed to answer the important clinical question as to whether extending dialysis in those who have poor clearances, improves long-term outcomes.

Based on observational studies reporting lower hemoglobin values are associated with poorer outcomes in CKD, intervention studies using erythropoiesis-stimulating agents (ESA's) were designed to increase hemoglobin to within the normal range. Such studies in ESKD and earlier stage CKD patients showed no demonstrable benefit for patients randomized to the higher hemoglobin.[15–17,21,22] In some studies, harm was demonstrated in those randomized to higher targets, and who ultimately received higher doses. Those failing to achieve hemoglobin values in the target range were more likely to die or suffer cardiovascular events than those in control or placebo arms. Closer scrutiny of observational data, upon which these studies were based, reveals that those with better survival and highest hemoglobin values actually received lower ESA doses than those with lower Hb and poor outcomes. Thus, low hemoglobin becomes a surrogate for being unwell and attempting to rectify this with high ESA doses may not only be futile, but dangerous. Quality of life is improved in most studies in patients achieving higher hemoglobin as in the TREAT study despite there being no impact on 'hard outcomes'. This leads us to reflect on what might be more important to patients in different circumstances.[16] Thus, attempts to normalize hemoglobin with ESA therapies using high doses, is not of value and may lead to harm. This has lead to both lowering of target hemoglobin values and lower doses of ESA being used. This again may be an over interpretation of the data, and does not take into account individual variability in responsiveness and baseline hemoglobin values. The focus on target hemoglobin, may have obscured alternative important questions such as why the hemoglobin might be low, what contributes to hemoglobin stability and how to minimize ESA dose to achieve outcomes of interest (reduced fatigue, improved exercise tolerance, and avoidance of transfusions). These questions may be more important for patient outcomes than ascertaining the target hemoglobin value.

Several observational and case–control studies suggest early dialysis initiation is associated with better quality of life, employment options and survival, and fewer complications.[23–25] The biological premise on which earlier dialysis might be beneficial is that when uremic toxins accumulate to the extent symptoms and laboratory abnormalities become excessive this leads to poor outcomes. Alternative observational studies suggested early dialysis initiation may be harmful.[26–29] These observations were tested in the IDEAL trial where patients were randomly assigned to two different dialysis starting times, eGFR 10.0–14.0 ml/minute or eGFR 5.0–7.0 ml/minute.[30] There was no difference in total mortality between groups. However, 75.9% of patients in the 'late-start' group actually started dialysis with eGFR greater than 7.0 ml/minute because of the onset of symptoms. The authors report that 'planned' early starters did not have improved outcomes but actual mean eGFR difference was only 2.2 ml/minute between the groups. Hence the statement that there is no difference between early and late starters can be perceived as misleading; the real difference remains unknown. Despite the best intentions of trial design, nephrologist practices, and perceptions, as well as patient symptoms may have attenuated the study conduct and thus influenced the outcomes. It remains an interesting observation that despite clinical equipoise in so many situations, nephrologists have difficulty with adherence to study protocols and even to participation in clinical trials relative to other specialist groups.[31]

Observational studies show high-serum phosphate levels are associated with increased mortality. The largest interventional study has failed to show lowering phosphate values with phosphate binders improve outcomes.[32] This may reflect deficiencies of trial design, the large drop out rate, the patient population, or it may truly reflect that targeting of an abnormal phosphate value, part of a complex system of mineral metabolism and ion homeostasis, may not impact long-term outcomes in dialysis patients.

Based on the association between hyperhomocysteinemia and CVD,[18] a large interventional trial using seemingly innocuous vitamin B and folic acid, in hyperhomocysteinemia showed no benefit. In fact, a signal of more

vascular events and harm in the treatment group was seen in patients with type 2 diabetes and impaired kidney function.

The identification of specific receptors involved cyst growth in polycystic kidney disease, led to testing mTOR inhibitors sirolimus and everolimus in randomized control trials.[33,34] Neither of these drugs appears to be of benefit in short-term studies. However, imaging studies used were possibly imprecise, or the timing of the intervention was not appropriate. Furthermore, while cyst and kidney size are important surrogates in polycystic kidney disease, they may not be the right endpoint for these trials. Furthermore, the issue of optimal timing of therapy for chronic inherited conditions like polycystic kidney disease is brought into question. Too early or too late introduction of therapy in these progressive conditions may undermine the utility of specific medications and too long an exposure to potentially toxic medication might be worse than the disease.

Based on observational study data showing increased mortality associated with increased PTH levels in ESKD, the EVOLVE randomized control trial assessed whether reducing PTH with cinacalcet could improve such outcomes. There was no significant difference in the primary outcome measure between the groups. This may have been due to a significant age difference between groups at randomization, many patients in the placebo group being prescribed cinacalcet despite no evidence for its benefit (high drop-in rate), many withdrawals from therapy in both the groups because of side effects, and duration of time to reach the event target. In addition, nephrologists were able to adjust other therapies, which resulted in cinacalcet treated patients receiving significantly larger quantities of calcium containing phosphate binders. Hence, in this case we may have missed finding a genuine benefit because of clinical trial design and execution. Again, the high 'drop-in' rate speaks to nephrologist uneasiness with abnormal laboratory values despite clinical uncertainty about the benefit of modifying those numbers.

Observational data show oxidative stress and inflammation are associated with CKD and CVD. Bardoxolone methyl, an nrf2 activator, was tested in an RCT and improved kidney function by 4 weeks, which was sustained at 12 months. Building on this surrogate outcome study, the BEACON trial assessed whether this intervention improved mortality and onset of ESKD requiring dialysis but was terminated prematurely due to adverse patient events in the bardoxolone-treated group. Note that the population studies in BEACON were sicker than those in the original clinical study (BEAM),[35] having lower eGFR and more albuminuria. This is a good example of the caution that should be taken when testing interventions in different populations, and underscores the importance of selecting appropriate populations and hard outcomes.

Most of the above studies focused on correcting laboratory abnormalities demonstrated to be associated with adverse outcomes in observational studies. An alternative approach in other related clinical areas involves using a fixed dose intervention without adjusting dose to achieve a specific target.

The HOPE trial used a fixed angiotensin-converting enzyme inhibitor (ACEi) dose in high-risk populations and found a morbidity and mortality benefit in the treated group.[36,37] Micro-HOPE found similar benefits in the subgroup with diabetes.[36] There were no target blood pressures (BPs) and the ACEi dose was fixed throughout. However, in the ON TARGET study which combined ACEi and angiotensin receptor blockers (ARB) there was evidence of harm.[38,39] In this latter study, doses were titrated to achieve a target BP in a general population at risk of CVD, but not as high risk as in HOPE. The different outcomes may relate to different study populations, degree of inhibition of the renin–angiotensin aldosterone system, or the desire to achieve specific targets.

Also in the HOPE trial, the vitamin E (antioxidant) component of the strategy did not benefit this general high-risk population. This may have been a genuine failure but the presence of oxidative stress was not determined in this population. A different outcome may have been seen if vitamin E was only tested in those with oxidative stress.

The powerful impact of lipid lowering therapies in general and high-risk populations without CKD led to evaluation of these therapies in CKD populations generally specifically excluded from the former studies. Statins given to dialysis patients in the 4D and AURORA studies showed no improvement in composite outcomes of death, CVD, and atherosclerotic events.[19,40,41] However, the SHARP trial, did show a reduction in atherosclerotic events using a fixed dose combination of statin and ezetimibe with no targeted lipid levels for study entry or treatment.[42] The SHARP trial did not demonstrate any effect on mortality: it was designed specifically to evaluate outcomes directly associated with the strategy: atherosclerotic events. Cardiovascular events in CKD patients occur related to 'traditional' and 'non-traditional' risk factors. SHARP investigators recognized that non-traditional risk factors leading to CVD in CKD would not be impacted by a single agent addressing one process (atherosclerosis).[42] 4D and Aurora may have failed to demonstrate an effect because of study duration, size, and population, but most probably because of the lack of an appropriately defined endpoint, instead using a composite one including processes unlikely to be affected by the intervention. SHARP in contrast had alignment of the intervention with the disease process. Alternatively, when risk ratios for 'clearly' atherosclerotic events from 4D and AURORA are examined, they too demonstrate similar risk reductions for those treated with lipid lowering strategies as seen in SHARP.

We have summarized these and some additional studies in Table 1, highlighting that often fixed dose interventions not aimed at achieving specific targets may have better results than those studies, which aimed for specific laboratory value targets or thresholds. On balance, those in which the intervention is targeting a physiological process with multiple effects (not a specific target or threshold value) have been promising. Note that the above discussion and the table are not exhaustive, but serve to illustrate our thesis.

Table 1 | A listing of key representative studies of interventions with hypothesis, study name (see text for details), type of intervention (target driven vs. non–target driven or fixed dose), outcomes, and caveats

Hypothesis	Name	Intervention/strategy: Specific target	Intervention/strategy: Fixed dose, no target	Outcomes	Reference number	Caveats
Increased hemodialysis dose will improve mortality	HEMO	Yes		+/−	11	All trial participants had to achieve a baseline Kt/V > 1.3
Earlier initiation of dialysis will improve mortality	IDEAL	Yes		+/−	20	Mean eGFR differed only slightly between the groups
Targeting higher Hb with ESA will improve 'composite CV endpoint'	TREAT, CHOIR	Yes		+/−	12,13	Increased stroke in darbepoetin-treated group; CHOIR: late-stage CKD, high comorbidities; adverse events in high target group
Non-calcium-containing phosphate binders will improve mortality	DCOR	Yes		−	21	Open labeled study, 46% patients discontinued early
Treatment of hyperparathyroidism with cinacalcet will improve outcomes in hemodialysis patients	EVOLVE	Yes			7	Placebo controlled trial of cinacalcet in those with HPTH; large well done study; no impact on outcomes of interest
mTOR inhibitor (sirolimus) will slow kidney volume increase in ADPCKD			Yes	−	22	Open labeled over only 18 months possibly too small a dose of sirolimus
mTOR inhibitor (everolimus) will slow cyst growth in ADPCKD			Yes	+ (kidney volume)—(kidney function)	23	Follow-up only 2 years; participants were late stage
Tolvapten for ADPCKD			Yes	Delay progression		Side effects of liver dysfunction and hyperuricemia problematic
Antioxidant (NAC)			Yes	+	5	Small sample size, short duration, and not blinded
Antioxidant (vitamin E)	SPACE		Yes	+	2	Negative trials such as HOPE in other populations may have influenced translation
Therapy for acidosis will slow CKD progression			Yes	+	3,53	Some patients with comorbidities excluded limiting generalization
Tighter hypertension control/therapy will slow CKD progression	RENAAL		Yes	+	42	Type II DM 5-year study
	ON TARGET	Yes		−	27,28	General population with CVD risk
Anti-hyperuricemia therapy will slow CKD progression			Yes	+	4,54	Open labeled studies with small sample size, limited duration; vascular indices improved
Treating hyperhomocysteinemia will improve kidney function and reduce CV events	DIVINe		Yes	−	15	Diabetic nephropathy only
Lipid lowering therapy will improve 'composite CV endpoint'	4D, AURORA	Yes		+/−	16,30	Dialysis patients only; 4D only diabetics; both composite endpoints included non-atherosclerotic events
Combination lipid lowering therapy will improve 'composite CV endpoint'	SHARP		Yes	+	31	Atherosclerotic events reduced
Vitamin D therapy (oral paricalcitol) will improve cardiac function	PRIMO		Yes	+/−	32	No change in LV structure or function; signal for reduced CV hospitalizations
Vitamin D therapy (oral paricalcitol) will improve urinary albumin excretion	VITAL		Yes	+	51	Only 24-week study, no measures of kidney function
Bardoxalone therapy will improve renal outcomes in type 2 diabetes with nephropathy	BEACON		Yes	−	6	Therapy that increases GFR in diabetics will be of benefit; stopped early due to severe adverse effects

Abbreviations: ADPCKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agents; HD, hemodialysis; HPTH, hyperparathyroidism; LV, left ventricular.
Reference numbers correspond to those in the text. Note that those interventions in which specific fixed doses were given or no targets were attempted, on balance, have demonstrated positive outcomes.
Outcomes: +, positive; −, negative; +/−, no effect.

DELAYING PROGRESSION OF CKD

CKD may progress from activity of the primary disease or from factors that promote ongoing kidney damage irrespective of initial insult. There are a plethora of experimental and clinical studies delineating the latter, which is complex, and new pathways are still being identified. Renal fibrosis is the final common pathway and has been described in expert reviews.[43,44] Factors important in progression, where there are opportunities to intervene, include metabolic factors (proteinuria, hyperglycemia, dyslipidemia, oxidative stress, and hypoxia), paracrine factors (AII, endothlin, growth factors), genetic factors, hemodynamic factors (arterial

hypertension, glomerular hypertension, shear stress, endothelial function, and arterial stiffness), cellular factors (epithelial–mesenchymal transition, myofibroblasts), and inflammatory factors (cytokines, chemokines, toll-like receptors). All of these inter-relate and so targeting one factor or process is not likely to have a major impact and may adversely alter other pathways.

In addition, there is clearly documented variability in patient and kidney outcomes in which some having rapid eGFR decline, others slow decline, some remain stable, and some may actually improve.[45–47] Because of this variation, the impact of interventions to slow CKD progression may be applied to some who do not need it, negating overall effects in clinical trials.

INTERVENTIONS TO DELAY CKD PROGRESSION

Therapies investigated to slow CKD progression have reflected our understanding of mechanisms involved and have included BP control, renin–angiotensin blockade, statins, hypouricemic medication, bicarbonate and vitamin D.

Clear evidence from multiple intervention trials, summarized elegantly by Bakris *et al.*,[48] show BP control with targets to lower elevated BPs to 130/80 are associated with significant slowing of CKD progression. In addition, specific use of ACEi or ARB, slow CKD progression. The REIN, RENNAL, IDNT studies among others, demonstrated the benefits of RAAS blockade.[49–52] Targeting of BP may be construed as different than targeting of laboratory abnormalities. BP values reflect complex physiological processes, and lowering of elevated values has been shown to improve outcomes in multiple populations. Thus, we acknowledge that targeting BP does improve outcomes of CKD patients, but also note that most studies aimed to reduce BP, and few achieved the targets as described in the study protocols. Unlike hemoglobin and phosphate studies, there were not precisely defined narrow ranges of BP to be achieved in the studies. However, we do note that combination of ACEi and ARB therapies have not been of benefit in the populations studied, as intensifying RAAS blockage to improve reduction of surrogate outcomes (proteinuria, or BP control) appears to lead to harm.[39,53]

Many studies including meta-analyses have focused on the potential effects of statins on CKD progression. Some have suggested a small benefit but others including the SHARP study using simvastatin 20 mg and ezetimibe 10 mg failed to show an effect. However, it may be that the wrong population has been targeted. Statins in other contexts have been shown to be more effective when inflammation or atherosclerosis is present.[54,55]

Associations between elevated serum uric acid and CKD progression have been noted in observational databases. Uric acid is potentially toxic to the vasculature and the kidneys and has been implicated in basic, animal, and human studies. Two small, short, RCT's, both using fixed dose allopurinol demonstrated benefit in progression of CKD.[4,56,57] These studies enrolled those with eGFR values <30 ml/min per 1.73 m^2, and all had elevated uric acid, though to variable degrees. A larger randomized double blind placebo controlled trial of slowing of kidney disease progression from the inhibition of xanthine oxidase trial is planned in Australia, with the aim to enroll over 600 patients. Doses of allopurinol, are titrated to impact lowering of uric acid values. Whether or not this study will be able to answer the important questions about uric acid and progression of CKD remains to be seen. Importantly, there is a commitment and recognition that a large study to address this question in a rigorous randomized control trial is required. Perhaps nephrologists will be more likely to participate in this and similar upcoming studies, given the paucity of solid evidence for so many treatments at this time, and our sincere desire to improve outcomes in CKD.

Vitamin D deficiency is linked to poor outcomes in multiple populations, and is evident at early stages of CKD[58] There are multiple studies linking the use of vitamin D compounds to improved outcomes[59,60] When testing apparently simple interventions such as 1, 25 OH_2D3 Vitamin D it is important to consider this as an important regulator of the immune system, cardiac contractility, bone health, renin inhibition and thus can indirectly control BP. The VITAL[61] trial, a randomized control trial conducted in patients with type 2 diabetes taking ACEi or ARB with optimal BP control demonstrated that adjunct fixed dose vitamin D therapy further reduced proteinuria by 15%, which is statistically and clinically significant. However, there was no change in kidney function, and no long-term outcomes were assessed.[61] This surrogate outcome study raised interesting observations, but was too short in duration and underpowered. The PRIMO study interestingly also tested fixed dose paracalcitol, aimed at reducing left ventricular mass index, through lowering of PTH, in a well designed but small randomized control trial of 280 patients. While the PTH was lowered, there was no demonstrable change in left ventricular mass index. Interestingly, there was a significant reduction in cardiovascular disease related hospitalizations.[62] Again, the use of surrogate outcomes and targeting laboratory abnormalities may not lead to the answers expected, or may mislead us away from a potential positive signal. Is it time for a large, longer study randomizing nondialysis CKD patients to use of fixed dose vitamin D or placebo, and determine the impact on cardiovascular disease and hospitalizations over a 5-year time horizon?

One cohort study suggests metabolic acidosis is independently associated CKD progression.[63] Studies addressing bicarbonate therapy to slow CKD progression are also based on physiological observations that acidosis fosters progression by multiple mechanisms, including hydrogen ion activation of complement, pH-induced changes in protein handling, and promotion of uric acid reabsorption. In one study, CKD patients with metabolic acidosis but without heart failure were randomized to fixed dose oral bicarbonate supplementation or no treatment for 24 months. Those taking bicarbonate had slowed CKD progression compared with the control group.[3] A second RCT conducted over 5-years demonstrated similar results.[64] Both of these studies had small numbers, but given the interesting

results, suggest that a larger long-term study is needed. We suggest that it is important to answer this simple question of whether fixed dose supplementation of bicarbonate in those with serum bicarbonate values below the normal range is of value in delaying progression of CKD over a time horizon of at least 5 years in a large cohort of patients receiving 'standard care' including BP control, with ACEi or ARB. This would necessitate a large pragmatic trial, with liberal entry criteria, simple data collection, and the will of nephrology teams around the world to answer the question.

CKD progression occurs through complex processes including but not limited to inflammation, oxidative stress, and fibrosis, which can be measured directly or indirectly. A large number of newer biomarkers are available to researchers, which measure different aspects of inflammatory processes, vascular health, cardiac stretch, volume overload, tissue damage, and fibrosis. Many biomarker assays are variable and subject to inconsistencies and nonstandardization, which limits use.[9,65] Notwithstanding these limitations, there is a lack of understanding of the relative roles of mediators of CKD progression at different points in its trajectory. There are uncertainties regarding what biomarkers to measure and which outcomes to assess; 'hard outcomes' such as death, dialysis, transplantation and cardiovascular events. Perhaps there is a need to develop a combined kidney centric set of outcomes that synthesizes processes, hard outcomes, and tissue so as to better understand disease.

There is the potential to understand CKD much better, with newer tools, collaborative ventures across countries and regions. Phenotypes need to be described in sufficient detail to characterize the key pathobiological processes in large cohorts by collecting blood and urine samples over time. The value of newer biomarkers for the use in clinical trials needs to more robustly tested. We need to understand the stability of values over time, their responsiveness to interventions, changes in disease states, or changes in kidney function. If newer biomarkers are to aid us in the design and execution of clinical trials, then, issues of assay standardization and reproducibility need to be addressed. We need to establish threshold values for disease states, and to determine whether values signify stepwise continuous risk across the spectrum of kidney disease. There are obviously sex and ethnic differences in CKD progression: Why do women progress to ESKD slower and less often than men? Is the role of estrogen as a vascular protector understudied in humans, or is it a more complex explanation? Further studies are required to understand these phenomena. Targeted balanced therapies need to be directed at processes, once well worked out, and with less concern about 'normalizing values', with more focus on resetting the balance of processes to favor health compared with disease. Closer collaboration with transplant kidney researchers should be considered so that we may be able to study the impact of strategies implemented at 'time zero' or in kidneys with similar structure and function. There is much to be learned from those who do not progress: more focus on those individuals may reveal insights for therapy.[13]

Currently a number of large cohort studies are underway,[66–71] which will collect clinical information and biological samples on large numbers of people in different regions of the world. There are significant biobanks already established from large observational and clinical trial cohorts:[66,72,73] we should soon be able to better characterize our patient populations and understand progressive and nonprogressive disease and cross validate findings through proteomic, metabolomic, and genomic studies that are planned. Large, better-characterised populations will be available for clinical intervention trials.

Clinical trials in nephrology have mainly focused on target values of easily measured laboratory values by identifying excesses and deficiencies of specific hormones of substances. This approach has limited our knowledge and therapeutic strategies to targeted levels of laboratory tests. Observational studies have been used to define thresholds for care, interventions, and target values, when in fact their role is to generate hypotheses, describe current state, and offer opportunities to detail cohorts receiving various therapies or care strategies. Voltaire quoted that 'perfect is the enemy of good', so, perhaps nephrologists should attempt to better understand the balance of pathological processes accruing in kidney disease and balance treatment strategies in such a way as to promote better outcomes, and not simply normalize parameters with disregard for potential benefit of the processes that have led to the abnormalities.

CKD patients that progress usually do so over many years hence studies of 5 years duration are often required to ensure useful outcomes. To create an appropriate culture within nephrology, which enhances our ability to answer these questions, we suggest that the majority of patients should be enrolled into clinical studies, whether purely observational, as part of coordinated registries, or into randomized control trials. We should develop a set of protocols to manage our patients and their conditions, which could be tested in pragmatic studies with sufficient rigor to inform future care, with nonrestrictive inclusion and exclusion criteria, so as to ensure generalizability of the results. We should consider large pragmatic studies with fixed doses or exposures to interventions based on physiological processes, and we should refrain from focusing on single value laboratory tests and targets as outcomes of interest.

TRANSLATION OF CLINICAL NEPHROLOGY TRIALS

The outcomes of clinical trials in nephrology have been inconsistently applied and promoted. For instance the results of the first REIN study report on 117 patients with mean follow-up 16 months was quite quickly translated into clinical practice. Perhaps with pharmaceutical industry support of work from highly respected researchers it was possible to convince regulators of its importance. The results of the SPACE trial recruiting 196 patients for a median of 519 days have not been translated or even progressed to validation in a larger population. This and the NAC trial in hemodialysis patients are the only trials to show any prospect

of a positive cardiovascular outcome for dialysis patients. So why have we not investigated this lead further? Is it because these are low cost drugs with little likelihood of a return on investment? Were the investigators not able to promote their findings as well? We are not suggesting that positive small trials be implemented without validation in larger studies, but rather that we must be diligent in critical evaluation of both positive and negative studies, and in our application of clinical study findings to clinical practice.

NEW PARADIGMS OF COLLABORATION AND INVESTIGATION

Nephrology research requires regeneration around key questions, which if answered, will impact patient outcomes substantially. Is it possible to slow the CKD progression and attenuate comorbidities with simple approaches to acidosis and hyperuricemia, alone or in combination? Can replacement with fixed doses of compounds known to be deficient in CKD, lead to improved outcomes? What are the benefits and harm of such strategies in large populations? Can large 10,000+ person trials of sufficient duration and rigor be conducted to answer these questions? Will it be possible to fund such studies, given that some of the simple, sometimes complementary, therapies offer little financial return for industry? It would be ideal if Governments and funders of health services could underwrite some of these trials to facilitate knowledge accrual, translation and reduce health-care costs.

Most importantly, we suggest there are complementary and different methodologies and issues that need to be addressed in order to design studies to address key questions in nephrology. It is not appropriate or feasible to describe the 'perfect study design'; rather we offer a framework for moving forward, which takes into account some key aspects of the population. We suggest that criteria for the development and execution of future clinical trials need to be developed and vetted with the larger international community of nephrology researchers. Ideally, establishing a set of fundamental questions that should be answered in the next decade would help to focus the community and generate enthusiasm for trial participation. In all study design considerations, we would urge investigators to (1) acknowledge the heterogeneity of CKD populations and appropriately characterize populations entered into studies; (2) develop methods to identify responders and nonresponders; (3) design interventions, which aim to mimic physiological processes (e.g., intermittent or cyclical therapy) and address multiple aspects of disordered physiology; (4) design pragmatic trials, large scale, adding intervention(s) of interest to current care; (5) change the culture of nephrology such that all patients are enrolled into available protocols, observational or interventional, so as to foster knowledge acquisition and dissemination.

CONCLUSION

Perhaps it is time to reevaluate Cannon's imperative of restoring physiological parameters to normal in acute and CKD states.[74] An improved understanding of the interactions of each of the biological mechanisms involved when correcting abnormalities should be the goal, as should an understanding of the resetting of the homeostat in individuals with disease. There are sufficient examples of how attempts at 'righting' the wrongs, has led to harm or no benefit. Perhaps more attention to the readings of Voltaire and his notion that 'perfect is the enemy of good' should be incorporated into current therapeutic strategies and evaluation of study designs, all in the interest of improving patient outcomes.

DISCLOSURE

All the authors declared no competing interests.

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