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REVIEW

Time for clinical decision support systems tailoring individual patient therapy to improve renal and cardiovascular outcomes in diabetes and nephropathy

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ABSTRACT

The current guideline treatment for patients with diabetes and nephropathy to lower the high risk of renal and cardiovascular (CV) morbidity and mortality is based on results of clinical studies that have tested new drugs in large groups of patients with diabetes and high renal/CV risk. Although this has delivered breakthrough therapies like angiotensin receptor blockers, the residual renal/CV risk remains extremely high. Many subsequent trials have tried to further reduce this residual renal/CV risk, without much success. *Post hoc* analyses have indicated that these failures are, at least partly, due to a large variability in response between and within the patients. The current 'group approach' to designing and evaluating new drugs, as well as group-oriented drug registration and guideline recommendations, does not take this individual response variation into account. Like with antibiotics and cancer treatment, a more individual approach is warranted to effectively optimize individual results. New tools to better evaluate the individual risk change have been developed for improved clinical trial design and to avoid trial failures. One of these tools, the composite multiple parameter response efficacy score , is based on monitoring changes in all available risk factors and integrating them into a prediction of ultimate renal and CV risk reduction. This score has also been modelled into a clinical decision support system for use in monitoring and changing the therapy in individual patients to protect them from renal/CV events. In conclusion, future treatment of renal/CV risk in diabetes should transition from an era of 'one size fits all' into the new era of 'a fit for each size'.

Keywords: diabetes, kidney, personalized medicine, response variation

INTRODUCTION

Diabetes is a growing disease with high renal and cardiovascular (CV) morbidity and mortality. Despite multiple efforts over the last decades to find therapies to halt the progression of renal and CV disease in both Types 2 and 1 diabetes, success remains limited, and a large part of the treated population remains unprotected and at high residual risk for renal/CV disease progression.

The current approach to tackling this disease is based on testing new therapies in large groups of patients with Type 2 diabetes with high renal and/or CV risk. Given the high residual risk, even after successful new drug approvals, the question remains whether this 'group strategy' is still efficient enough, or whether should we reorientate ourselves and start thinking that we will deliver much more renal/CV protection for our patients by approaching them on a more individual basis?

CURRENT ADD-ON TREATMENT STRATEGIES TO HALT RENAL AND CARDIOVASCULAR DISEASE PROGRESSION

Halting renal and CV disease progression are currently based on targeting risk factors that are causally related to progression of disease. Multiple modifiable risk factors have been identified that each contribute to renal and CV risk in patients with diabetes, e.g. smoking, increased food consumption combined with physical inactivity, increase in body weight, blood pressure, blood glucose, cholesterol, potassium and urine albumin. Changing lifestyle and starting therapies that lower the risk factors was the logical approach to reduce renal and CV risk. To this end, many clinical trials have been carried out over recent decades, and important steps have been made in halting or slowing the morbidity. Lowering glucose and high blood pressure seemed to be the most logical starting point in diabetic patients, and indeed this did create an impact [1]. However, the effect was relatively small, and new targets and therapies were tested. It is important to note that these new therapies were always tested as an add-on to the established therapies found in previous trials. Breakthrough therapies like the intervention in the renin–angiotensin system (RAS), by first angiotensin-

converting enzyme inhibition (ACEi) in 1993 and later angiotensin-receptor blockade (ARB) in 2001, were indeed a valuable add-on to 'standard' glucose- and blood pressure-lowering therapies [2–4]. The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and IDNT (Irbesartan Diabetic Nephropathy Trial) trials showed that losartan and irbesartan, respectively, reduced renal/CV risk in patients with diabetes and chronic kidney disease by ∼20% compared with standard therapy. However, despite this big success (ACEi and ARBs are still the main component of the current guideline to treat renal and CV risk in patients with diabetes and nephropathy!), the residual renal and CV risk remained extremely high, equalling the mortality of treated cancers [5].

Since then, many attempts have been made to further lower this high residual risk by testing different new therapies in large clinical trial settings, such as additional interventions in the RAS using dual RAS blockade (ACEi + ARB in the Veterans Affairs Nephropathy in Diabetes, VA-NEPHRON-D, or ARB + renin inhibition in the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints, ALTITUDE) and lowering new risk targets like albuminuria (sulodexide, the SUlodexide Nephropathy study, SUN), haemoglobin (erythropoietin-stimulating agent, Trial to Reduce Cardiovascular Events with Aranesp Therapy, TREAT), endothelin (endothelin antagonist, A Study of Cardiovascular Events iN Diabetes, ASCEND) or inflammation (bardoxolone, the Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events trial, BEACON). Intriguingly, both further RAS blockade and other risk target changes did not result in further renal/CV protection, and sometimes even an increase in risk [6–10]!

REASON FOR HIGH RESIDUAL RISK

Why did these new therapies fail? Did we choose the wrong new drugs, or could it be that we have been selecting the wrong patients for the different drugs?

Multiple (*post hoc*) analyses have been carried out diving into the data from the failed trails (as well as the successful trials). These analyses show that we do not appear to have chosen the wrong new drugs. In fact, although the overall trials' results were neutral or even negative, the drugs did lower the intended risk factors and did lower the renal and/or CV risk, but only in a selected group of patients in the trial [11, 12]. Further *post hoc* analyses of these trials showed that if we had selected our patients more carefully before starting the trials, we may have had totally different and positive results. As an example: if we had selected patients in ALTITUDE that showed an initial (first couple of months) response of >30% albuminuria lowering, the trial would have ended after several years with a >50% reduction in renal risk [13]. Another example: if we had selected patients in the BEACON study that were not at risk for sodium retention, we would have avoided the increased risk for heart failure that came with starting bardoxolone therapy, and that in turn would have likely resulted in a positive renal protection trial [14]. Even when we went back to further analyse the early positive trials like the RENAAL trial, we found that the positive trial results in renal protection were mainly based on the selected group of patients that showed clear reduction in albuminuria at start of the therapy; patients that showed no effect on albuminuria or even an increase showed no signs of renal protection, or even renal harm [15].

All this unmet need and trial failures may thus well have been the result of the fact that we appear to have completely overlooked the so-called variability in drug response of the individual patients that were recruited in all our trials. In addition, we may have overlooked that the add-on strategy (new drugs are tested in patients that are required to receive the guideline recommended therapies) does not help to achieve positive trials when we are dealing with variability in response—patients that are responders to the guideline therapy do not need new drugs and do not contribute to a change in risk, it is the non-responders that need the new therapy.

TIME FOR PERSONALIZED/PRECISION MEDICINE

What is the existing evidence that a more individual approach would have been much better to advance renal and cardiovascular protection therapies in diabetes?

First, there is valuable information and experience showing that add-on therapy strategies are not always the best. Lowering of blood pressure used to be approached in the far past by an add-on structure—if a diuretic did not lower blood pressure enough, a beta-blocker, and in addition a vasodilator, were added (so-called triple therapy). Later, we realized that some people just do not respond to certain blood pressure-lowering therapies and that it is better to stop the drug if there is no response and switch to/try a new drug from another antihypertensive class [16]. Does this history of 'add-on' or 'switch' strategy apply to our diabetes treatments? In our opinion, it does. We demonstrated some time ago that patients who do not show a reduction in albuminuria when given an ARB also do not respond well to dose increase, or to addition of an ACEi [17]. Could this explain why we did not see an effect of dual RAS therapy compared with single RAS therapy in ALTITUDE or VA-NEPHRON-D?

Secondly, there is clear evidence that one needs to select a specific drug for a specific patient to obtain a desired response. The clear example comes from treating infections with antibiotics—one selects an antibiotic drug that kills the bacterium (if needed diagnosed in a Petri dish). The same is now happening in oncology; the drug is selected to inhibit the growth of the specific cancer cell of the patient (diagnosed in a tumour biopsy).

In diabetes, renal/CV risk is also likely not driven by one cause, and patients also have different causes for the rise of their risk factors. Thus, responses to a single drug will vary between patients: the drugs that have little or no (or even an opposite) effect on the intended risk factor will not protect, or will even harm, the patient, and should not be given!

The lessons we learned from these multiple trial failures and the *post hoc* analyses of the trials is that we should look at our patients with much more focus on the variability in the response of the targeted risk factor to the new intervention: patients with 'bad' responses should be excluded from trials and patients with 'good' responses should be included. New trials

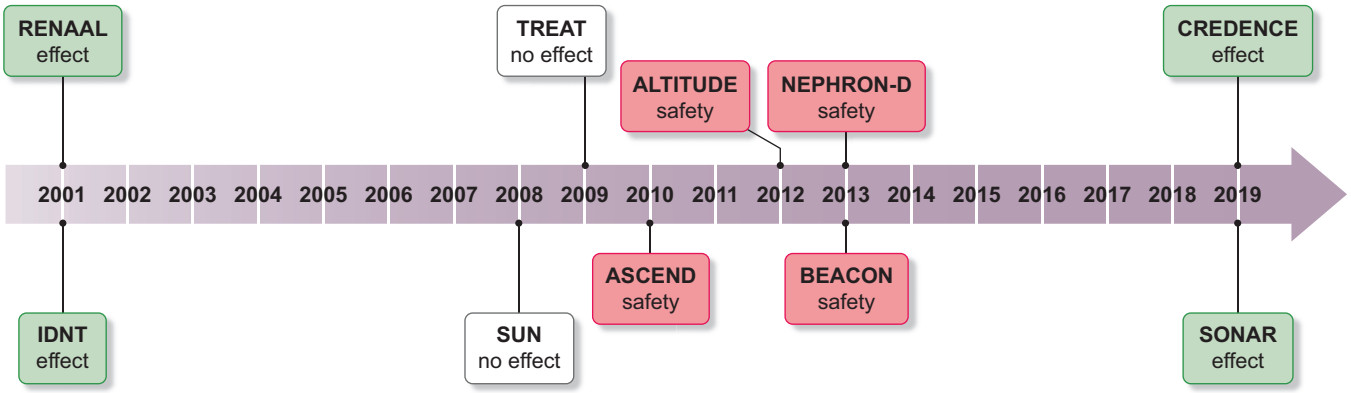

FIGURE 1: Clinical trials testing new drugs for renal/cardiovascular protection in Type 2 diabetes with nephropathy: nearly 20 years of no success due to stopping of trials for safety reasons or due to no success on the surrogate or hard endpoint [3, 4, 6–11, 17, 18].

are indeed going into this direction, like the Study of Diabetic Nephropathy with Atrasentan (SONAR) trial, which is only enrolling patients that have >30% albuminuria reduction to the tested endothelin antagonist atrasentan, whereas those patients that show excess sodium retention to atrasentan exposure are excluded from the trial. This way the trial population is 'optimized' in response for a good trial outcome. Another example is the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial (CREDENCE), in which an inhibitor of sodium-glucose cotransporter 2 (SGLT2 inhibitor) has a beneficial effect on four important renal risk markers (glucose, blood pressure, body weight and albuminuria), without any known negative effect on other renal risk markers.

Intriguingly, these two trials (SONAR and CREDENCE), after nearly 20 years, are the first trials to show renal protection in the patients with diabetes and nephropathy above and beyond RAS blockade. Impressive results were obtained of >30% risk reduction for the primary endpoints, including doubling of serum creatinine and end-stage renal disease [18, 19].

Although this major breakthrough will benefit a lot of our high-risk patients, we still have a high residual risk left. In CREDENCE and in SONAR a limited amount of patients are the good responders, which leaves still a lot of non-responders and thus patients with still high residual risk.

How can we further optimize this personalized approach in the future?

NEED FOR INDIVIDUAL PATIENT APPROACH TO CARE (CLINICAL DECISION SUPPORT SYSTEMS)

To avoid individual non-response or 'bad' response to therapy, we ideally need to find out what the mechanism of renal and CV disease progression is in each individual patient, find a drug that 'attacks' that specific mechanism and treat the patient with that drug. Currently, several large consortia are searching worldwide for new insights into these disease mechanisms, including studies using renal biopsies (even in patients with diabetes and kidney disease). The European BEAt-DKD (Biomarker Enterprise to Attack Diabetic Kidney Disease) consortium is an example of such an initiative. A system biology approach on the renal tissue, in concert with the phenotypic expression of known risk markers in that patient, should give us more insight into what drug we should use or design for that type of patient [20]. However, in the treatment of renal and CV risk in diabetes, that type of approach still needs a lot of study, including studies into the role of gut microbiome in risk and drug response.

In the meantime, the next best approach is to establish the individual drug response of the patient to a drug in how it is lowering the risk factors for renal/CV disease progression. We should be looking not only at the change of the target risk factor. But also at the effect of the drug on other off-target risk factors. It is well known that drugs have multiple effects in a single patient, e.g. intervention in the RAS not only lowers the target risk factor (blood pressure) but also lowers the albuminuria, lowers uric acid, lowers cholesterol, lowers haemoglobin, increases serum potassium, etc. Each of these changes in the different risk factors contributes on its own to renal/CV outcome, whereas blood pressure, albuminuria and cholesterol reduction contribute to renal/CV protection, and reduction in haemoglobin and rise in serum potassium increase renal/CV risk of that patient. Thus looking at the changes in the target risk factor is not enough to know whether the drug will protect that patient. We will need to know the sum of the effects of the drug on the different risk factors in a single patient to know and predict what will happen with renal/CV risk in that patient.

We have designed a multiple parameter risk score, so-called parameter response efficacy (PRE) score, which can predict the long-term renal/CV protective effect of the drug on a group of patients by integrating the short-term (several weeks) responses of multiple available risk factors and calculate their overall effect on outcome [21]. Indeed, this PRE score has been proven to accurately predict the renal/CV outcome of Phase III clinical trials like ALTITUDE [22], SONAR [23] and CREDENCE (H.J.L.Heerspink et al., unpublished data) based on the observed Phase II changes in multiple risk factors.

We have recently designed a method that allows application of this technique to the individual patient. This prototype clinical decision support system can be used at the doctor's desk. It takes the changes in multiple risk factors (e.g. glucose, blood pressure, creatinine, potassium, albuminuria, cholesterol, plasma brain natriuretic peptide, body weight, etc.) that occur several weeks after starting or changing a therapy. By integrating these changes and their individual effect on renal/CV progression, we can estimate what the drug is doing for that individual patient. It also relates the residual renal/CV risk to the residual levels of the multiple risk factors, and advises the doctor and patient what therapy strategy should be followed to further lower the risk. This approach will avoid keeping patients on long-term guideline-recommended treatments that do not actually reduce (or even increase) the long-term risk of that patient. Clearly, we will need to validate this approach in practice. However, continuing on the current path of treating our patients with drugs that do not protect that individual is unethical and should clearly be avoided. In analogy to the treatment practice of choosing a specific antibiotic for an infected patient, and in analogy to selecting a specific drug for a cancer patient, the treatment of renal/CV risk in diabetes should transition from an era of 'one size fits all' into the new era of 'a fit for each size'.

If this works, then we need a new approach in trial designs methodologies, like platform and or basket designs. This will help us to identify which patient is benefitting from which new (old) drug and how that drug then performs in a registration trial against a placebo in that specific patient population. This is analogous to what is currently happening in the drug and trial design development in cancer treatment. To achieve this, we need to do trials in groups of patients with the 'same' type of disease mechanism and the same type of response to a new drug. To find these specific groups of patients, we will need the international renal community to put their 'heads' together and form a large international database filled with patients with different renal diseases that can participate in such new trial designs [24].

We are facing a huge challenge if we want to implement all this and make it a success. But if our 'trade' is truly patient oriented, we need to make that change today rather than tomorrow.

CONFLICT OF INTEREST STATEMENT

D.d.Z. has served on advisory boards and/or as speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma and Mitsubishi-Tanabe; has served on steering committees and/or as a speaker for AbbVie and Janssen; and has served on Data Safety and Monitoring Committees for Bayer.

H.J.L.H. has served as a consultant for Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck and Mitsubishi-Tanabe; and has received grant support from Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen.

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