Does SGLT2-inhibition with dapagliflozin overcome individual therapy resistance to RAAS inhibition?

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Abstract

Aims: Individual patients show a large variation in their response to renin-angiotensin-aldosteron-system blockade both in surrogates like albuminuria and hard renal outcomes. Sodium-glucose co-transporter 2 inhibitors (SGLT2) have been shown to lower albuminuria and to confer cardiovascular and possibly renal protection. To establish whether individual therapy resistance to RAASi can be overcome by adding an SGLT2 inhibitor we assessed individual albuminuria responses in patients exposed both to RAASi and the SGLT2 inhibitor dapagliflozin.

Materials and Methods: We used data from a randomized controlled cross-over trial designed to assess the albuminuria lowering effect of 6-weeks treatment with dapagliflozin 10 mg/d. We extracted from the electronic medical records data on the albuminuria response upon start of

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RAASi before the trial period, and analyzed the individual albuminuria response to RAASi and to dapagliflozin.

Results: We retrieved data on RAASi use from 26 patients (age 62 (SD 8); female gender 6 (23%); 24-hour urinary albumin excretion 521 [187 – 921] mg/24hr. The mean albuminuria lowering response to RAASi was 26.5% (range -76.1 to +135.1%). The addition of dapagliflozin resulted in a further reduction of 34.9%, (range -83.9 to +94.2). Interestingly, the albuminuria response to RAASi significantly correlated with response to dapagliflozin (Pearson correlation coefficient 0.635 (95%CI 0.328 to 0.821); $p<0.001$) indicating that patients who did not respond to RAASi also did not respond to dapagliflozin.

Conclusion: Individual therapy resistance to RAASi cannot be overcome with the addition of a completely different class of drugs, SGLT2 inhibitors. These data suggest that the individual drug response is an intrinsic individual characteristic possibly unrelated to the type of intervention, unless the mode of action of dapagliflozin on albuminuria is through the RAAS.

Introduction

Type 2 diabetes mellitus is a chronic condition with a rapidly increasing prevalence. It is expected that 10% of the worldwide population will be diagnosed with type 2 diabetes in 2040.[1] About 30% of all diabetes patients develop kidney disease and half of all patients cardiovascular disease.[2] In addition to drugs that lower risk factors such as high glucose and high blood pressure, intervention in the renin angiotensin aldosterone system (RAAS) is the current mainstay of treatment for renal and cardiovascular complications due to diabetes. Despite Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARB) are proven effective on a population level, it is known that approximately 30% of patients do not adequately respond to ACEI or ARB and continue to show a progressive renal function loss.[3] This individual response variability in long-term renal preservation is predicted by the variability in short-term responses in renal risk markers such as blood pressure, albuminuria, and renal hemodynamics.[4]

A couple of studies aimed to develop approaches to overcome therapy resistance to RAAS-intervention. These studies investigated whether up-titrating the dose of the drug, adding an ARB to an ACEi,[5] or switching from an ACEi to an ARB or vice versa would improve individual response.[6] It appears that the individual response is remarkably consistent regardless of the dose or type of RAAS-intervention. In other words, non- or poor-responsive patients to one dose or type of ACEi or ARB continue to have high blood pressure and albuminuria after dose up titration or switching from ACEi to ARB or vice versa. Novel drugs are thus particularly desired for the non- or poor-responding patients.

An example of a promising new class of renoprotective drugs are sodium-glucose cotransporter-2 inhibitors (SGLT2). These drugs do not only decrease HbA1c on a population level, but have, just like ACEi and ARBs, beneficial effects on multiple renal and cardiovascular risk markers including albuminuria.[7] Recent data indeed suggest that SGLT2 inhibitors confer renal protection.[8] However, when looked at the individual, a wide individual variability in surrogate response markers to SGLT2 inhibitors has been observed.[9] Since SGLT2 inhibitors target a different hormone system than RAAS intervention, it may be a novel approach to overcome individual therapy resistance to ACEi or ARBs. There are, however, no data as to whether individual patients who do not respond to RAAS intervention will respond when new interventions such as SGLT2 inhibitors are added. To address this question on the level of a

surrogate outcome, we analyzed post-hoc the individual albuminuria response to RAASi and with the addition of the SGLT2 inhibitor dapagliflozin.

Methods

We used data from a randomized placebo controlled cross-over trial designed to assess the albuminuria lowering effect of dapagliflozin. The study design and main outcomes were previously published.[9] A total of 33 patients with type 2 diabetes aged between 18 and 75 years were enrolled from the outpatient clinic of the Department of Internal Medicine Ziekenhuis-Groep Twente, Almelo/Hengelo, the Netherlands. To be eligible, patients needed to have a first morning void albumin:creatinine ratio ≥100 mg/g and <3500 mg/g (11 – 396 mg/mmol), eGFR ≥ 45 ml/min/1.73m^2, HbA1c between 55 and 100 mmol/mol (7.2 and 11.3 %), and were required to be on stable RAAS-inhibiting therapy for more than 4 weeks. The study employed two consecutive cross-over treatment periods of 6 weeks each, in which patients were treated with dapagliflozin 10 mg per day or placebo in random order, with wash-out periods of 6 weeks in between. The percentage change from baseline in 24-hour urinary albuminuria excretion at 6 weeks was the primary end point. Therapy adherence in this study was excellent with 97.5% of all medications being taken. We extracted from the electronic medical records data on the albuminuria response upon start of RAASi before the trial period. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen, the Netherlands. The study was registered with the Netherlands Trial Register (NTR 4439). All patients signed informed consent before any specific study procedure commenced.

Comparisons of changes in albuminuria during RAASi and when dapagliflozin was added were performed using Deming linear regression which accounts for errors in observations in both the x-value and y-value. A Fisher's z' transformation was performed to calculate the 95% confidence interval of the correlation. Comparison of baseline characteristics between responder (≥30% reduction in albuminuria) and non-responder patients (<30% reduction) to dapagliflozin were tested with t-tests. Univariate linear regression analyses were performed to assess which baseline characteristics associated with albuminuria response to dapagliflozin. Analyses were conducted with SAS software version 8·2 (SAS Institute, Inc., Cary, NC, USA) and Stata SE software 13.0 (Statacorp, College Station, TX, USA). Statistical tests were two-sided, with a statistical significance level of 5%.

Results

We retrieved data from 26 patients of whom thirteen were treated with an ACEi and thirteen with an ARB. The characteristics of these patients are shown in Table 1. In this population, the mean albuminuria lowering response to RAASi was 26.5% with a large between individual variability (range -76.1 to +135.1%). The mean albuminuria lowering response when dapagliflozin was added was 34.9%, again with a large between individual variability (range -83.9 to +94.2). Interestingly, there was a significant positive correlation between the response to RAASi and dapagliflozin (Pearson correlation coefficient 0.635 (95%CI 0.328 to 0.821); $p<0.001$) indicating that patients who did not respond to RAASi also did not respond to dapagliflozin (Figure 1). Several baseline characteristics were tested to explore whether they were associated with the response to RAASi or dapagliflozin, but none of these were different in patients with more or less than 30% albuminuria reduction during dapagliflozin treatment (Table 1), also when analyzed on a continuous scale.

Discussion

Personalized or precision medicine, which aims to target the right drug to the right patient at the right time, is increasingly recognized as the future approach to maximize effectiveness for the treatment of many diseases. RAASi is the current mainstay of treatment to slow progression of renal function decline but individual patients should a wide variation in response with approximately one-third of patients not responding at all. In this study we showed that individual therapy resistance to RAASi cannot be overcome with the addition of a completely different drug class, SGLT2 inhibitors.

The results of the present study are unexpected and intriguing given the differences in mechanism of action of RAAS and SGLT2 inhibition. Although we have previously found that non-responders to ACEi also do not respond to ARB,[6] it was not so much a surprise because these drug classes interfere in the same hormone system, known to be mechanistically involved in the progression of renal disease. The hope for non-responders is that we identify other mechanisms that drive disease progression in these patients, and drugs that interfere effectively in that mechanism. The current finding that a completely different class of drugs, SGLT22 inhibitors, does not lower albuminuria in patients who are non-responsive to RAAS intervention suggests that the individual drug response is an intrinsic individual characteristic possibly

unrelated to the type of intervention. If this is confirmed, and if indeed the two drug classes target different renal progressive disease mechanisms, we need additional research efforts to better understand the factors driving therapy resistance in order to specifically develop therapeutic/pharmacological measures to overcome therapy resistance. It could be argued that non-responders to both RAAS and SGLT2 inhibition may reflect a general lack of response to hemodynamic interventions given that both RAAS and SGLT2 inhibition have profound hemodynamic effects albeit through different mechanisms: RAAS inhibitors cause efferent vasodilation whereas SGLT2 inhibitors cause afferent vasoconstriction.[7] We evaluated several biochemical and physical biomarkers to differentiate responders from non-responders, including RAAS parameters, but failed to identify any. The difference in albuminuria at baseline between responders and non-responders may be interpreted as if higher albuminuria levels are associated with therapy resistance to SGLT2 inhibition. However, the albuminuria difference did not reach statistical significance ($p=0.40$), also in continuous analyses, and is likely a chance finding. Future analyses in larger studies are therefore required to identify biomarkers of therapeutic response.

It is known that the day-to-day variability in albuminuria is substantial.[10] Accordingly, the between patient variability in changes in albuminuria after treatment initiation may reflect a true variability in pharmacological response or random day-to-day variability in albuminuria. In previous studies we showed that the individual response to ACEi, ARB, and dapagliflozin was reproducible for the individual at re-exposure to the same dose and drug.[9, 11] This finding suggests that the large between patient heterogeneity in albuminuria response is a true pharmacological variation in response and not a random phenomenon.

This study was a *post-hoc* analysis of a clinical trial and therefore should only be interpreted as hypothesis generating, specifically because of the small sample size and short follow-up duration. Another limitation is the retrospective design and the use of historical data to determine the response to ACEi and ARB. Prospective clinical trials designed to assess variations in individual response to different interventions, such as the ROTATE trials (NTR5602; NTR5603), will provide more definitive and mechanistic insight in the individual response to different albuminuria lowering interventions including an ARB (telmisartan) and SGLT2 inhibitor (empagliflozin). Unfortunately, adherence to RAASi was not recorded at the time patients started with ACEi or ARB. Finally, we note that although SGLT2 and RAAS

inhibitors have different targets, an interaction between the RAAS and SGLT2 transporters has been postulated.[12] It cannot be excluded that this explains the observed consistent response to RAAS intervention and dapagliflozin.

The current drug development and registration approach is focused at establishing drug efficacy and safety at a population level. The present findings highlight the importance to focus on the individual and develop specific strategies to overcome therapy resistance to current guideline recommended therapies since non- or poor-responding patients to currently used interventions may also not respond when new interventions are added.

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Contributors

SP and HJLH were responsible for data collection, analysis, data interpretation and manuscript preparation. DdZ and GL contributed in data interpretation and contributed to critical revision of the publication. The corresponding author had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the analysis.

Acknowledgment

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Conflicts of interest

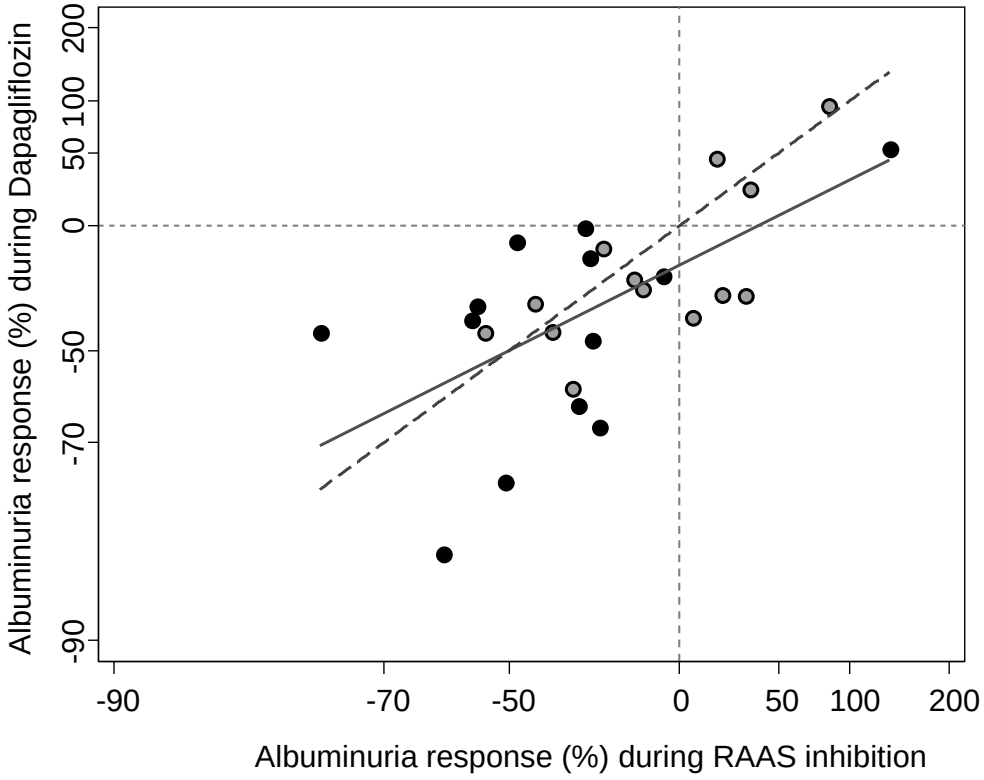
SP reports no conflicts of interest. DdZ is consultant for and received honoraria (to employer) from AbbVie, Astellas, Boehringer Ingelheim, Bayer, Eli Lilly, Fresenius, Janssen and Merck. . HJLH is consultant for for AbbVie, Astellas, Astra Zeneca, Boehringer Ingelheim, Fresenius, Janssen, and Merck and has a policy that all honoraria are paid to his employer. GL received lecture fees from Sanofi, Astra Zeneca, Jansen. He served as a consultant for Abbvie, Sanofi, Novo Nordisk, Astra Zeneca, Boehringer Ingelheim, and MSD. He received a research grant from Astra Zeneca.

Tabel 1: Baseline characteristics at entry into the trial and stratified by the albuminuria lowering response to dapagliflozin. Mean and standard deviations are reported except otherwise indicated

	Overall population (N=26)		Non-Responder (N=10)	Responder (N=16)
Age (year)	62.2 (8)		62.0 (6)	62.3 (9)
Female gender (n, %)	6 (23.1)		2 (20.0)	4 (25.0)
Systolic BP (mmHg)	142.0 (14)		144.5 (10)	140.5 (17)
Diastolic BP (mmHg)	76.6 (6)		79.6 (4)	74.6 (6)
Body Mass Index (kg/m^2)	31.0 (5)		29.2 (4)	32.1 (6)
Hba1c (mmol/mol)	57.3 (10)		57.6 (13)	57.1 (9)
eGFR (ml/min/1.73m^2)	72.8 (22)		69.1 (15)	75.2 (25)
Renin (pg/ml)‡	20.0 [10.4 – 52.3]		20.6 [10.8 – 56.1]	19.7 [9.6 – 52.3]
Aldosteron (pg/ml)‡	63.6 [30.4 – 112.2]		59.8 [28.0 – 155.0]	63.6 [41.6 – 112.2]
Urine:				
Albumin excretion (mg/24hr)‡	521 [187 – 983]		817 [413 – 1198]	407 [159 – 832]
Sodium excretion (mmol/24hr)‡	176 [125 – 249]		180 [125 – 259]	175 [127 – 244]
Potassium excretion (mmol/24hr)‡	74 [61 – 97]		66 [61 – 107]	78 [56 – 91]

‡ Median with 25th and 75th Percentile reported

Figure 1: Individual albuminuria response to SGLT2 inhibition and RAAS intervention. The grey circles indicate patients who used an ACE-inhibitor, the black circles indicate patients who used an ARB. The straight black line indicates the regresion line. The dashed grey line indicates the line of identity.



References:

1. International Diabetes Federation, IDF Diabetes Atlas 6th edition. 2013.
2. de Boer, I.H., T.C. Rue, Y.N. Hall, P.J. Heagerty, et al., Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA, 2011. 305(24): p. 2532-9.
3. Rossing, P., E. Hommel, U.M. Smidt, and H.H. Parving, Reduction in albuminuria predicts a beneficial effect on diminishing the progression of human diabetic nephropathy during antihypertensive treatment. Diabetologia, 1994. 37(5): p. 511-6.
4. Schievink, B., D. de Zeeuw, H.H. Parving, P. Rossing, et al., The renal protective effect of angiotensin receptor blockers depends on intra-individual response variation in multiple risk markers. Br J Clin Pharmacol, 2015: 80(4):678-86.
5. Laverman, G.D., G. Navis, R.H. Henning, P.E. de Jong, et al., Dual renin-angiotensin system blockade at optimal doses for proteinuria. Kidney Int, 2002. 62(3): p. 1020-5.
6. Bos, H., S. Andersen, P. Rossing, D. De Zeeuw, et al., Role of patient factors in therapy resistance to antiproteinuric intervention in nondiabetic and diabetic nephropathy. Kidney Int Suppl, 2000. 75: p. S32-7.
7. Heerspink, H.J., B.A. Perkins, D. Fitchett, M. Husain, et al., Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes: Cardiovascular and Kidney Effects, Potential Mechanisms and Clinical Applications. Circulation, 2016: 6: 134(10):752-72 .
8. Wanner, C., S.E. Inzucchi, J.M. Lachin, D. Fitchett, et al., Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med, 2016 28;375(4):323-34.
9. Petrykiv, S.I., G.D. Laverman, D. Zeeuw, and H.J. Heerspink, The albuminuria lowering response to dapagliflozin is variable and reproducible between individual patients. Diabetes Obes Metab, 2017 doi: 10.1111/dom.12936.
10. Witte, E.C., H.J. Lambers Heerspink, D. de Zeeuw, S.J. Bakker, et al., First morning voids are more reliable than spot urine samples to assess microalbuminuria. J Am Soc Nephrol, 2009. 20(2): p. 436-43.
11. Petrykiv, S.I., D. de Zeeuw, F. Persson, P. Rossing, et al., Variability in response to albuminuria lowering drugs: true or random? Br J Clin Pharmacol. 2017 Jun;83(6):1197-1204.
12. Muskiet, M.H., D.H. van Raalte, E.J. van Bommel, M.M. Smits, et al., Understanding EMPA-REG OUTCOME. Lancet Diabetes Endocrinol, 2015. 3(12): p. 928-9.