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Chronic Kidney Disease - Combination of Rasb and Sglt2 Blockade- Effect on Progression

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I. Introduction

The UAE, a relatively small country in its inception in 1971, has since come a long way in terms of the growth of its population and the development of the health infrastructure. The burden of CKD (chronic kidney disease) is increasing in the MENA region due to the high prevalence of Diabetes mellitus and other risk factors[1,2]. The UAE has a CKD stage 3-5 prevalence of 4-5%[3,4] and the rate of renal replacement therapy yearly is projected at 12-15%, although a more recent review estimates it to be annually increasing at 6-7% [5]. With CKD and the need for renal replacement therapy presenting earlier in the MENA (Middle east North Africa) population than in the European counterparts [6], it would be well-nigh impossible for the country to provide for all the persons who reach ESRD despite the tremendous progress in the health-related infrastructure. Evidence exists for the retardation of CKD in diabetic nephropathy and other glomerulonephritis by using RASB (renin angiotensin system blockade) even in advanced disease[7,8, 6,9-16]. The efficacy of RASB varies in individuals and with race and gender [17,18]. There is now evidence of the benefit of this strategy even in non-proteinuric states, at doses above the typical antihypertensive dosages [6]. The development of SGLT2 receptor blockade has further spurred interest in this field with the discovery of its significant cardiac and nephroprotective properties as evidenced in large clinical trials [7,8.]

Being well attuned to the use of ACEI/ARBs (angiotensin converting enzyme inhibitors/ angiotensin receptor blockers) in our clinic for the last several years, we had the additional advantage of our colleagues in the diabetes center using the SGLT2i(sodium glucose cotransporter 2) inhibitor for diabetes and CKD control. The aim of this study was to determine the efficacy of the effect of RASB in our population and to also determine if adding the SGLT2 blockade did confer additional benefits.

II. Materials And Methods

Four hundred and ninety consecutive patients who attended the nephrology and Diabetic clinics from 1st Jan 2021 to 31 Dec 2021 were screened. 210 had eGFR between 20 and 60(or more) and were studied. Historical records of patients seen in the period from Jan 2015 to Feb 2018, who did not have a systematic graded optimization of the RASB, including those who did not have ACE/ARB exposure were used as controls. Of these, 42 had EGFR between 20 and 60, and were used for analysis. Hence, a total of 252 patients were studied. The minimum follow up was 1 year and the last follow up data was collected on 30th April 2025.

Exclusion criteria were as follows- 1) Those who had active renal disease being controlled with immunosuppressives 2) Those who had acute renal failure at presentation 3) Those who underwent correction of obstructive uropathy or renal artery stenosis.

Our clinic has 4 nephrologists, each having varying propensity with respect to the aggressiveness in the use of RASB and hence it was possible to obtain RASB of varying degrees. The general protocol followed were described below [6]

PROTOCOL-

- Start ACEI or ARB at 10-25% of maximal dose and gradually increase dose, allowing for a 30% rise of creatinine or serum potassium upto6meq/l. BP is allowed fall to 110/70mmhg, or even lower if tolerated physically.
- Concomitant antihypertensives to first get the BP down to 130/80mmhg, after which, the other drugs are gradually tapered, allowing for an increase in the dose of ACEI or ARB
- Salt restriction to less than 5gm/day, Potassium restriction if levels go beyond 4meq/l, and protein restriction to 0.75gm/kg (additional supplementation as determined by individual case needs).
- Anti lipidemic agents to get the total cholesterol to less than 200 and LDL to less than 130 (lower if CVS risk factors present)

- Increase the dose of ACEI or ARB till the maximal dose achieved, and even beyond till the proteinuria comes below 150mg and/or the BP comes to less than 110/70 or lower.
- From Jan 2021, all the above patients who did not have contraindications for the use of SGLT2 I, received the said drug. Some received SGLT2 I in isolation, but they were not analysed separately. The doses of SGLt2 I varied between 5 and 10mg and that difference in effect was not sought to be analysed as it is beyond the scope of this study. Those who received ACEI/ARB in any dose along with SGLT2i were classified as dual therapy and those who received supramaximal doses of ACEI/ARB were classified as Max RASB.

MAXIMAL DOSE
The maximal antihypertensive dose recommended by the manufacturer for individual agents are summarized as follows-
ARB-Losartan 100mg, Valsartan 320mg, Telmisartan 80mg, Irbesartan 300mg
ACEI-Enalapril 40mg, Ramipril 20mg, Lisinopril 40mg, Perindopril 16mg

METHOD OF MONITORING AND GUIDING THERAPY
BP, urea, creatinine, serum potassium weas monitored every week (or as and when the patient could), and modification in the dose was done in a gradually increasing fashion after seeing the results. An unplanned control group formed within this population, which were due to- Thos who did not bother to get the tests done or take the medications as per advice and those who were advised by other primary physicians against the escalation in the dose of ACEI/ ARB. Those who could not come to SKMCA for testing were asked to get it done in the PHC and they were contacted telephonically.

RASB QUANTIFICATION
The amount of RASB achieved between the patients sought to be quantified by dividing the dose received by the actual maximal recommended antihypertensive dosage. Eg- if someone received 160mg of valsartan, the RASB was 160/320= 0.5.
Adverse effects thought to be related to ACEI/ ARB and SGLT1 were asked for and documented when found.
In this paper, dual meant use of RASB+ SGLT2 blockade and supramaximal meant exceeding the recommended antihypertensive doses in RASB.

eGFR ESTIMATE AND OTHER VALUES
The eGFR(equilibriated glomerular filtration rate) was estimated by the laboratory and formally documented in the cerner (the hospital Health Information system). Delta eGFR was the difference between the baseline and the last visit. Rate of change of eGFR was calculated dividing this value by the duration of follow up in years and was expressed as ml/min/1.73m2/year

RENAL OUTCOMES
Rate of eGFR fall by more than 50%, or starting dialysis/ transplant

STAISTICAL ANALYSIS
The values were expressed as mean± SD unless otherwise specified. The categorical variables were compared using the X2 test and the continuous ones using the students t test. COX regression analysis was used to determine the factors influencing the renal outcome. In addition to age and gender, the independent variables with P- values less than 0.1 were included in the COX- regression analysis. The analysis was done using the SPSS 17.0 software (Chicago, IL, USA)

III. Results

The mean age was 48.3± 11.2 years and 69 percent were male. The demographic data and the laboratory parameters at baseline and last follow up are indicated in tables 1 and 2.

Table-1

characteristics	All patients N=252(%)	No RASB N=42(%)	Dual N=172(%)	Max RASB N=38(%)
Age- years	48.3±11.2	47.8±11.8	48.3±10.6	48.1±10.8
Gender, male	174(69)	30(71)	115(67)	29(76)
BMI(kg/m2)	26±14.5	26.8±18.4	26.1±17.2	25.5±5.9
Diabetic nephropathy	66(26.4)	7(17)	59(32)	11(28)
Hypertensive nephropathy	34(13)	8(19)	22(12.7)	7(17)
Chronic GN	63(25)	13(31)	36(20.9)	10(25)
Chronic IN/ CPN	72(28.5)	11(26)	44(25.5)	11(27)
Others	17(6.7)	3(7)	11(6.3)	3(7.2)

Proteinuria(>1gm)	130(51.5)	36(86)	88(51.1)	34(89)
SBP baseline	153.3±23	156.2±24.2	154.1±25.1	151.1±22.1
Baseline				
SBP Follow up	136.7±24	143.9±22.8	132.4±24	130.9±25.1
DBP- baseline	89.2±11.2	89.1±12.5	89.3±10.5	89.1±11.6
Baseline				
Follow up	78.8±9	81.0±8.4	77.8± 10.2	77.1±11.3

BMI- body mass index, GN- glomerulonephritis, IN- interstitial nephritis, SBP- systolic blood pressure, DBP- diastolic blood pressure, RASB- renin angiotensin system blockade, gm- grams, kg- kilogram, m2- meter squared, CPN- chronic pyelonephritis

Table-2

characteristics	All patients N=252	No RAASB N=42	Dual N=172	Max RASB N=38
Serum creatinine gm/dl				
Baseline	1.95± 0.88	2.1± 0.6	1.89± 0.5	1.87±0.4
Last follow up	2.82±1.53	3.53±1.9(a)	2.43±1.4(a)	2.5±1.3
Serum albumin				
Baseline	3.71±0.26	3.7±0.5	3.75±0.3	3.68±0.5
Last follow up	3.77±0.3	3.33±0.5	4.01±0.3	3.98±0.7
Serum potassium				
Baseline	3.92±1.4	4.56±0.8	4.2±0.6	4.3+/ 0.5
Last follow up	4.63±1.2	4.5±0.8	4.58±0.6	4.8±0.7
Hemoglobin				
Baseline	10.8±2	10.5±1.5	10.9+-0.7	11±1.0
Last follow up	10.61±3.41	10.1±2	10.8±1.8	10.92+-2.1

RASB- renin angiotensin system blockade, gm- grams, dl- deciliter,a-P value<0.05

The EGFR at baseline, and last follow up, and the delta eGFR between RASB and different disease groups are shown in table 5

Table-3

characteristics	All patients N=252	No RASB N=42	Dual N=172	Max RASB=38
eGFR(ml/min/1.73m2				
Baseline	40±9.8	38.6±11.3	38.8±8.9	39.8±8.8
Last follow up	31.3±13.6	24.8/-12.1(a)	35.4±12.6(a)	35.2±12.1
Rate of change of eGFR	-3.1±5.5	-6±5.4(a)	-1.49± 4(a)	-1.53±5
Diabetic nephropathy	-5.7±6.6	-8.3±6.3(b)	-4.0±5.9(b)	-4.1±6.3
Hypertensive nephropathy	-1.7±5	-3.7±6.5	-1.3±4.4	-0.85±4.3
Chronic GN	-2.6±4.6	-6.7±5	-1.76± 3.6	-1.78±3
Chronic IN	-1.9±4.6	-2.4±1.2	-0.5± 1.9	-0.5±1.1
Others				
Proteinuric at baseline	-4.8±5.7	-7.7±5.4(a)	-2.86±5.3(a)	-2.9±5.2
Non proteinuric at baseline	-1.4±4.7	-4±4.6	-0.18±4.5	-0.17±4.4
Number with eGFR decline more than 50%	43(17%)	11(24.7%)©	21(12.2%)©	5(13%)

a-pvalue<0.001, b- pvalue<0.05, c-pvalue<0.03

-. Comparison of Max- RASB and Dual blockade are shown in table 6

Table-4

characteristics	Total number N=210(%)	Max RASB N=38(%)	Dual N=172(%)
Total RASB score	2.19±1.44	2.33±0.8	2.05± 1.2
Rate of egfr decline(ml/min/1.73m2/year	1.51±6.4	1.53±5(a)	1.49±4(a)
Number with egfr decline more than 50%	26(12.38)	5(13)(b)	21(12.2)(b)

a-Pvalue=0.99, b=0.86

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The COX regression analysis to identify variables influencing the eGFR decline > 50% or reaching dialysis are in Table 5

Table-5.

variable	Exp(B)	P value	95% confidence interval
Age	1.02	0.24	0.99-1.05
Gender (male vs Female)	0.64	0.25	0.3- 1.4
RASB- yes/no	3.4	0.001	1.63-7.12
SGLT2i	2.6	0.05	1.2-3.65
Baseline proteinuria (more than 1gm/day)	0.45	0.03	0.22- 0.94

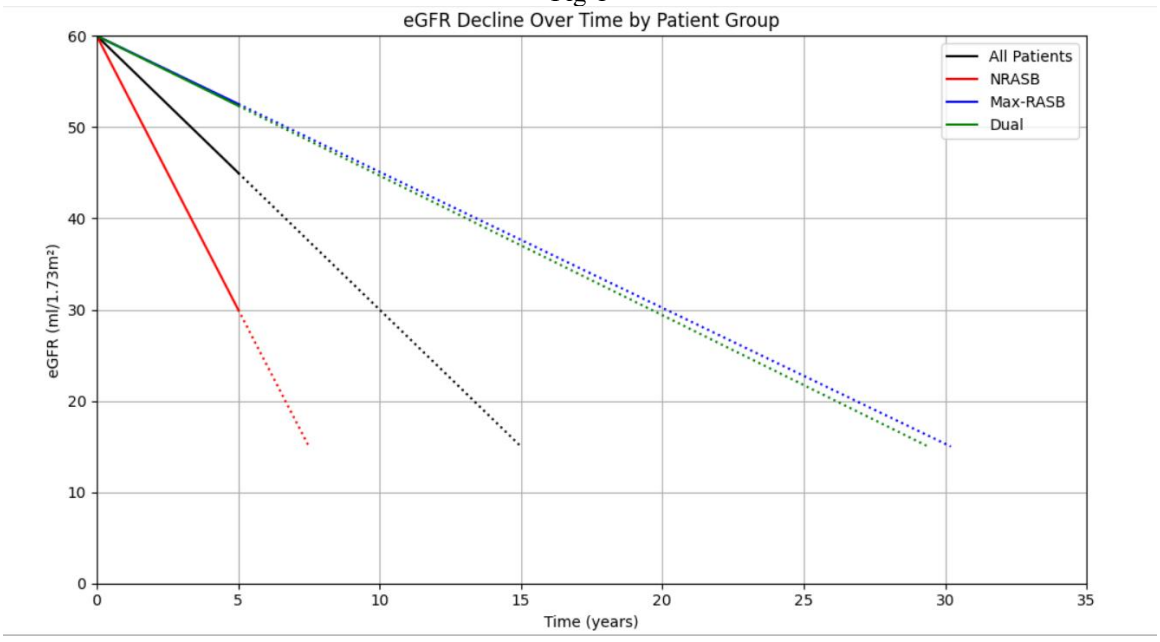
Serum albumin	0.49	0.03	0.25- 0.95
Systolic BP last follow up	1.02	0.05	1.00-1.05
Diastolic BP last follow up	1.01	0.68	0.97- 1.05

Exp(B)- for a continuous variable, the increase in hazard ratio for 1 unit change of the continuous variable, RASB- renin angiotensin blockade, BP- blood pressure, SGLT2i- sodium glucose cotransport inhibitor

The total number of antihypertensive drugs used were 2.1± 1 in the full RSAB group and 2.3±1.1 in the N RASB group and 2.1±1.1 in the RASB+SGLT2i group. Diuretics were used in 57 (22%) (13% of RASB group, 17% in those non- RASB and 18% in RASB+SGLT2 I group; P=0.7 between groups). The other drugs used were- CCB 46% (82% N- RASB, 52% RASB- p< 0.01), 51% RASB+SGLT2- P< 0.05),
A- blockers 18% (48% NRASB, 8% RASB, P < 0.001, 8.2% RASB+SGLT group, P+ 0.76).
Adverse effects were hyperkalemia in 32 (12.6%), Hypotension 18(7.1%), cough 11(4.3%) and azotemia (> 25% increase in creatinine) in 14(5.5%)
210 patients (83%) received RASB at baseline with a mean RASB score of 0.49±3. When last analysed, 172 had RASB with a mean score of 2.05±1.1(such score achieved in 20% in those with ACEI and 48% in those with ARB). Only 9% had RASB score more than 1 at the beginning, but it increased to 66% at last follow up. 38 of them went on to have an RASB score of 2.33±0.8 at last follow up.
SBP < 130 achieved in 132(52.4%)- 62% RASB group, 38% NRASB group, P < 0.01and 58% RASB+ SGLT group.
DBP < 80 was seen in 187 patients (74.2%)- 77% RASB, 76% RASB+ SGLT and 61% NRASB group, P=0.001.
A subgroup analysis was done in those with RASB (210) to assess the effects of RASB. Patients were arranged serially from those with the lowest to those with the highest RASB score and then divided into two equal parts- lowest to median n=105, RASB score 0.63±0.38 and from median to highest n=105, RASB 2.5±0.7. The follow up duration being similar in both (3.4± 2.1 y) in low dose and 3.1±2.1 in the high dose group, P= 0.28). The rate of fall of eGFR was 2.01± 5.1 in the low dose, 1.89± 4.8 in the high dose group, P=0.13. 21 in the RASB+SGLT and 5 in the Max-RASB group had rapid decline in eGFR > 50% or reached ESRD in the follow up (P=0.67)

The relationship between the delta eGFR and the projected time to reach ESRD is shown the fig 1 , compared between the NRASB, RASB, and RASB+SGLT2 groups.

Fig-1



The relationship between the degree of RASb and the delta eGFR is shown in Fig 2.

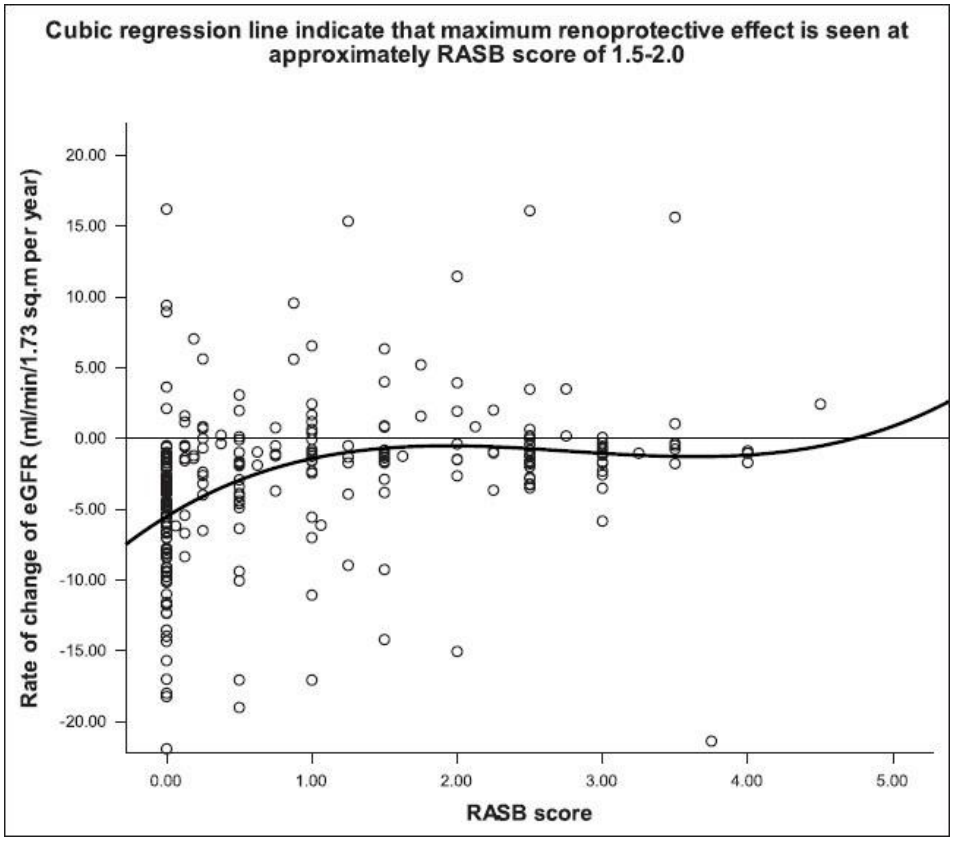


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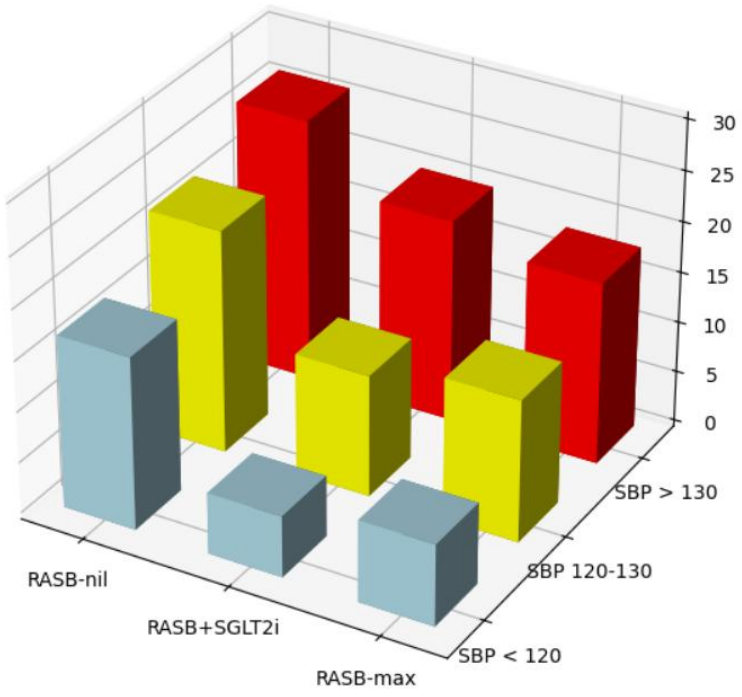
Fig 3 shows the RASB score and BP control, with relation to > 50% decline in eGFR or ESRD.



IV. DISCUSSION

This study assessed the effects on GFR decline in those who received RASB to those who did not. Among those who did receive, there were those who could not get the full dose of RASB due to various reasons, but who were added on to the SGLT2 i. The patients who received some form of RASB preserved the renal functions over time compared to those who did not. Among those who received low- dose RASB, the ones who got added on to the SGLT2i had a comparable decline in eGFR. The projected time to ESRD clearly shows the marked improvement in those receiving RASB or RASB and SGLT2i compared to controls. The independent determinants associated with the slowing of eGFR decline were RASB scores, SGLT2i use, non- proteinuric states (< 1gm) and higher serum albumin achieved with therapy.

The ideal dose of ACEI or ARB for nephroprotection is not known but it is increasingly clear that it is higher than the maximal recommended anti- hypertensive dose [29]. Higher supramaximal doses (2.5±0.7 were associated with better eGFR preservation than the lower submaximal doses (0.63+_ 0.38) over a 3.4 year follow up. Cubic regression analysis (Fig 2) showed that optimal protection was achieved with a RASB of 1.5 to 2 (around 3 in DN, 1.5 in CGN and 1 in CIN on the average), showing that the more the proteinuria, the more the RSAB score needed, to confer protection.

Could it have been that resistant hypertension drove up the need for more RASB, leading to better nephroprotection? It is to be noted that the dose of RASB was not driven by the BP alone. In fact, other agents were used concurrently to control the pressure, with them slowly being withdrawn once BP was controlled, while the RASB was being increased. The COX regression teased out SBP and the RASB score as determinants to renal outcome. Further analysis (Table 5) revealed that the RASB score was more associated with protection than SBP control. Fig 3 further strengthens this assertion by demonstrating that RASB had the Reno protective effect at each level of BP control (fig 3).

The concerns regarding supramaximal dose are based more on speculation than hard evidence. The safety of RASB has been demonstrated in multiple trials even at eGFR below 30 [15,16,17,18]. Burgess et al even used dose of Candesartan upto 8 times the normal recommended and demonstrated no side effects or death [18]. In this study, RASB blockade was associated with hyperkalemia (12.6%), cough (4.3%), hypotension (7.1%) and azotemia (5.5%). However, as there was close follow up, with gradual incremental doses, there was time to deal with the complications and hence there were no life-threatening situations.

We were able to demonstrate the effectiveness of supramaximal doses of RASB and RASB combined with SGLT2I, compared with submaximal dose of RASB or no RASB in preserving eGFR in CKD of diverse etiology. It is also shown that non-proteinuric diseases too benefited from this intervention.

The drawbacks of the study are to be noted too. This was retrospective and hence the population and interventions could not be planned. However, due to the differences in the enthusiasm among the nephrologists in the unit, varying doses of RASB blockade were achieved and meaningful conclusions could thus be drawn. Proteinuria was not quantified in all and hence we could not use it as a marker to study effectiveness on intervention. Instead, the serum albumin was used as a surrogate marker and studies attest to this [31,32]. It improved significantly in those on supramaximal RASB or RASB+SGLT2i and not so in control groups. We did not study the effect of smoking and animal protein intake in our study because most of the patients did not actively smoke and most were seen repeatedly by a dietician and the animal protein intake was in most cases within range of compliance. The RASB scoring was evolved by another research group [6] based on the assumption that the renoprotective dose should be equal to the maximal anti-hypertensive dose(unproven). Quantification of antihypertensive drugs in studies on hypertension are known, and the same principle was followed [34.]

V. CONCLUSISON

This study has shown that carefully tailoring the dose of ACEI or ARB so as to achieve the maximal tolerated scores of RASB can be safely undertaken in CKD patients. In those not able to achieve higher RASB scores, or in situations where it was added on, the presence of SGLT 2 inhibitors provided renoprotection in-par with the high scores of RASB. The above effects were seen in CKD of varying etiology including in non-proteinuric diseases and appears to be dose dependent. This makes a strong case for tailored escalation of RASB, often beyond the recommended antihypertensive doses, with use of SGLT2 inhibitors in CKD to postpone ESRD.

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