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Diabetology

RETROSPECTIVE STUDY OF ELECTROLYTES CHANGE WITH CONCOMITANT USAGE OF SGLT2I AND DIURETICS IN T2DM PATIENTS

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ABSTRACT

BACKGROUND: SGLT-2Is (sodium glucose co-transporter 2 Inhibitors) group of drugs lead to diuresis and might be associated with the electrolyte loss when used concomitantly with diuretics in T2DM patients (Type 2 Diabetes Mellitus). This was a single center, retrospective, non-interventional real world observational study to evaluate changes in sodium and potassium levels with use of diuretics and SGLT-2Is together.

METHODOLOGY: The study was conducted on 62 type 2 diabetics (HbA1C ≥ 6.5) patients (under prevailing international guidelines). All the patients received Empagliflozin (EGF) or Dapagliflozin (DFG) and various diuretics like Chlorthalidone (CTD), hydrochlorothiazide (HTZ), torsemide or eplerenone or combinations of these components (as per labeled indications). Patients with both baseline and post-treatment values of body weight, sodium (Na), potassium (K) and blood pressure were considered for further evaluation. The mean duration of study was 4 weeks. The purpose of study was to find out any change in sodium, potassium levels as well as weight and BP after 4 weeks from baseline.

RESULTS: After a mean study duration of 4 weeks in 62 patients, no significant alterations were observed in Na levels from a baseline level of 138.40 ± 3.62 mmol/L (mean ± SD) to 137.95 ± 3.68 mmol/L after 4 weeks (p=0.238) and K levels from a baseline level of 4.31 ± 0.48 mmol/L (mean ± SD) to 4.28 ± 0.52 mmol/L (p=0.709) after 4 weeks. However, significant reductions were achieved in the body weight and blood pressure.

CONCLUSIONS: Concomitant usage of SGLT2I with diuretics in real world setting doesn't cause sodium and potassium electrolyte abnormalities but there is significant weight loss and BP lowering capacity due to the multiple modes of actions of this molecule.

KEYWORDS :

INTRODUCTION

Type 2 diabetes is a chronic disease with multiple complications arising out of it, if not properly controlled. The complications of diabetes are broadly divided into macrovascular or microvascular complications. Cardiovascular disease (CVD) is the main cause of morbidity and mortality for patients with type 2 diabetes. Diabetic kidney disease increases the risk of cardiovascular-related morbidity and mortality and serves as a surrogate marker of CVD [1]. But in patients of T2DM, there is improved Cardiovascular and renal outcomes with SGLT2Is in the large, randomised, placebo-controlled trials namely, empagliflozin cardiovascular outcomes and mortality in type 2 diabetes trial (EMPA-REG outcome) and canagliflozin cardiovascular assessment study (CANVAS) (Ingelheim, 2018) [2]. SGLT2I (sodium glucose co-transporter 2 Inhibitors) group of drugs cause electrolyte loss along with glucose through urine in type 2 diabetics as the SGLT2 receptors are increased in number due to increased m-RNA expression for SGLT2 receptors [3]. In addition to the glycosuria and electrolyte loss, there is also decrease in body weight after therapy [4], reduction of arterial stiffness [5], and reduction in uric acid levels [5-9]. This study was done to see the changes of the most common electrolytes sodium and potassium with the use of SGLT2I and diuretics concomitantly in T2DM (type 2 diabetes mellitus) patients.

METHOD

This was a retrospective, single center, non-interventional observational study to evaluate the changes in serum electrolytes with SGLT-2Is, conducted on type 2 diabetics (HbA1C≥6.5) patients who received Empagliflozin (EGF) or Dapagliflozin (DFG) and various diuretics like Chlorthalidone (CTD), hydrochlorothiazide (HTZ), torsemide or eplerenone or combinations of these components (as per labeled indications). Data of only those patients having both baseline and post-treatment values of body weight, sodium (Na), potassium (K) and blood pressure (both systolic and diastolic) were considered for analysis. The mean duration of follow-up was 4 weeks.

Research Questions and Hypotheses

As already stated, SGLT2I group of drugs are known to cause electrolyte loss along with glucose through urine in type 2 diabetics [3]. Hence, this study was done to see the changes of the most common electrolytes, sodium and potassium, with the use of SGLT2I and diuretics used concomitantly in T2DM patients (both used under labelled indications). The outcome parameters of the study were change in sodium and potassium level, and change in weight and blood pressure (BP) after 4 weeks from baseline. The analysis of research questions could be done in two ways. First is direct investigation of the effect of the concomitant use of SGLT2I and diuretics on the four outcome parameters of the study. Second is through medic treatment study, assessing how the CTD, EGF, DFG and HTZ therapy impacts on the outcome parameters.

The hypotheses are:

- There is no statistically significant change in sodium or potassium levels after concomitant use of SGLT2I and diuretics.
- There are significant changes in BP component after using diuretics and SGLT2I together.
- Are there any direct and indirect effects of treatment used in the study?

Participants

Medical records of Type 2 Diabetes Mellitus (T2DM) patients who visited our hospital and treated during July 2017 to august 2017 were retrieved. Inclusion criteria were: type 2 diabetes patients, estimated glomerular filtration rate (eGFR) ≥ 45 ml/min/1.73 m^2, had been on stable dose of any form of diuretics under prevailing guideline indications for more than 3 months prior to study initiation, HbA1c ≥ 6.5%. Exclusion criteria were: any form of MI, stroke, ACS or NHYA class 3 or 4 of heart failure in the last 3 months of study initiation, any change in diuretic or SGLT2I dose during the study period, any acute illness that might lead to body fluid alterations during study period, any contraindications to SGLT2i, pregnancy and lactation. Sodium and potassium level, weight, SBP (Systolic blood pressure) and DBP (Diastolic blood pressure) at base line and after 4 weeks with CTD, EFG, DFG and HTZ usage were recorded as presented in Appendix Table 1. Details of diuretics received by the patients are presented in Appendix Table 2.

Statistical Analysis

The data was statistically analyzed using IBM SPSS version.21. Descriptive statistics, pair-wise comparison and repeated measures test were conducted to answer the research questions and hypotheses. P-value <0.05 was considered statistically significant.

RESULTS

Descriptive analysis

A total of 62 T2DM patients (M:F=1:1) who satisfied the inclusion and exclusion criteria were included in the analysis. The mean age of the study participants was 55.05 ± 10.47 years with a mean duration of diabetes of 6.61 ± 3.86 years. The effect of concomitant use of SGLT2I and diuretics on the outcome parameters of the study at baseline and

after 4 weeks was compared. After a mean study duration of 4 weeks, Na level decreased from the baseline value of from 138.40 ± 3.62 mmol/L to 137.95± 3.68 mmol/L (p=0.238), K level decreased from 4.31 ± 0.48 mmol/L to 4.28 ± 0.52 mmol/L (p=0.709), the mean weight decreased from 69.21 ± 10.74 kg to 68.57 ± 10.78, HPB reduced from 141.03 ± 16.67 to 133.87 ± 12.981, and LBP reduced from 82.32 ± 9.426 to 80.65 ± 7.384.

From the study of group, Empagliflozin (EGF) was used by 15 patients (24.2%) where 10 of them received EGF 10, and 5 patients received EGF 25. Dapagliflozin 10 was used by 47 patients (75.8%), Chlorthalidone was used by 43 patients (69.4%), CTD 6.25 was used by 28 patients (45.2%), CTD 12.5 by 15 patients (24.2%), and Hydrochlorthiazide 12.5 by 18 patients (29%). It may be noted that patients who did not use EGF, used DFG. The usage of Hydrochlorthiazide 12.5 and Chlorthalidone are equally distributed including levels of usage between EGF and DFG users. Empagliflozin * Chlorthalidone Chi=4.848, p=0.303; Empagliflozin * Hydrochlorthiazide Chi=0.339, p=0.844; Dapagliflozin * Chlorthalidone Chi=3.524, p=0.172; Dapagliflozin * Hydrochlorthiazide Chi=0.178, p=0.673. These outcomes with relative tests from contingency tables show that therapies were equally distributed within sample, and that the samplings were made correctly. During the analysis, it was confirmed that variances for measures and within groups are homogeneous.

Pair wise comparisons

The pair-wise comparisons of parameters at baseline and after 4 weeks are presented in Table 1 and Table 2. Table 1 shows high and significant correlation between all the paired parameters at baseline and after 4 weeks. It can be seen that Na and K levels correlation are high enough but less than correlations for weight, SBP and DBP. Table 2 shows that there are no significant differences in Na and K levels at baseline and at 4 weeks of concomitant use of SGLT2I and diuretics. The difference in Na level was 0.45±3.14 (p=0.264, t=1.128) and that in K level was 0.03±0.49 (p=0.663, t=0.438). There was significant differences in weight (0.64±1.43 kg, p=0.001, t=3.517), SBP (7.16 ± 10.94, p=0.000, t=5.154), and DBP (1.71 ± 5.71, p=0.022, t=2.356).

Table 1. Paired Samples Correlations.

	N	Correlation	Sig.
Na at baseline & Na after 4 weeks	62	0.629	0.000
K at baseline & K after 4 weeks	62	0.528	0.000
Baseline weight & Weight After 4 weeks	62	0.991	0.000
Baseline SBP & SBP after 4 weeks	62	0.755	0.000
Baseline DBP & DBP after 4 weeks	62	0.796	0.000

Table 2. Paired samples test.

	Paired Differences- Mean	SD	SEM	95% Lower	95 % Upper	t	df	Sig. (2-tailed)
Na at baseline - Na after 4 weeks	0.45	3.14	0.399	-0.348	1.248	1.128	61	0.264
K at baseline - K after 4 weeks	0.03	0.49	0.062	-0.097	0.152	0.438	61	0.663
Baseline weight - Weight After 4 weeks	0.64	1.43	0.181	0.275	0.999	3.517	61	0.001
Baseline SBP - SBP after 4 weeks	7.16	10.94	1.389	4.383	9.939	5.154	61	0.000
Baseline DBP - DBP after 4 weeks	1.71	5.71	0.726	0.259	3.160	2.356	61	0.022

Repeated measures tests

The tests for Na with therapy effects show that there are not direct and indirect effects on Na from drugs usage at 0.05 levels. The tests confirms that variances of Na levels are homogeneous at baseline (p=0.412, F=1.050) and after 4 weeks (p=0.184, F=1.487). The Box's tests (p=0.667) confirms that covariance matrices are equal across groups. Mauchy's test of Sphericity shows p=1.000, Chi=0.000. The tests of between subject effects confirm that there are not direct and indirect significant effects of drugs on Na levels at 0.05 level (EGF p=0.908, CTD p=0.441, HTZ p=0.468). For DFG, the significance is the same as for EGF because DFG was used when EGF was not in use.

The tests for K with therapy effects show that there are no direct and indirect effects on K from drugs usage at 0.05 levels. The tests confirms that variances of K levels are homogeneous at baseline (p=0.246, F=1.338) and after 4 weeks (p=0.089, F=1.845). The Box's tests (p=0.285) confirms that covariance matrices are equal across groups. Mauchy's test of Sphericity shows p=1.000, Chi=0.000. The tests of between subject effects confirm that there are not direct and indirect significant effects of drugs on K levels at 0.05 level (EGF p=0.274, CTD p=0.961, HTZ p=0.374). For DFG, the significance is the same as for EGF because DFG was used when EGF was not in use. As the differences between weights in pair wise tests were found the reasonable, the question is how this could be explained by therapy differences For SBP pressure, the tests confirm that variances of SBP groups are homogeneous at baseline (p=0.471, F=0.967) and after 4 weeks (p=0.323, F=1.190). The Box's test p=0.601 confirms that covariance matrices are equal across groups. Mauchy's test of Sphericity shows p=1.000, Chi=0.000. The test of within subject effects shows that there is not effect of therapy type within and between groups at 0.05 levels. This means that therapies have equal impact on SBP.

For DBP pressure, the tests confirm that variances of DBP groups are homogeneous at baseline (p=0.045, F=2.164) and after 4 weeks (p=0.229, F=1.376). The Box's test (p=0.100) confirms that covariance matrices are equal across groups at 0.05 level. Mauchy's test of Sphericity shows p=1.000, Chi=0.000. The test of within subject effects shows that there is not effect of therapy type within and between groups at 0.05 levels. This means that therapies have equal impact on DBP. The significant result on border for baseline group variances can be ignored because other and stronger tests match the model assumptions.

DISCUSSION

There were no statistically significant changes in any electrolyte measured after the study period even after the concomitant use of diuretics and SGLT2Is as evidenced by the p-value changes of K (p=0.709)and Na (p=0.238) after 4 weeks of therapy. The renal handling mechanism of sodium and water is shown on Figure 1 [10]. More details about chemistry of the electrolyte handling process in connection to the diuretic types can be seen on Figure 2 [11].

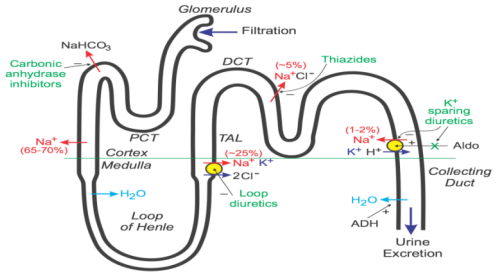

Figure 1. Renal handling of sodium and water. Reproduced from Klabunde [10].

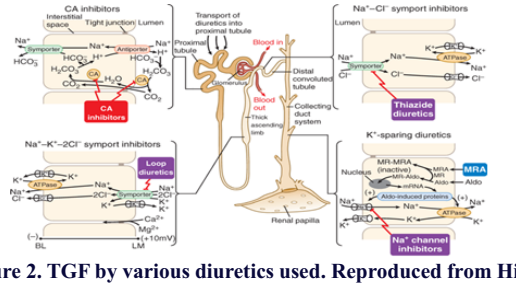

Figure 2. TGF by various diuretics used. Reproduced from Hilal-Dandan and Brunton [11].

It is recognized that thiazide diuretic as well as loop diuretic may cause electrolyte loss by virtue of their action. According to Klabunde, Thiazide is the most commonly used diuretics [10]. They inhibit the sodium chloride transporter in the distal tubule. This transporter may reabsorb about 5% of filtered sodium, which is why the efficacy of these diuretics are less than loop diuretics in producing diuresis and natriuresis. The other type of diuretic commonly used is carbonic anhydrase inhibitor (CAI). Acetazolamide (a prototype of CAI) might lead to an action similar to that seen with SGLT2I due to their site of action in proximal tubules [12]. The reduced blood flow (RBF) and glomerular filtration rate (GFR) observed after administration of the

carbonic anhydrase inhibitors were due to activation of the tubuloglomerular feedback (TGF) mechanism which is activated by distal delivery of sodium near the Macula densa region leading to a pseudo sensation of the kidneys of fluid loss, subsequently activating TGF and causing renal afferent arteriolar vasoconstriction [12]. The mechanism for TGF by SGLT2I is almost identical, but the unwanted side-effect profile of CA Inhibitors is not seen with them [13].

In the present study, SGLT2Is did not show any statistically significant change in electrolytes even when used concomitantly with diuretics; thus it reassures us of their use with diuretics if indicated.

As already stated in the introduction section, the body weight reduction by SGLT2I caused by sodium glucose co-transporter 2 inhibitors is by urinary glucose excretion via the inhibition of renal glucose re-absorption, and improved glycemic control [14]. The meta-analysis shows that increasing dapagliflozindose from 2.5 to 20 mg led to significant decrease in body weight by 1.30 to 2.24 kg per month. Treatment with canagliflozin (50-300 mg)–resulted in decreased rate of weight loss (1.2-2.37 kg per month). The results of our study are similar to that of Cai et al. [14]. The overall weight loss in our case after 4 weeks was 0.64 kg for the whole group. There was more weight loss at high doses compared to that at low dosage [15]. The weight loss was primarily due to visceral fat loss and calorie loss, similar to that reported by Tosaki et al. [7]. There was no statistically significant lean mass loss which would have been detrimental for T2DM. Napolitano et al. observed weight loss with remogliflozin and sergliflozin in non-diabetic healthy obese individuals, suggesting that these molecules are safe and that the mechanism of weight loss is largely by calorie loss through urine [16].

The difference in BP was confirmed by pairwise comparison and repeated measure tests. The average SBP reduction was 7.16 and DBP reduction was 1.71, which attests the effectiveness of the therapy and overall normal health. Therefore, this study successfully confirms the hypotheses and the results of other similar studies [17,18]. The proposed mechanisms for antihypertensive action of SGLT2 inhibitors are: osmotic diuresis, weight loss, mild natriuresis, possible indirect effects on nitric oxide release secondary to reduced oxidative stress by better glycemic control [19], decrease in inflammatory markers [20], reductions in sympathetic tone [21], decrease in uric acid levels, and reduction in arterial stiffness [18].

This study shows that natriuresis is the major reason for BP reduction. However, Maiorana et al. reported that vascular function is not improved after 4 weeks of therapy, and is related to life style changes [22]. Hamdy et al. observed significant effect of therapy after 6 months [23]. Similar criterions about sodium reduction were not confirmed in this study, which could possibly be due to effect of life style changes and natriuresis or both. As vascular endothelial function is associated with obesity and metabolism, it is reasonable to assume in or study that the effect of concomitant usage of SGLT2I and diuretics has started and that we may expect enhanced outcome of the therapy at more time [24-29]. BP-lowering effect resulting from urinary sosdium excretion increases as the vascular endothelial function is related to body weight loss [30].

CONCLUSIONS

Concomitant use of SGLT2I with diuretics in real world setting did not cause sodium and potassium electrolyte abnormalities, but significantly reduced body weight and blood pressure. The body weight reduction by SGLT2I appears to be mainly caused by urinary glucose excretion which itself causes calorie loss via the inhibition of renal glucose re-absorption, and also by improved glycemic control. Decrease in BP is attributable to natriuresis, decrease in body weight, reduction in arterial stiffness and to some extent decrease in uric acid levels. One of the limitations of the study is that the analysis was done on a homogenic group of patients without considering the influence of age on therapy outcomes. Therefore future studies are warranted on considering the influence of age on therapy outcomes.

Appendix Table 1. Raw data

Serial Number	Na at baseline	Na after 4 weeks	K at baseline	K after 4 weeks	Baseline Weight, Kg	Weight After 4 weeks, Kg	Baseline BP	BP after 4 weeks
SL 1	137	138	4.1	4.0	65	63	150/98	140/92
SL 2	137.58	131.95	3.77	3.88	62	64	160/92	166/90
SL 3	142	140	4.8	4.3	52	51	130/80	132/82
SL 4	139	139	4.5	4.1	71	70	124/70	116/68
SL 5	142	140	4.5	4.9	64	62	120/74	112/72
SL 6	141	138.20	3.78	3.59	94	94	160/90	142/82
SL 7	140	140	4	3.9	67	67	130/82	130/82
SL 8	143	141	3.6	3.4	84	83.5	120/70	110/70
SL 9	137	134	4.7	4.43	67	66	122/70	118/66
SL 10	145	148	4.6	5.1	79	78	124/78	120/78
SL 11	144	142	3.3	4.1	62	62	160/80	150/80
SL 12	138	135	4.8	4.0	73	72	160/90	152/86
SL 13	136	137	4.3	5.1	56	55	160/90	118/86
SL 14	135.30	134.60	4.2	4.20	88	88	170/88	140/88
SL 15	137	139	3.0	3.6	52	53	136/70	138/74
SL 16	140	141	5.0	5.0	77	78	138/76	150/92
SL 17	131	136	4.5	4.7	80	77	140/92	140/90
SL 18	135.70	136.50	4.2	3.70	62	62	114/68	118/70
SL 19	141	142	3.6	3.7	101	101	140/98	120/86
SL 20	137.70	133.40	4.18	3.48	69	67	128/82	126/84
SL 21	135.30	136.80	4.16	4.01	65	63	140/98	136/90
SL 22	140.10	137.1	4.07	3.87	58	58	144/96	130/84
SL 23	139	136	4.4	3.7	74	74	144/82	138/80
SL 24	135	136	4.0	4.2	66	66	146/80	140/84
SL 25	136.80	143	6.0	5.8	69	69	130/72	138/74
SL 26	132.7	135	4.49	3.8	71	70	160/100	152/90
SL 27	135	142	5.1	4.5	63	62	148/90	140/80
SL 28	137.80	134.40	4.20	4.10	84	85	160/100	150/94
SL 29	136	140	4.7	4.5	72	73	130/80	114/76
SL 30	136	126	3.30	3.77	63	61	124/80	118/80
SL 31	139	141	4.4	4.3	74	73	160/80	138/84
SL 32	128	131	5.1	4.1	64	63	146/74	128/78
SL 33	141.2	144.6	4.47	4.54	64	65	160/88	138/80
SL 34	134.91	138	4.18	5.0	63	65	140/76	130/72
SL 35	142	144	4.2	4.8	64	66	144/82	140/84
SL 36	137	134.29	4.4	3.41	66	66	130/80	132/80
SL 37	141	141	3.9	4.3	62	64	146/78	142/72
SL 38	144.8	138.1	4.10	4.13	70	70	140/80	138/80

SL 39	139	140	4.9	4.5	69	65	150/82	140/80
SL 40	133.80	131.85	4.07	3.53	58	55	150/80	130/74
SL 41	140	137	4.1	4.4	74	73	140/82	138/84
SL 42	140	139	3.7	4.2	65	64	162/64	150/62
SL 43	135.60	137.20	4.5	4.70	56	55	120/70	124/70
SL 44	144	140	4.6	4.0	80	80	136/84	138/84
SL 45	142	138	4.30	3.7	85	82	200/108	160/96
SL 46	140	139	4.2	4.1	76	75	150/84	150/80
SL 47	132	137	4.3	4.5	83	81	120/92	120/82
SL 48	139	139	4.3	3.8	80	79	140/84	138/82
SL 49	138.90	137.30	4.60	4.65	70	70	150/80	120/66
SL 50	132	131.50	4.82	5.14	84	82	114/80	118/82
SL 51	134.30	132.90	4.96	4.13	70	69	112/78	120/90
SL 52	145.3	141.2	4.17	4.2	71	70	140/94	138/90
SL 53	140	140	4.6	4.6	52	52	120/90	118/86
SL 54	144.0	140.1	4.19	4.58	85	84	140/80	120/80
SL 55	142.3	140	4.32	4.4	75	75	130/90	124/86
SL 56	137	136	3.9	5.5	66	68	160/80	150/82
SL 57	139	138.7	4.1	4.2	70	70	140/80	138/80
SL 58	141	142	4.0	4.2	50	47	160/62	156/70
SL 59	140	137	4.5	4.6	64	64	120/70	120/80
SL 60	136	138	4.7	5.1	49	48	150/80	150/82
SL 61	137	140	4.8	5.0	67	62	142/82	130/74
SL 62	137.5	135	4.2	4.0	55	55	120/76	130/78

Appendix Table 2. Details of diuretics received by the patients

Sl No	Initial treatment
SL 1	Empagliflozin 10 + chlorthalidone 6.25 + teneligliptin 20 + metformin 1000 + telisartan 40
SL 2	30/70(200IU) 40 BBF, 24 B.DINNER + metformin 1000 + dapagliflozin 10 +hydrochlorthiazide 12.5 + telmisartan 40 + amlodipine 2.5 + prazosin XL 2.5
SL 3	Glimepiride 4 + pioglitazone 15 + dapagliflozin 10 + CTD 6.25 + teneligliptin 20 + telmisartan 40
SL 4	Ryzodeg 40 B.LUNCH + empagliflozin 25 + torsemide 10 + eplerenone 25 + glimepiride 1 + teneligliptin 20 + telmisartan 80 + rosuvastatin 10 + aspirin 75 + acebrophylline 200 + LT4 75
SL 5	Pantoprazole 40 + domperidone 30 SR + pregabalin 300 + clonazepam 0.5 + 30/70(pen) – 25 B.DINNNER; 50/50(pen) – 82 BBF + metformin 1500 + dapagliflozin 10 + HTZ 12.5 + teneligliptin 20 + telmisartan 40 + atorvastatin 10
SL 6	Nevibolol 2.5 + prazosin XL 7.5 + olmesartan 40 + CTD 12.5 + dapagliflozin 10 + metformin 1000 + glimepiride 2 + teneligliptin 20 + rosuvastatin 10 + aspirin 75
SL 7	30/70(ANALOGOUE) – 25 BBF; 12 B.DINNER + metformin 2000 + teneligliptin 20 + empagliflozin 10 + HTZ 12.5 + telmisartan 80
SL 8	LT4 50 + dapagliflozin 10 + HTZ 12.5 + metformin 1000 + teneligliptin 20 + pioglitazone 15 + olmesartan 20 + amlodipine 5
SL 9	Glimepiride 4 + metformin 1500 + teneligliptin 20 + dapagliflozin 10 + HTZ 12.5 + pioglitazone 15 + escitalopram 10 + clonazepam 0.5 + rosuvastatin 10 + amlodipine 5 + olmesartan 20
SL 10	Glimepiride 4 + teneligliptin 20 + dapagliflozin 10 + HTZ 12.5 + pioglitazone 15 + metformin 500 + telmisartan 80
SL 11	Teneligliptin 20 + empagliflozin 25 + HTZ 12.5 + 30/70(200IU) – 48 BBF; 18 B.DINNER + pregabalin 50 + escitalopram 10 + clonazepam 0.5 + olmesartan 40 + amlodipine 5
SL 12	Pioglitazone 15+ glimepiride 1 + metformin 500 + dapagliflozin 10 + CTD 6.25 + telmisartan 40 + LT4 100
SL 13	LT4 50 + telmisartan 40 + CTD 12.5 + dapagliflozin 10+ metformin 1000
SL 14	Iron supplement + 30/70(100IU) – 25 BBF; 20 B.DINNER + dapagliflozin 10+ CTD 12.5 + ramipril 10 + metformin 1000
SL 15	Teneligliptin 20 + pioglitazone 30 + glimepiride 4 + metformin 2000 + acarbose 100 + telmisartan 40 + CTD 12.5 + dapagliflozin 10
SL 16	Metformin 500 + glimepiride 2 + teneligliptin 20 + dapaliflozin 10 + HTZ 12.5 + olmesartan 40 + amlodipine 5
SL 17	Teneligliptin 20 + metformin 500 + dapagliflozin 10 + CTD 6.25
SL 18	Sitagliptin 100 + metformin 2000 + empagliflozin 25 + CTD 6.25
SL 19	Amlodipine 5 + telmisartan 20+ teneligliptin 20 + empagliflozin 25 + CTD 6.25 + Ryzodeg 30/70 16U B.Lunch
SL 20	Clopidogrel 75 +aspirin 75 + atorvastatin 10 + pioglitazone 7.5 + teneligliptin 20 + glimepiride 4 + acarbose 100 + metformin 500 + ranolazine 500 + telmisartan 80 + CTD 12.5 + dapagliflozin 10
SL 21	Pioglitazone 7.5 + dapagliflozin 10 + CTD 6.25
SL 22	Teneligliptin 20 + metformin 1000 + olmesartan 40 + CTD 12.5 + dapagliflozin 10
SL 23	Glimepiride 1 + pioglitazone 15 + metformin 500 + dapagliflozin 10 + CTD 6.25
SL 24	Glimepiride 3 + metformin 1000 + pioglitazone 15 + teneligliptin 20 + dapagliflozin 10 + HTZ 12.5 + telmisartan 80
SL 25	LT4 50 + iron supplement + pioglitazone 7.5 + nevibolol 5 + olmesartan 40 + amlodipine 5 + HTZ 12.5 + dapagliflozin 10
SL 26	Glimepiride 1 + metformin 500 + dapagliflozin 10 + CTD 6.25 + olmesartan 20
SL 27	LT4 50 + aspirin 75 + atorvastatin 10 + teneligliptin 20 + metformin 1000 + gliclazide XR 120 + dapagliflozin 10 + CTD 6.25 + telmisartan 40
SL 28	Teneligliptin 20 + glimepiride 1000 + glimepiride 0.5 + dapagliflozin 10 + CTD 6.25 + telmisartan 40
SL 29	Ryzodeg 32 B.LUNCH + acarbose 150 + glimepiride 4 + metformin 1000 + teneligliptin 20 + dapagliflozin 10 + CTD 12.5 + telmisartan 80 + atorvastatin 10 + LT4 75
SL 30	Glimepiride 3 + metformin 500 + teneligliptin 20 + dapagliflozin 10 + CTD 6.25
SL 31	Glimepiride 4 + metformin 1500 + pioglitazone 15 + teneligliptin 20 + dapagliflozin 10 + HTZ 12.5 + olmesartan 20 + amlodipine 5
SL 32	Ryzodeg – 10 B.LUNCH + teneligliptin 20 + metformin 1000 + glimepiride 1 + dapagliflozin 10 + HTZ 12.5 + olmesartan 40 + amlodipine 5 + nevibolol 5 + rosuvastatin 10
SL 33	Rosuvastatin 10 + teneligliptin 20 + dapagliflozin 10 + CTD 12.5 + telmisartan 40

SL 34	LT4 50 + teneligliptin 20 + pioglitazone 15 + metformin 1500 + glimepiride 4 + dapagliflozin 10 + CTD 12.5 + olmesartan 40 + prazosin xl 5 + nevibolol 10 + atorvastatin 10 + aspririn 75
SL 35	Mirtazapine 15 + metformin 2000 + dapagliflozin 10 + HTZ 12.5 + amlodipine 5 + olmesartan 40 + rosuvastatin 10
SL 36	Rosuvastatin 10 + aspirin 75 + nevibolol 5 + amlodipine 5 + telmisartan 80 + CTD 12.5 + dapagliflozin 10 + glimepiride 1 + teneligliptin 20 + metformin 1500 + LT4 50
SL 37	Seretide 250 INHALER + monteleukast 10 + acebrophylline 200 SR + telmisartan 40 + CTD 6.25 + dapagliflozin 10 + teneligliptin 20 + metformin 1500 + glimepiride 1
SL 38	Teneligliptin 20 + metformin 1000 + pioglitazone 15 + glimepiride 4 + dapagliflozin 10 + HTZ 12.5
SL 39	Cintapride XR 3+ pantoprazole 40 + sitagliptin 50 + metformin 500 + empagliflozin 25 + CTD 6.25
SL 40	Telmisartan 40 + CTD 6.25 + dapagliflozin 10 + teneligliptin 20 + metformin 1000
SL 41	Human insulin 50/50 – 40 BBF; Human insulin 30/70 – 32 B.DINNER + glimepiride 1 + metformin 2000 + teneligliptin 20 + empagliflozin 25 + CTD 6.25 + olmesartan 20
SL 42	Pantoprazole 40 + rosuvastatin 10 + aspirin 75 + telmisartan 80 + CTD 12.5 + dapagliflozin 10 + pioglitazone 15 + teneligliptin 20 + metformin 1000
SL 43	Glimepiride 4 + metformin 1500 + teneligliptin 20 + pioglitazone 15 + dapagliflozin 10 + CTD 6.25 + telmisartan 40 + clonazepam 0.5 + escitalopram 10
SL 44	Rosuvastatin 10 + teneligliptin 20 + metformin 2000 + pioglitazone 15 + CTD 12.5 + dapagliflozin 10
SL 45	Glimepiride 1 + metformin 500 + dapagliflozin 10 + CTD 12.5 + telmisartan 40
SL 46	Human insulin 30/70 (200IU) – 52 B.DINNER + Insulin Lispro – 20 BBF, 26 B.LUNCH + teneligliptin 20 + metformin 1000 + dapagliflozin 10 + CTD 12.5 + olmesartan 40 + rosuvastatin 10 + aspirin 75
SL 47	Teneligliptin 20 + metformin 1000 + dapagliflozin 10 + CTD 6.25 + linezolid 600 BD + Cefixime 200 BD
SL 48	Glimepiride 1 + metformin 500 + dapagliflozin 10 + CTD 12.5 + telmisartan 40
SL 49	Tamsulosin 0.4 + rosuvastatin 10 + teneligliptin 20 + metformin 500 + dapagliflozin 10 + CTD 6.25 + telmisartan 40
SL 50	Amlodipine 5 + telmisartan 40 + CTD 6.25 + empagliflozin 25 + glimepiride 0.5 + metformin 1000 + teneligliptin 20 + aspirin 150 + clopidogrel 75 + rosuvastatin 20 + metoprolol XL 25 + pregabalin SR 75
SL 51	Teneligliptin 20 + dapagliflozin 10 + CTD 12.5 + telmisartan 40
SL 52	Teneligliptin 20 + glimepiride 2 + metformin 500 + pioglitazone 15 + dapagliflozin 10 + CTD 6.25 + tamsulosin 0.4
SL 53	Pregabalin 150 + glimepiride 1 + metformin 1000 + insulin 30/70 – 60 BBF, 25 B.DINNER + dapagliflozin 10 + CTD 6.25
SL 54	Pantoprazole 40 + domperidone 30 SR + metformin 2000 + glimepiride 2 + sitagliptin 100 + empagliflozin 25 + CTD 6.25
SL 55	Pioglitazone 15 + glimepiride 4 + metformin 2000 + empagliflozin 25 + CTD 6.25
SL 56	LISPRO/ LISPRO PROTAMINE 25/75 – 28 BBF, 12 B.DINNER + teneligliptin 20 + metformin 1000 + dapagliflozin 10 + HTZ 12.5 + telmisartan 40 + amlodipine 5 + atorvastatin 10
SL 57	Human premixed insulin 30/70(200 IU) – 64 BBF, 40 B.DINNER + teneligliptin 20 + metformin 500 + empagliflozin 10 + HTZ 12.5 + telmisartan 80 + amlodipine 5 + nevibolol 10 + prazosin XL 10 + pregabalin 75 + nortryptiline 25
SL 58	Acebrophylline 200 + telmisartan 200 + torsemide 10 + dapagliflozin 10 + glargine 14 at 10pm + metformin 500 + teneligliptin 20 + LT4 75 + carvedilol CR 10 + rosuvastatin 10 + clopidogrel 75 + digoxin 0.25 (5 days a week) +
SL 59	Metformin 500 + dapagliflozin 10 + CTD 6.25
SL 60	Pantoprazole 40 + domperidone 30 SR + LT4 50 + aspirin 75 + atorvastatin 10 + nevibolol 5 + telmisartan 80 + HTZ 12.5 + empagliflozin 25 + teneligliptin 20 + pioglitazone 7.5 + glimepiride 4 + metformin 2000
SL 61	LT4 50 + terbenefine 250 BD + glimepiride 2 + metformin 1000 + empagiflozin 25 + HTZ 12.5 + telmisartan 40
SL 62	Telmisartan 40 + CTD 6.25 + dapagliflozin 10 + metformin 1500 + glimepiride 1 + pioglitazone 15 + teneligliptin 20

Abbreviations: CTD = chlorthalidone; HTZ = hydrochlorthiazide

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