Review Article

Deciding oral drugs after metformin in type 2 diabetes: An evidence-based approach

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ABSTRACT

The most commonly used oral drug in treating type 2 diabetes (T2DM) after metformin are sufonylureas (SUs) based on the confidence gained over the several decades and because of its cheaper cost. Unfortunately, SUs are associated with secondary failure and sometimes associated with therapy related severe hypoglycaemia limiting its compliance and wider utility in current clinical practice. Although large randomised trials could not associate SUs with any obvious increase in cardiovascular (CV) mortality, some recent larger databases showing divergent results suggesting increasingly CV signals and this might put SUs in difficulty given the availability of other safer alternatives. In recent years, incretin-based therapies like dipeptidyl peptidase-4 inhibitors (DPP-4I) and glucagon-like peptide-1 (GLP-1) agonist (GLP-1A) are gaining popularity primarily because of their advantage of weight reduction/neutrality and minimal hypoglycemia along with the perception of possible pleiotropic CV benefit mainly derived from pooled CV data of their trials. Sodium glucose transporter 2 inhibitors (SGLT-2I) are another new promising molecule currently looking for its space in the management of T2DM. Insulin could be utilized at any place when required and in this regard outcomes reduction with an initial glargine intervention (ORIGIN) study also suggested that basal insulin glargine could be safely used even in early stage. This review will discuss what could be possibly be the best option as a second line oral agent, once metformin monotherapy becomes ineffective.

Key words: Cardiovascular mortality, dipeptidyl peptidase-4 inhibitors, incretin based therapies, Sodium glucose transporter 2-2 inhibitors, sulfonylureas,type 2 diabetes

Introduction

With rapid changes in our understanding in etio-pathogenesis of type 2 diabetes (T2DM), there have been a paradigm shift in treatment modalities and currently entire focus is shifted from classical "triumvariate" to ominous "octet" concept. With this advancement, approach to diabetes management has also moved from being "gluco-centric" to "patient-centric." The last two decades have witnessed the development of a wide variety of new therapeutic options to treat T2DM. Although each class of these agents broadly shows similar efficacy as monotherapy with hardly any clinically meaningful differences in glucose-lowering potency at least in short term, each therapeutic class has distinct adverse-event profile that either could be related to their specific mechanism of action and/or potential off-target effects. The glucose lowering did depend in part on the study design populations and baseline glycated hemoglobin (HbA1c) levels. Some of these adverse effects (in particular hypoglycemia and weight gain) could be clinically meaningful to patients and physicians, and it is conceivable that these adverse events may further increase the cardiovascular (CV) risk in T2DM or may negate the potential CV benefits of some of the glucose-lowering agents.

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Although there is general agreement and almost all recent guideline from American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) and American Association of Clinical Endocrinologist (AACE) recommends metformin as first-line drugs, uncertainty

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remains regarding the choice of second-line therapy once metformin is no longer effective.[1] This review will discuss what could be possibly be the best option as a second-line oral agent once metformin monotherapy becomes ineffective, based on the evidence collated through the study published in recent literature.

Second-Line Oral Drugs After Metformin: Options Left Open

Currently, multiple options are available as a second-line drug after metformin. Agents which can be used orally include sufonylureas (SUs), pioglitazone, dipeptidyl peptidase-4 inhibitors (DPP-4I) and sodium glucose transporter 2 inhibitors (SGLT2I). Agents which can be used in injection form include glucagon-like peptide-1 (GLP-1) agonist and insulin (preferably basal or premix). As pioglitazone is another insulin sensitizer, this may not be a very suitable second-line drug once one sensitizer like metformin becomes ineffective except in certain subset of patients and therefore this will not be discussed further in this review. Although, alpha glucosidase inhibitors and Bromocriptin QR (immediate release preparation) are also used in treatment of T2DM and could be a useful in certain subgroup of patients, their utility is limited with poor tolerability and these agents may not be considered as preferred second-line agent and thus will not be discussed further in this review.

How to address the best second line oral drug after metformin?

To answer this big question, what we need is to search some concrete evidence and to review the literature to find the data of their head-to-head trials or systemic reviews and met-analysis. Following head-to-head studies and met-analysis could be retrieved and will be analyzed in this review.

a. SUs versus DPP-4 inhibitors
b. SUs versus SGLT-2 inhibitors
c. DPP-4 inhibitors versus SGLT-2 inhibitors.

Comparing SUs versus DPP-4 inhibitors

SUs are most frequently used second-line therapy because of their well-established efficacy and low cost but with known side effects of hypoglycemia and weight gain [Table 1]. Results from some studies (ADOPT and RECORD) have also led to the uncertainty about their durability and long-term CV safety (UGDP), which may potentially be related to the fact that SUs not only bind to the SU receptor (SUR) subunit (subtype SUR1) of the potassium adenosine triphosphate (ATP; K_{ATP}) channel in the beta-cell membrane, but may also bind to the SUR receptor (subtype SUR2) on cardiac myocytes and

Table 1: SUs: Lessons learnt so far

Advantages	Disadvantages
Time tested	Gluco-centric without disease-centric properties
Robust glucose reduction in early stage	Durability-less
Cheap	Hypoglycemia-big issue
Randomised trials did not give bad CV signal	Weight gain
	Possible beta cell apoptosis
	Observational studies and overall meta-analysis shows increasingly bad CV signals and mortality

CV: Cardiovascular, SUs: Sufonylureas

on endothelial cells, and could have direct effects on CV function. The controversy regarding the CV safety profile of SUs started with UGDP, conducted in the 1960s that first gave rise to concerns about the safety of the first-generation SU, tolbutamide. In this study, a significantly increased risk of all-cause and CV mortality was observed among participants receiving this SU versus placebo. However, the UGDP was neither designed nor powered to test the hypothesis of inferior CV safety for SU versus placebo. Nevertheless, as a consequence of these data, every SU approved for use in the US has in its product label that SU use has been associated with increased CV mortality. It is unclear whether the findings of the UGDP are applicable to current clinical practice, where modern diabetes management includes a multifactorial approach to reduce the risk of CV complications. Furthermore, it is uncertain whether the UGDP findings apply to all SUs. Beside this, majority of the large CV outcome trials have essentially assessed the impact of multiple combinations of glucose-lowering agents as part of an overall treatment regimen (e.g. UKPDS, ACCORD, ADVANCE, VADT, and ORIGIN)[2-7] and very few, long-term head-to-head trials have compared the effects of single diabetes drugs on CV outcomes (PROactive) or CV surrogates (CHICAGO, PERISCOPE, and APPROACH).[8-10] Thus, a comparative understanding of the CV impact of this most widely used diabetes drugs is actually lacking. Notably, data from longer-term RCT and observational studies also remain discordant regarding the CV safety of SUs. But recent met-analysis of largest SUs trials do suggest increasingly bad CV signals (27% higher CV mortality and 11% higher myocardial infarction) for SUs primarily derived from observational, case-control and cohort studies[11] [Table 2].

DPP4I are already in use for last 7 years and results of some larger CV studies like VIVIDD, SAVOR TIMI, and EXAMINE are also published recently. The initial concern of increasing nasopharyngeal infection and urinary tract infection (UTI) has largely been ruled out in these studies. Also noteworthy to find pancreatitis (a big concern associated with these drugs) not significantly higher in these long term studies. Although these studies revealed CV neutrality

of these drugs, some concerns remained in terms of significantly higher hospitalization due to heart failure seen in SAVOR TIMI trials and this trend continued in EXAMINE trial although insignificantly[12,13] [Table 3]. Although no mechanistic reason could be cited behind this unexpected outcome, it could be assumed to be related to unknown off-target side effects of DPP-4I. It should be noted that there are number of DPP4 substrate apart from GLP-1 which can influence vascular outcomes [Table 4]. Some of them could be beneficial like stromal-derived factor-1α (SDF-1α), brain natriuretic peptide (BNP), and substance P, others could be detrimental like peptide YY (PYY) and neuropeptide Y (NPY). Interestingly, substance *P* is a potential vasodilator but it does increases sympathetic activity when accumulated substantially. Substance *P* is degraded in to inactive metabolite both by ACE and DPP-4. Though earlier studies suggested harmful link between DPP4-I and NPY, recent reviews cites substances *P* as a putative agent inducing increased sympathetic activity and in turn augmenting latent heart failure, when DPP-4I is used in combination with ACE inhibitors.[14] It's worthwhile to mention that 53.8% of patients in SAVOR TIMI were using ACEI and 27.6% ARBs, whereas 82% of patients had been using ARBs in EXAMINE trial along with DPP4I. Currently, all these theories seems to be merely assumptions and no clear reason behind increased heart failure hospitalisation with saxagliptin holds conclusive. Nevertheless, this heart failure data should also be interpreted with caution considering the heterogeneity of priori heart failure patient recruited in different studies [Table 5]. Interestingly, there was no increase in CV mortality in spite of hospitalization due to heart failure in these trials which actually included such a high risk patient (within 90 days of acute coronary events). Results from awaited TECOS and CAROLINA trial will shed some light on these issues further.[15,16]

Table 2: Meta-analysis of 33 SUs trials (*n*=1,325,446)

	Relative risk	95% confidence interval
Cardiovascular mortality		
Summary of randomized controlled trials	1.22	0.63-2.39
Summary of cohort studies	1.26	1.18-1.34
Summary of observational studies	1.26	1.18-1.34
Summary of all studies	1.27	1.18-1.34
Myocardial infarction		
Summary of randomized controlled trial	0.88	0.74-1.05
Summary of case-control studies	1.30	1.09-1.54
Summary of observational studies	1.20	1.06-1.36
Summary of all studies	1.11	1.00-1.24

SUs: Sufonylureas

Table 3: DPP-4 inhibitors: Lessons learnt so far

Advantages	Disadvantages
A1c reduction at par with SUs	Cost
Minimal hypoglycemia with weight neutrality or loss	Slightly higher mortality in VIVIDD trial
Possible pleiotropic benefit and beta cell protection	Issues of increased hospitalisation due to heart failure in SAVOR TIMI needs further clarification
Meta-analysis of pooled data from phase 2/3 showed CV benefit	Possible off-target effects
Randomised trials–VIVIDD, SAVOR TIMI, and EXAMINE suggested CV neutrality	
Issues of pancreatitis and UTI/ Nasopharyngitis do not seems to be any large issue from these results	

CV: Cardiovascular, DPP-4: Dipeptidyl peptidase-4, UTI: Urinary tract infection, VIVIDD: Vildagliptin in ventricular dysfunction in type 2 Diabetes, SAVOR: Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus, TIMI: Thrombolysis in myocardial infarction

There have been indirect comparisons between SUs and DPP-4 inhibitors from their individual trials as evident from several systemic reviews and meta-analysis done by Monami *et al.,* 2010, Park *et al.,* 2012, Liu *et al.,* 2012 and Karagiannis *et al.,* 2012. Almost all of them were the general comparisons and the information on separate analyses between DPP-4 inhibitors and sulphonylureas were limited. Because of the substantive increase in data on DPP-4 inhibitors versus SUs as add-on therapy to metformin or as monotherapy, expanded data was necessary. Very recently a meta-analysis of 12 head-to-head trials between SUs versus DPP-4 inhibitors (Zhang Y *et al.*) published which is discussed here[17] [Table 6].

This meta-analysis suggested a marginal superiority of SUs especially glimepiride in A1c reduction when trial duration was less than 32 weeks but this benefit disappeared when trials duration exceeded 32 weeks suggesting poor durability of SUs. DPP4I showed better efficacy when compared to second generation SUs like glipizide and gliclazide and also in patient with chronic kidney disease (CKD). DPP4I was clearly superior to SUs in any adverse effects, hypoglycemia, weight gain, and CV events [Tables 7 and 8].

Table 4: DPP-4 substrate which can potentially influence CV outcome

DPP-4 substrate	CV action	Metabolites	CV action
GLP-1 (7–36)	Decrease apoptosis and promotes preconditioning	GLP-1 (9-36)	Vasodilator
SDF-1α	Stimulates bone marrow mobilisation of endothelial progenitor cell (repair of endovascular damage)	Inactive metabolites	inactive
BNP	Natriuretic and vasodilator	BNP (3–36)	Minimal vasodilator
Substance P	Vasodilator and increase sympathetic acivity	Substance P (5-11)	Inactive
Peptide YY (1–36)	Vasoconstrictor via Y1R	Peptide YY (3-36)	Vasodilator via Y2R
Neuropeptide Y (1-36)	Vasoconstrictor via Y1R	Neuropeptide Y (3-36)	Vasodilator via Y2R

CV: Cardiovascular, DPP-4: Dipeptidyl peptidase-4, UTI: Urinary tract infection, GLP: Glucagon-like peptide-1, SDF1-α: Stromal-derived factor-1α, BNP: Brain natriuretic peptide

In summary, SUs and DPP-4I are both insulinotropic, but with different mechanisms. SUs may cause (severe) hypoglycemia, whereas DPP-4I does not. Whether SUs elicit cardiovascular problems is still not known. By direct (head-to-head) comparison, DPP-4I are associated with less cardiovascular events than SUs. Whether this indicates a harm of SUs or a benefit of DPP-4I needs to be clarified from further CV outcome studies. Because of their advantages (no hypoglycaemia and weight gain) and some expectations regarding CV benefit, DPP-4I are increasingly used worldwide but as the cost remains a major limitation with DPP-4I, SUs still remains a valuble drug in developing countries like India. The results from large ongoing CAROLINA trial comparing glimepiride with linagliptin will likely shed some light on this controversial CV issues in the future.

Comparing SUs versus SGLT-2 inhibitors

SGLT-2 inhibitors are class of drug recently being used in treatment of T2DM. Both Canagliflozin and Dapagliflozin have received US FDA approval and very soon we expect these agent available in India as well. These agents primarily inhibit glucose reabsorption in kidney through SGLT-2 receptors and thereby reduce plasma glucose by enhancing glucosuria. Because of this glucosuric effect these drugs seems to reduces blood pressure and body weight but at the cost of increasing genito-urinary infections [Table 9]. Only few head-to-head studies have compared SUs with SGLT-2 inhibitors.[18,19] Both this study shown non-inferiority of SGLT-2 inhibitors in A1c reduction compared to SUs but with significant weight loss and blood pressure reduction. A very recent result from 4-year follow-up study revealed that SGLT-2 inhibitors had clear benefit over SUs as it had better durability and consistent wt loss along with much lesser (10-fold less) hypoglycemia [Table 10].

Table 5: Incidence of heart failure in patients recruited in some of large studies

Priori HF in clinical trials
EXAMINE - 28%
SAVOR TIMI - 13%
ADVANCE - 4.8%
ACCORD - 2%
VADT/ORIGIN/UKPDS/DCCT - HF excluded

SAVOR: Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus, TIMI: Thrombolysis in myocardial infarction, VADT: Veterans affairs diabetes trial, ORIGIN: Outcomes reduction with an initial glargine intervention trial, UKPDS: United Kingdom Prospective Diabetes Study, DCCT: Diabetes control and complications trial, HF: Heart failure

Comparing DPP-4 inhibitors versus SGLT-2 inhibitors

Four head-to-head study compared DPP4I with SGLT2I either in treatment naive patient (Roden *et al.*) or on background metformin therapy (Rosenstock *et al.*) or background SU plus metformin therapy (Schernthaner *et al.*).[20] There was no significant difference among this agent in A1c reduction but SGLT2I were associated with consistent weight loss and BP reduction. In fact in one study, canagliflozin 300 mg was superior to sitagliptin 100 mg [Table 11].

Although SGLT2I seems to have certain advantage from weight and blood pressure angle but few recent studies

Table 6: Met-analysis of 12 head-to-head studies (*n*=11,000): SUs vs DPP-4I

Study, year weeks	Intervention	HbA1c (%)	HbA1c<7% (%)	Body Wt	Hypo-glycemia (%)	CV events (%)
Seck *et al.* 2010	Sitagliptin	−0.54−0.51	63	−1.6	5	NA
104 week	Glipizide		59	0.7	34	NA
Arechavaleta *et al.* 2011	Sitagliptin	−0.47−0.54	52	−0.8	7	NA
30 week	Glimepiride		60	1.2	22	NA
Srivastava *et al.* 2012	Sitagliptin	−0.64−1.17	12	−0.10	4	NA
18 week	Glimepiride		36	0.49	8	NA
Arjona Ferreiera *et al.* 2012*	Sitagliptin	−0.8−0.6	47	−0.10	6.2	NA
54 week	Glipizide		42	0.49	17	NA
Arjona Ferreira *et al.* 2013*	Sitagliptin	−0.72−0.87	44	−0.2	6.3	7.8
54 week	Glipizide		56	0.8	10.8	9.2
Foley *et al.* 2009*	Vildagliptin	−0.5−0.6	22	0.8	0.7	NA
104 week	Gliclazide		28	1.6	1.7	NA
Matthews *et al.* 2010	Vildagliptin	−0.1−0.1	37	−0.3	2	NA
104 week	Glimepiride		38	1.2	18	NA
Filozof *et al.* 2010	Vildagliptin	−0.81−0.85	30	0.08	NA	1.4
52 week	Gliclazide		32	1.36		2.4
Jeon *et al.* 2011	Vildagliptin	−0.94−1.0	50	0.23	1	NA
32 week	Glimepiride		56	2.35	10	NA
Goke *et al.* 2013	Saxagliptin	−0.41−0.35	23	−1.5	3.5	NA
104 week	Glipizide		23	1.3	38.4	NA
Gallwitz *et al.* 2012	Linagliptin	−0.16−0.36	30	−1.4	7	1.5
104 week	Glimepiride		35	1.3	36	3.4
Rosenstock *et al.* 2013*	Alogliptin	−0.14−0.09	49	−0.62	5.4	0.5
52 week	Glipizide		45	0.60	26.0	0.9

*Life style intervention, all others were on background metformin; NA: Not available

suggested losing effectiveness after its chronic uses. SGLT2I were associated with paradoxical increase in endogenous glucose production (EGP) due to increase in glucagon to insulin ratio.[21,22] Chronic dosing of SGLT2I also shifted substrate utilisation from carbohydrate to lipids whose long-term metabolic consequence is still not fully known to us at current point of time.[21,22]

Table 7: Results of the met-analysis of 12 head-to-head studies: SUs vs DPP-4I

Parameters	DPP-4 inhibitors (DPP4I) versus SUs
A1C reduction#	DPP4I produced less A1c reduction by 0.11%
A1c<7%*	9% less with DPP4I when trial<32 weeks
Hypoglycaemia	87% less with DPP4I
Weight	1.65 kg less with DPP4I
Any adverse effect	21% less total adverse event with DPP4I
CV events	47% less with DPP4I
Beta cell effect	Better PI/I ratio and HOMA-IR with DPP4I

#DPP4I showed better efficacy when compared to 2nd generation SU and also in CKD patient, *Same percentage of patient had A1C<7% when trial was >32 weeks, DPP-4: Dipeptidyl peptidase-4, SUs: Sufonylureas, CV: Cardiovascular

Table 8: MH-OR ratio for CV events from 4 head-to-head studies: SUs vs DPP-4I

Study	Drug comparator	M-H odds ratio (fixed)	95% CI
Arjona Ferreira 2013	Sitagliptin *vs* Glipizide	0.83	0.24-2.88
Filozof *et al.* 2010	Vildagliptin *vs* Gliclazide	0.56	0.22-1.42
Gallwitz *et al.* 2012	Linagliptin *vs* Glimepiride	0.45	0.23-0.90
Rosenstock *et al.* 2013	Alogliptin *vs* Glipizide	0.49	0.04-5.45
Total		0.53	0.32-0.87
	Favours DPP-4 inhibitors		

CV: Cardiovascular, DPP-4: Dipeptidyl peptidase-4, MH-OR: Mantel-Haenszel-odds ratio, CI: Confidence Interval

Table 9: SGLT-2 inhibitors: Lessons learnt so far

Advantages	Disadvantages
A1c reduction at par with metformin, SU, Gliptins	Genital and urinary infection
	Volume depletion with loop diuretics
	Postural hypotension with RASB and diuretics
	Safety in elderly>75 year
Durability seems superior to SU	Loosing effectiveness in renal insufficiency
Wt loss superior to metformin and gliptins	eGFR<60: Dapagliflozin
	eGFR<45: Canagliflozin
	eGFR<30: Empagliflozin
BP reduction robust than metformin and gliptins	Increase in endogenous glucose production (EGP) due to increased glucagon/insulin ratio
	CV safety: Increase LDL and fatal and nonfatal stroke with Canagliflozine in CANVAS trial
	Malignancy: Increased breast & bladder cancer with Dapagliflozin (?chance association)
	Bone health : Increase in PTH

CV: Cardiovascular, SU: Sufonylureas SGLT: Sodium glucose transporter 2 inhibitors, PTH: Parathromone, LDL: Low density cholesterol , CANVAS: CANagliflozin cardiovascular assessment study, RASB: Renin angiotensin receptor blocker

Conclusion

SUs remains the most popular second-line drug after metformin over the years primarily because of its low cost but it does carry the baggage of severe hypoglycaemia at a time, with significant weight gain and secondary failure. SUs also seem to have some of the CV safety concern seen in retrospective case-control, observational and cohort studies. In comparison, DPP-4 inhibitors are safer oral alternative with more or less same HbA1c reduction without the baggage of severe hypoglycemia and weight gain. DPP-4 inhibitors also seems to be good alternative especially in the light of reassuring results from two recently published large CV trials like SAVOR TIMI and EXAMINE, which neither gave any significant bad signals of increased pancreatitis nor showed increased CV mortality in such high-risk CV cases but these drugs are limited with their cost compared to SUs.

SGLT-2 inhibitors seems to be another promising oral agent as their HbA1c reduction capability is as at par with SUs and DPP-4I with added benefit of weight loss and blood pressure reduction which seems to be consistent. However, recent study suggesting loosing effectiveness in chronic use due to increase in endogenous glucose production derived from increase in glucagon/insulin ratio. If this increase in EGP is further substantiated in larger studies with SGLT2I, than prior use of glucagon lowering drugs with incretin based therapies along with metformin (which directly reduces EGP), makes more sense. Nonetheless, as very few trials results are available currently, these agents still have to go long way especially in the context of more safety data and results from larger prospective CV trials.

Type 2 diabetes has a complex etio-pathogenesis as evident from its "ominous octet" concept. No single anti-diabetes

Table 10: SUs versus SGLT-2 inhibitors

Author (Weeks)	Drugs	A1c changes %	Wt changes Kg	S.B.P/D.B.P mm Hg	Hypoglycaemia %
Cefalu WT *et al.* 2013	Glimepiride	−0.81	0.7	0.2/−0.1	34
CANTATA-SU study	Canagliflozin 100 mg	−0.82	−4.4	−3.3/−1.8	6
(54 weeks)	Canagliflozin 300 mg	−0.93	−4.7	−4.6/−2.5	5
Nauck M *et al.* 2011	Glipizide	−0.52	1.4	NA	40.8
(52 weeks)	Dapagliflozin	−0.52	−3.2	NA	3.5
Nauck M *et al.* 2013	Glipizide	0.20	0.73	−0.02/NA	NA
(208 weeks)	Dapagliflozin	−0.10	−3.65	−3.69/NA	NA

SGLT: Sodium glucose transporter 2 inhibitors, SUs: Sufonylureas, S.B.P: Systolic blood pressure, D.B.P: Diastolic blood pressure , NA: Not assessed

Table 11: SGLT-2 inhibitors versus DPP-4 inhibitors

Study (Weeks)	Drugs	A1c changes (%)	FPG changes (mmol/L)	BW changes (kg)	SBP changes (mmHg)
Empagliflozin					
Roden# *et al.* (24 weeks)	Placebo	0.08	0.65	−0.33	−0.3
	Empagliflozin 10 mg	−0.66	−1.08	−2.26	−2.9
	Empagliflozin 25 mg	−0.78	−1.36	−2.48	−3.7
	Sitagliptin 100 mg	−0.66	−0.38	0.18	0.5
Rosenstock+*et al.* (12 weeks)	Placebo	0.15	0.28	−1.2	−2.2
	Empagliflozin 10 mg	−0.56	−1.22	−2.7	−4.4
	Empagliflozin 25 gm	−0.55	−1.50	−2.6	−8.5
	Sitagliptin 100 mg	−0.45	−0.72	−0.8	−1.8
Canagliflozin					
Rosenstock+*et al.* (12 weeks)	Placebo	−0.22	0.20	−0.9	−1.3
	Canagliflozin 100 mg	−0.76	−1.40	−2.3	1.0
	Canagliflozin 300 mg	−0.92	−1.40	−3.0	−4.9
	Sitagliptin 100 mg	−0.74	−0.70	−0.5	−0.8
Schernthaner* *et al.* (52 weeks)	Canagliflozin 300 mg	−1.03	−1.70	−2.3	−5.1
	Sitagliptin 100 mg	−0.66	−0.30	0.1	0.9

#on dietary changes alone, +on background metformin therapy, *Background SU plus metformin, SGLT: Sodium glucose transporter 2 inhibitors, DPP-4: Dipeptidyl peptidase-4, FPG: Fasting plasma glucose, BW: Body weight , SBP: Systolic blood pressure

agent can correct all of the patho-physiologic disturbances present in T2DM and therefore multiple agents will be required for optimal glycemic control. It is for the physician to choose which combination suits the individual needs of the patient at given point of time.

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