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COMPARATIVE EFFICACY OF TENELIGLIPTIN AND SITAGLIPTIN AS ADD-ON THERAPY IN TYPE 2 DIABETES

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Abstract

Teneligliptin and sitagliptin are both dipeptidyl peptidase-4 (DPP-4) inhibitors used as add-on agents when metformin or other drugs no longer keep glycaemia on target in type 2 diabetes. This narrative review summarises published evidence on how the two compare in pharmacology, glycaemic efficacy, safety and practical use. Sitagliptin has the larger body of randomised and cardiovascular outcome data, whereas teneligliptin has a distinct structure, dual elimination and mainly Japanese and Indian experience. Reductions in glycated haemoglobin appear broadly similar across the class, and direct head-to-head evidence is limited by small trials and short follow-up. This review reports no new patient data.

1. INTRODUCTION

Type 2 diabetes seldom stays controlled on a single drug. Beta-cell function declines over the years, and the UK Prospective Diabetes Study showed that glycaemia drifts upward whatever the initial treatment, so that most patients need a second or third agent within a decade of diagnosis [1]. Guidelines from the American Diabetes Association and the European Association for the Study of Diabetes describe an individualised approach, with metformin usually first and a choice of add-ons guided by cardiovascular risk, weight, hypoglycaemia risk, kidney function and cost [2, 3, 4]. That drift is the reason clinicians speak of treatment intensification as a routine part of care rather than a sign of failure. Patients, though, often hear it as the latter, and a drug that is easy to take and unlikely to cause a hypoglycaemic episode

can make the conversation less fraught. Choosing well at this step shapes years of therapy [3, 4].

Within that menu, DPP-4 inhibitors occupy a comfortable middle position. They are taken by mouth once or twice daily, carry a low risk of hypoglycaemia when used without a sulphonylurea or insulin, and are weight neutral [5, 6]. Their glucose-lowering effect is modest, usually a fall in glycated haemoglobin of well under one percentage point on top of existing treatment, but they are generally easy for patients to accept [7, 8]. Cost-effectiveness analyses and national formularies have shaped how far the class is used, and the recommendations differ by country, with some guidelines placing DPP-4 inhibitors after drugs that protect the heart and kidneys. Even so, they remain among the most prescribed second-line drugs worldwide because of their simplicity, which keeps the comparison between members of the class relevant [2, 3].

India has an especially large stake in this question. National survey work has shown a high prevalence of diabetes in both urban and rural India, and the disease tends to appear at lower body mass and younger age than in Western populations [9, 10]. Cost matters a great deal where patients pay out of pocket. Teneligliptin, introduced in Japan in 2012 and later marketed in India at a low price, has become one of the commonly prescribed DPP-4 inhibitors there, often alongside the older and better documented sitagliptin [11, 12]. The disease burden is substantial. Estimates from national surveys suggest tens of millions of adults with diabetes in India alone, many of them undiagnosed or poorly controlled, so even small differences in price, tolerability or dosing convenience between two otherwise similar drugs can add up to large effects on a health system [9, 10]. Older treatment guidance based largely on Western trials has also had to be adapted to the metabolic features seen in South Asian patients.

This review asks a plain question: what does the published literature say about teneligliptin and sitagliptin when each is added to existing therapy? It covers their pharmacology, efficacy, safety and the situations in which one might be preferred. The key studies are collected in table 1. The article is a narrative synthesis of published trials and reviews, it reports no new patient data, and where head-to-head evidence is thin it says so. The scope is deliberately narrow. Other add-on classes, such as sodium–glucose co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, are mentioned only where guidance affects the place of DPP-4 inhibitors. The studies discussed are those published up to 2022, and the comparisons are those the literature allows, not those a clinician might wish for. The spread of the evidence in table 1 across groups is plotted in fig. 1, and it is weighted towards sitagliptin efficacy trials.

2. PHARMACOLOGY OF THE TWO AGENTS

DPP-4 is a serine peptidase that cleaves the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide within minutes of their release. Blocking it prolongs their action, which raises glucose-dependent insulin secretion and lowers glucagon, so the pharmacological effect fades as glucose falls [5, 13]. This mechanism explains both the low hypoglycaemia risk and the limited potency, because the inhibitors only amplify a signal that the patient's own gut is producing. Incretin biology also explains why the effect depends on meals. The hormones are released when nutrients reach the intestine, and their levels fall back quickly, so a DPP-4 inhibitor is most active around eating. Studies in which sitagliptin was given before an oral glucose load showed higher active incretin concentrations and lower glucose excursions afterwards, which is the mechanistic basis for the whole class [13, 14]. Reviews comparing the class on potency and selectivity make the same point [15].

Despite a shared target, the two molecules are chemically different. Sitagliptin is a beta-amino acid derivative with a triazolopiperazine group. Teneligliptin has a distinctive structure with five rings joined in a J-shape and binds to additional subsites of the enzyme in crystallographic studies, which gives it a long-lasting inhibition and a high potency in vitro [11, 16]. Whether this

translates into clinical advantage is the open question, since a stronger enzyme binding does not guarantee a bigger fall in glucose. Selectivity is a further consideration. DPP-4 belongs to a family of related enzymes, including DPP-8 and DPP-9, and early toxicology work in animals linked inhibition of those relatives with adverse findings. Modern inhibitors, sitagliptin among them, were selected to leave the related enzymes largely untouched, and published binding studies of teneligliptin describe similarly selective behaviour. Selectivity does not by itself guarantee safety, but it removes one concern [5, 16].

Elimination differs more obviously. Sitagliptin is cleared mostly by the kidney as unchanged drug, with only a small fraction metabolised, so its dose must be reduced as renal function falls [14, 17]. Teneligliptin is eliminated by both hepatic metabolism, partly through cytochrome P450 3A4 and flavin-containing monooxygenases, and renal excretion, and the human disposition work found that no single route dominates [18]. In consequence, dose adjustment in renal impairment has not been considered necessary in Japanese labelling, although experience in advanced kidney disease is limited [11, 19]. Drug interactions follow from the metabolic route. Sitagliptin is a weak substrate of CYP3A4 and CYP2C8 and of transporters such as organic anion transporter 3, but interactions in practice are few. Teneligliptin's reliance on CYP3A4 and flavin-containing monooxygenases means that strong inhibitors of those enzymes could raise exposure, although clinically important interactions have not been prominent in the published studies [17, 18, 19].

Table 1: Selected published evidence on teneligliptin and sitagliptin as add-on therapy

Study or source	Reported finding	Ref.
Sitagliptin + metformin placebo-controlled	Added to metformin it lowered glycated haemoglobin versus placebo and was well tolerated.	[20]
Sitagliptin + pioglitazone placebo-controlled	Improved glycaemic control over pioglitazone alone without weight loss or notable hypoglycaemia.	[21]
Sitagliptin + glimepiride with or without metformin	Greater reduction in glycated haemoglobin than placebo; hypoglycaemia more frequent with sulphonylurea.	[22]
Sitagliptin versus glipizide metformin background	Similar glycaemic effect, with fewer hypoglycaemic events and less weight gain on sitagliptin.	[23]
Teneligliptin dose-response Japanese patients	Dose-related reduction in glycated haemoglobin with good tolerability in a 12-week trial.	[24]
Teneligliptin + pioglitazone Japanese patients	Added to pioglitazone it improved control compared with placebo.	[25]
Teneligliptin 24-hour profile short trial	Once-daily dosing lowered 24-hour glucose including post-meal peaks.	[26]
Asian versus non-Asian meta-analysis	Class efficacy on glycated haemoglobin was greater in Asian participants.	[27]
Class meta-analysis randomised trials	DPP-4 inhibitors lower glycated haemoglobin modestly, with few differences between members.	[7, 8]
TECOS cardiovascular outcomes	No increase in major cardiovascular events with sitagliptin versus placebo on usual care.	[28]
Saxagliptin and alogliptin trials cardiovascular outcomes	Heart failure hospitalisation raised with saxagliptin; alogliptin neutral on the primary endpoint.	[29, 30]

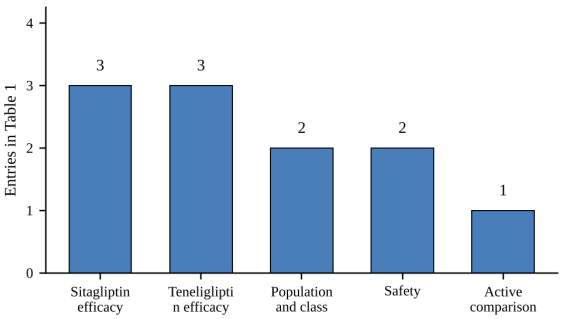


Fig. 1: Number of entries in table 1 by evidence group

Dosing also differs. Sitagliptin 100 mg is taken once daily in people with normal renal function, while teneligliptin 20 mg is taken once daily and may be increased to 40 mg in Japanese practice. Pharmacodynamic studies of teneligliptin showed that a once-daily dose

gave inhibition of DPP-4 and a reduction of 24-hour glucose, including post-meal peaks, in a short placebo-controlled trial [24, 26]. Corresponding data for sitagliptin showed a similar pattern of sustained enzyme inhibition across the dosing interval [14]. Reading such pharmacodynamic data requires a note of caution. Inhibition of the enzyme above about 80 per cent over the day is generally considered adequate for the class effect, and both drugs achieve it at their usual doses, which is why gains from stronger or longer enzyme blockade have been hard to demonstrate in clinical trials [5, 19]. The difference between the molecules is therefore more important for kinetics and elimination than for efficacy.

Beyond glucose, researchers have wondered about pleiotropic effects. DPP-4 cleaves many peptides, including some that act on blood vessels, and laboratory work suggests that DPP-4 inhibition might alter endothelial function, inflammation or blood pressure [12, 31]. Teneligliptin has attracted special attention in this respect, with suggestions of antioxidant and vascular effects in experimental models. These ideas are interesting, but they remain hypotheses in people and should not be read as demonstrated benefit [12, 31]. Preclinical work in animal models of diabetes has suggested that teneligliptin may reduce markers of oxidative stress and vascular inflammation, and that it may influence blood pressure through effects on natriuretic peptides and other DPP-4 substrates. Human data are sparse, and randomised trials with hard vascular endpoints have not been run, so these suggestions remain an interesting research direction only [12, 31].

3. EFFICACY AS ADD-ON THERAPY

Sitagliptin has been tested in nearly every combination. When added to metformin in patients inadequately controlled on metformin alone, it lowered glycated haemoglobin more than placebo, with improvements in fasting and post-meal glucose [20]. Similar results were obtained when it was added to pioglitazone and to glimepiride, with or without metformin [21, 22]. The pattern is consistent: a placebo-corrected fall of roughly half to three-quarters of a percentage point, larger in people starting from higher baseline values [7, 32]. Not all trials report the same outcome in the same way. Some give the change from baseline, others the placebo-subtracted difference, and others the proportion reaching a target of 7 per cent. Reading across tables therefore needs care, and pooled analyses that standardise these measures are more informative than any single trial [7, 8]. The effect on fasting glucose is smaller than that on post-meal glucose, consistent with the mechanism.

Teneligliptin's evidence base is smaller and more concentrated in Japan. Trials there compared different doses, found a dose-related effect on glycated haemoglobin, and assessed combination with pioglitazone, again showing improved control over placebo [24, 25]. A short crossover study using continuous glucose profiling showed lower 24-hour mean glucose [26]. Outside Japan the data come largely from smaller Indian studies and post-marketing reports, and the quality of those studies varies considerably. The comparison with sitagliptin is also complicated by the dose range and by the length of trials. Many teneligliptin studies lasted twelve weeks, long enough to see the main effect on glycated haemoglobin but not to show whether it lasts. Sitagliptin trials extended to a year or more in some cases, and the slow rise in glycated haemoglobin that follows initial improvement is better documented for that drug [22, 25]. Sitagliptin has also been given alone to Japanese patients with comparable results, which helps place the Japanese teneligliptin data [33].

What about direct comparison? Head-to-head randomised trials of teneligliptin and sitagliptin as add-on therapy are few, tend to be small and run for twelve to twenty-four weeks, and generally conclude that the two drugs reduce glycated haemoglobin to a similar degree. A meta-analysis of randomised trials of the whole class found modest differences between members that did not clearly favour any agent, and the numbers needed for a formal comparison are far larger than most published trials have enrolled [7, 8]. Table 1 lists the studies that inform the comparison most. Reviews of Cochrane type have concluded that inhibitors in the class

have broadly equivalent glycaemic efficacy when indirect comparisons are made through placebo, but they stress that such analyses cannot replace head-to-head trials, since differences in baseline characteristics can distort the result [8, 34]. The practical point, visible in fig. 1, is that most entries in table 1 concern a single agent rather than a comparison between agents, which is why indirect methods dominate.

Ethnicity may matter more than the choice of inhibitor. A pooled analysis of trials found that DPP-4 inhibitors lowered glycated haemoglobin more in Asian than in non-Asian patients, by a difference that was greater than the gap between individual drugs [27]. The proposed explanations include lower body mass, greater reliance on postprandial hyperglycaemia and differences in incretin physiology. This finding means that Japanese teneligliptin data cannot be assumed to apply to other populations, nor can Western sitagliptin trials be compared directly with them [10, 27]. Why might the East Asian response be larger? Several explanations are offered, among them differences in dietary patterns, in the share of insulin deficiency in the population, and in the baseline glycated haemoglobin of trial participants. None has been proven, and the finding carries a practical lesson: results from one region should not be generalised without checking [7, 27].

Combination choice shapes the result. Added to a sulphonylurea, any DPP-4 inhibitor increases hypoglycaemia relative to placebo, although the absolute rates stay small [8, 22]. Added to metformin, the pairing is well tolerated and weight neutral. Fixed-dose combinations of sitagliptin with metformin are widely available, and similar teneligliptin and metformin tablets are marketed in India, which may help adherence by reducing the pill burden [12, 20]. Patients also differ in what they care about. Reducing the pill burden through fixed-dose combinations is valued, but these tablets lock in doses of both components, which is a drawback when kidney function changes. Adherence to once-daily dosing is better than to twice-daily regimens in most studies of chronic disease, and both drugs are used once a day [12, 20].

4. SAFETY AND TOLERABILITY

The overall tolerability of sitagliptin is well described. A pooled analysis of more than ten thousand participants in clinical studies found that adverse events were generally similar to placebo, with no signal for serious toxicity in the trial population [35]. Nasopharyngitis, headache and upper respiratory infections were the common complaints, and these were not clearly drug related. Teneligliptin has shown a similar low-key profile in Japanese studies, with adverse events that were mostly mild and comparable with placebo [24, 26]. Adverse-event reporting in the teneligliptin trials was generally limited to short periods, and the numbers of participants exposed were small compared with the sitagliptin programme, so rare events cannot be excluded. Pooled safety data for sitagliptin remain the standard for the class because of their size and because they include a range of background therapies, renal function groups and ages [11, 35].

Cardiovascular safety has been examined in dedicated outcome trials of the class. The sitagliptin trial TECOS showed no increase in major cardiovascular events or hospitalisation for heart failure compared with placebo in patients with established disease [28]. Trials of saxagliptin and alogliptin reached different conclusions about heart failure, with an increase in hospitalisation reported for saxagliptin, which is why regulators now ask that cardiovascular safety be demonstrated for new antidiabetic drugs [29, 30, 36]. No comparable outcome trial exists for teneligliptin, so its cardiovascular safety rests on smaller studies and on class evidence. Regulatory agencies required outcome trials after concerns that some glucose-lowering drugs, rosiglitazone among them, increased cardiovascular risk. The US guidance published in 2008 made cardiovascular assessment a condition of approval for new antidiabetic therapies, and the class was among the first to be examined under it [28, 36]. The outcome trial results for the class are therefore not interchangeable; each drug has to be judged by its own data.

Pancreatitis has been the most debated issue. Spontaneous reports and some analyses of incretin-based drugs raised the possibility of

pancreatitis and pancreatic changes, though the data were open to criticism [37]. Meta-analyses of randomised trials did not show a clear increase in pancreatitis with DPP-4 inhibitors, while observational studies are inconsistent, and the absolute risk if present is small [8, 38]. Prescribers are still advised to stop the drug if pancreatitis is suspected, and this applies to both agents. A pragmatic reading of these data is that pancreatitis is a rare event for which causation is not established, but for which vigilance is justified. Patients with a history of pancreatitis, heavy alcohol use or very high triglycerides are usually considered poor candidates for the class, and the label advice to report persistent severe abdominal pain applies equally to both drugs [37, 38].

A separate safety question for teneligliptin concerned electrocardiographic effects, since it was found to prolong the QT interval modestly at high exposure in dedicated studies, and labelling in some countries advises caution in patients with risk factors for arrhythmia. This is a point where it differs from sitagliptin and deserves attention in the elderly or in people taking other QT-prolonging drugs [11, 12]. The published clinical data have not shown arrhythmic events attributable to the drug at therapeutic doses, but long-term surveillance data are limited. It would be unwise to lean too heavily on the QT observations. They come from exposure studies at doses above those used clinically, and there is no evidence in the literature of excess arrhythmia in treated patients. Nevertheless, in people with long QT, severe bradycardia, electrolyte disturbance or interacting drugs, sitagliptin is the more conservative choice, since its record is longer [11, 12].

Rare class effects continue to be reported, including severe joint pain, bullous pemphigoid and hypersensitivity reactions, mostly from pharmacovigilance reports. They are uncommon and their causal link is still being assessed. Because sitagliptin has been used by many millions of patients, its rare events are easier to find; the shorter exposure history of teneligliptin means such signals may simply not have emerged yet [8, 35]. Hypoglycaemia deserves a closing word. With either drug alone or with metformin it is rare, and rates rise when a sulphonylurea or insulin is also used. Reducing the dose of the sulphonylurea when starting a DPP-4 inhibitor is a common precaution, particularly in older adults [8, 22].

5. SPECIAL POPULATIONS AND PRACTICE

Kidney disease is the main practical dividing line. Because sitagliptin is renally cleared, labelled doses are halved and then quartered as the estimated glomerular filtration rate falls, which is straightforward but sometimes forgotten in busy clinics [14, 17]. Teneligliptin's mixed elimination has attracted interest for patients with advanced kidney disease, where choices are narrow, but published trials are small, and evidence of efficacy and safety at the lowest filtration rates is not yet strong [11, 18, 19]. In dialysis patients the question becomes sharper still. Sitagliptin is given at a quarter of the usual dose, and its use in end-stage disease is supported by limited trial data. Teneligliptin has been studied in small Japanese groups on haemodialysis with encouraging tolerability, but these studies are too small to rule out important risks, and the quality of the evidence should not be overstated [18, 19].

Older adults are another group where a low-hypoglycaemia drug is attractive. Glycaemic targets are relaxed in frail patients, and DPP-4 inhibitors suit such goals, since they allow simplification of treatment and avoid the dangers of sulphonylureas and insulin [2, 3]. Neither teneligliptin nor sitagliptin has been compared in this group, and trial participants are usually younger and healthier than the patients seen in practice [5, 8]. Hepatic impairment is a minor consideration for sitagliptin, which is mostly excreted unchanged, whereas for teneligliptin, which is partly metabolised in the liver, exposure rises in moderate hepatic impairment. Labelling advises caution in severe hepatic disease for the latter, though clinical studies on this point are limited. The practical lesson is to review liver tests before prescribing either drug [11, 17, 18].

Cost and access often decide the choice. Where generic sitagliptin and teneligliptin are

both available, the price difference may be small, but in markets where only the originator sitagliptin can be bought, teneligliptin is the cheaper way to reach the same therapeutic class [10, 12]. The pharmacist's role is to ensure that the choice is not made on price alone, but on the basis of kidney function, concomitant drugs, the cardiovascular profile and evidence for the specific product. Local formularies often settle the matter. In public hospitals in India, the choice may depend on what the tender has secured, and in private practice the patient's budget decides. Pharmacists asked to substitute one gliptin for another should remember that doses, renal adjustments and interactions are not identical, and that a switch should be accompanied by a note to the prescriber [10, 12].

Monitoring does not differ greatly between the two. Glycated haemoglobin at three-month intervals shows whether the add-on is working, and a trial of three to six months without a meaningful fall is a reason to change course rather than persist [2, 4]. If control is lost, the usual step is to escalate to agents with larger effects or proven outcome benefits, including SGLT2 inhibitors, GLP-1 receptor agonists or insulin, in line with current guidance [2, 3]. Counselling points are the same for both agents: take the tablet at about the same time each day, continue the lifestyle measures that remain the foundation of therapy, report severe abdominal pain, and do not stop the drug without advice. Patients should also be told that a DPP-4 inhibitor is not a replacement for metformin when metformin is tolerated [2, 4]. Written instructions in the local language and a check of understanding at the next visit improve the chance that these messages are retained.

Patients with established atherosclerotic cardiovascular disease, heart failure or chronic kidney disease are now steered toward agents with outcome benefit regardless of glycated haemoglobin, so DPP-4 inhibitors are usually reserved for those without those compelling indications or for people who cannot take other classes [2, 3]. Within this smaller role, the evidence for teneligliptin versus sitagliptin is unlikely to change a guideline. For people with a longer history of diabetes or marked insulin deficiency, a DPP-4 inhibitor will help less, because the drug depends on residual beta-cell function. Selecting patients with a shorter duration and moderately raised glycated haemoglobin gives the best chance of seeing a worthwhile response [5, 7].

6. LIMITATIONS AND FUTURE DIRECTIONS

The comparison drawn in this review has real limits. Sitagliptin's data come from large, multinational, well-monitored trials, while those for teneligliptin come from fewer and often single-region studies, so a comparison between them confuses differences between drugs with differences between study populations and designs [24, 27, 32]. Surrogate outcomes dominate, and no trial of teneligliptin has followed patients long enough to detect effects on complications. Publication bias is another difficulty. Small positive studies from single centres are more likely to be published than null ones, and industry-sponsored trials may report favourable subgroups. For teneligliptin in particular, a good deal of the Indian literature appears in regional journals and may not be indexed in the databases that systematic reviewers rely on [8, 34]. Few studies have enrolled enough patients over the age of seventy-five to describe how either drug behaves in the very old.

Better evidence would come from adequately powered, double-blind head-to-head trials in a single population, with pre-specified endpoints of glycated haemoglobin, hypoglycaemia, renal function and cardiovascular events. Real-world registries could complement these, especially in India, provided prescribing data are linked to laboratory results. Such work should also report adherence and cost, which strongly affect real outcomes [10, 12]. Methodological improvements would be simple to describe even if costly to carry out. They include blinded assessment of outcomes, intention-to-treat analysis, defined handling of rescue therapy and a report of the proportion reaching target without hypoglycaemia. Trial registration and sharing of patient-level data would let independent groups verify the findings and carry out

indirect comparisons with greater confidence [7, 8].

Investigators should also examine whether the structural differences between the drugs matter clinically, for instance in inhibition of related peptidases, effects on vascular markers and long-term durability of glycaemic control. For now, the argument for preferring teneligliptin over sitagliptin, or the reverse, rests on practical grounds such as kidney function, QT risk, cost and clinician familiarity rather than on a proven difference in efficacy [16, 31, 34]. Practice-oriented studies that follow people for several years may provide the most useful answer, because the question in the clinic is seldom whether a drug works for twelve weeks but whether it keeps patients within target and out of hospital. Data on the costs of treatment failure, titration and monitoring would complete the picture for health systems with limited budgets [1, 9].

Systematic reviews of the class from before 2022 call for longer follow-up and standard reporting of adverse events [8, 34]. Such calls would apply with extra force to newer products. Findings on pleiotropic effects need confirmation before they influence practice [12, 31].

7. CONCLUSION

For most patients needing an add-on to metformin, the published evidence does not show that teneligliptin and sitagliptin differ much in how far they lower glycated haemoglobin. Both act through the same incretin mechanism, both are weight neutral with a low hypoglycaemia risk when no sulphonylurea is present, and both are generally well tolerated [5, 20, 24]. Sitagliptin has by far the larger trial programme and a dedicated cardiovascular outcome trial, which gives it a firmer evidence base [28, 35]. Differences in trial size and design, not in the drugs, explain much of the apparent gap.

Teneligliptin's attractions are practical: dual elimination that may simplify use in renal impairment, low cost in several markets, and a body of Japanese and Indian experience [11, 12, 18]. Its limitations are less evidence, short comparisons and a modest QT effect to bear in mind. Clinicians should choose between the two on kidney function, other drugs, cost and local availability, and should avoid overstating differences that trials have not demonstrated. Better head-to-head studies would settle what is currently a matter of judgement [8, 27].

8. ABBREVIATIONS

ADA-American Diabetes Association, DPP-4-Dipeptidyl peptidase-4, eGFR-Estimated glomerular filtration rate, GIP-Glucose-dependent insulinotropic polypeptide, GLP-1-Glucagon-like peptide-1, HbA1c-Glycated haemoglobin, QT-Interval from start of Q wave to end of T wave on the electrocardiogram, SGLT2-Sodium–glucose co-transporter 2, TECOS-Trial Evaluating Cardiovascular Outcomes with Sitagliptin, UKPDS-UK Prospective Diabetes Study

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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