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REVIEW

Metformin for the Treatment of Type 2 Diabetes in Asian Adults: A Systematic Review

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Video abstract

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Abstract: Metformin is a cheap, orally administered, guideline recommended glucose-lowering drug (GLD), initiated as monotherapy in treatment naïve newly diagnosed type 2 diabetes (T2D), and in combination with other GLDs in T2D not controlled on metformin. The unique Asian T2D phenotype that is markedly different than Western population, and warrants T2D treatment approaches unique to the Asian population. However, the bulk of metformin literature is from Western population and may not be generalizable for Asians. The systematic review evaluated the efficacy and safety of metformin monotherapy and combination therapy in Asians. Literature on other GLDs recommended by the 2023 American Diabetes Association guidelines as add-on therapy to metformin were included from Asia. The systematic review concluded that metformin is effective and safe for long-term T2D control of T2D in Asians. Metformin monotherapy may be initiated and continued in treatment naïve Asian patients with T2D and/or obesity if the monotherapy is adequate for achieving glycemic control. Other GLDs may be added for better glycemic control for those who fail on monotherapy. Patients inadequately controlled on another first-line GLD can achieve glycemic control and target HbA1c of <7% by adding metformin in a once daily dose. The use of metformin reduces the risk of hypoglycemia, and its gastrointestinal side effects are mild and manageable in Asians.

Keywords: metformin, guideline directed, type 2 diabetes, Asians

Background

Type 2 diabetes (T2D) is a global pandemic.[1] T2D is three times more common in Asian than Western population, occurs at a younger age, at lower body mass index (BMI) of 23 kg/m^2, at lower lean muscle mass, and has worse trajectory and prognosis than Western population.[2–6]

T2D in Asians is commonly characterized by early pancreatic β-cell dysfunction and diminishing insulin secretion.[2] Thus, T2D progresses at a faster pace in Asian than in Western population.[7] Young age at diagnosis, high baseline HbA1c, high BMI, higher number of glucose lowering drug (GLD) use, and Malay ethnicity were found to be independent determinants of diabetes progression in Asians with T2D.[7]

Metformin is a cheap, orally administered GLD commonly initiated in treatment naïve newly diagnosed T2D.[8–20] The Research Society for the Study of Diabetes in India (RSSDI) guidelines also recommend initiating sulfonylurea (SU),

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dipeptidyl-peptidase 4 inhibitors (DPP4i) and sodium-glucose cotransporter 2 inhibitors (SGLT-2i) or oral glucagon-like peptide 1 receptor agonists (GLP-1 RA) where metformin is contraindicated or not tolerated.[20]

Rationale

Despite the increasing T2D prevalence in Asia, there is scant literature on T2D management with metformin from this region, and clinical decisions are usually dominated by literature on Caucasian and/or Western populations.[2] Systematic review (SR) and meta-analysis (MA) analyzing randomized trials provide high quality of literary evidence; however, majority of SR/MA on metformin use in T2D are from the Western world. Since Asian T2D phenotype is quite different from the Western world, therefore it may not be possible to extrapolate the results of SRs from the Western world for the Asian population.

Further, older SR/MA may not include GLDs considered to have intermediate to very high efficacy for glycemic control and weight control based on individual patient needs and risk factors (Box 1) (*hence forth mentioned as ADA 2023 recommended GLDs*).[21] For example, one SR/MA published in 2005 included randomized controlled trials (RCTs) published that compared metformin with oral GLDs such as glucosidase inhibitors, meglitinides, SUs, and thiazolidinedione.[22] Another recent SR published in 2020 included RCTs (results published until 2019) compared the effects of metformin monotherapy in T2D with placebo, diet/exercise, and other GLDs such as sulphonylureas; thiazolidinediones, DPP4i, meglitinide, insulin and GLP-1RA.[23] This SR did not compare metformin with SGLT2i.

Hence, there is a need for literature from Asia comparing metformin combinations with these GLDs. However, to the best of our knowledge, SRs from Asia comparing the effect of metformin monotherapy or combination therapy are lacking.

Metformin Use in Asia

Metformin is the most prescribed oral GLD in Asia.[8–17] Metformin exerts its glucose-lowering effects by inhibiting increased hepatic gluconeogenesis and improving peripheral glucose uptake and utilization.[19,24]

Physicians from Asia prefer initiating patients with pre-diabetes on metformin because it improves insulin resistance, and therefore delays progression to T2D. Further in drug-naïve patients with T2D, metformin use is associated with significant postprandial plasma glucose (PPG) and glycated hemoglobin (HbA1c) lowering effects.[19] Metformin use is also associated with a decrease in fasting plasma glucose (FPG).[19,24] Results from the landmark UKPDS study showed that metformin use is associated with reduction in microvascular risk, myocardial infarction (MI), and all-cause mortality.[18] Moreover, metformin is off patent, comparatively inexpensive, and associated with a low risk of hypoglycemia and lactic acidosis.[18,19]

Metformin monotherapy is effective and safe even after prolonged use.[25] However, continued long-term use of metformin monotherapy is limited by the natural history of progressive decline in β-cell function in T2D.[25] Metformin

Box 1 ADA 2023: Effective Therapies for Achieving and Maintaining Glycemic and Weight Management goals

	Effective Glucose-Lowering Therapies	**Effective Weight Loss Therapies**
Very high efficacy	Dulaglutide (high dose), semaglutide, tirezepatide, insulin, combinations of oral GLDs, combinations of injectable GLDs (GLP-1RA/insulin)	Semaglutide, tirezepatide
High efficacy	Metformin, SGLT2i, SU, TZD, other GLP-1RAs not listed above	Dulaglutide, liraglutide
Intermediate efficacy	DPP4i	SGLT2i, other GLP-1RAs not listed above
Neutral	-	Metformin, DPP4i

Notes: Data from ElSayed et al.[21]
Abbreviations: ADA, American Diabetes Association; DDP4i, Dipeptidyl peptidase 4 inhibitors; GLD, glucose lowering drugs; GLP-1RA, Glucagon-like peptide-1 receptor agonist; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas; TZD, TZD, thiazolidinedione.

up-titration is associated with a significant decrease in C-peptide ($P < 0.05$) and proinsulin ($P < 0.05$), and therefore helpful in preservation of β cell function.[26]

Further, clinical inertia on metformin monotherapy is very common in Asians and there have been concerns regarding adherence to metformin therapy due to gastrointestinal side effects.[8,27] However, data from various regions from Asia has also shown that metformin use was associated with least treatment failure rates.[9,28] Thus, to achieve and maintain optimum glycemic control, metformin co-prescription or fixed-dose combinations (FDCs) with other GLDs is recommended after the failure of metformin monotherapy.

Asian patients on early combination therapy with metformin consistently achieve lower HbA1c levels over the years (over 5-years in VERIFY study from Korea).[29] Since metformin is not a insulin secretagogue, it does not cause hypoglycemia, unless combined with other GLDs or being taken by debilitated, malnourished or calorie deficient patients.[30] Nor is metformin use associated with hyperinsulinemia.

Moreover, metformin can be prescribed to a broad range of patient population except those with severely affected liver or kidney function.[19]

Metformin Use in T2D: Recommendations from Asian Guidelines

T2D patients usually need a glucose lowering drug (GLD) life-long.[27] Metformin monotherapy is usually the first-line oral GLD approved along with lifestyle modification by guidelines such as the 2023 American Diabetes Association (ADA),[21] the 2022 Research Society for the Study of Diabetes in India (RSSDI),[31] 2020 Chinese expert consensus,[32] and the 2020 Consensus Recommendations from the South Asian Health Foundation.[33] The guidelines also recommend metformin in combination with other GLDs for T2D not managed by metformin and lifestyle modification.[21,31,33] The GLDs for combination with metformin should be selected based on patient's risk factors.[21,31,33]

Further metformin is also recommended in people with prediabetes along with lifestyle modification, especially in younger adults with risk factors for diabetes such as obesity), or impaired fasting glucose (IFG; FPG 110 to 125 mg/dL) or impaired glucose tolerance (IGT) with 2-h plasma glucose (2-h PG) ranging from 140 to 199 mg/dL during 75-g oral glucose tolerance test (OGTT) or HbA1c ≥5.7%–6.4%.[31] Obesity was defined as body mass index (BMI) ≥35 kg/m^2 by ADA[21] and a lower BMI of ≥25 kg/m^2 by RSSDI.[31]

Lines of Glucose Lowering Therapies Prescribed in Asia

The most common first-line GLDs prescribed in Asia are metformin combinations, insulin secretagogues, and metformin monotherapies (29.5%, 25.9%, and 19.2%, respectively).[10] Metformin plus SUs were the most popular combination used in Asia.[11,34,35]

Treatment preference was based on HbA1c levels. T2D patients with HbA_{1c} level of <7% were usually prescribed metformin monotherapy as first-line, while those with HbA_{1c} ≥8% received an insulin containing treatment as first line. Patients with HbA_{1c} ≥8% persisting on first line received an insulin containing treatment as second line more often than a metformin-based combination. Patients with an HbA_{1c} ≥8% on second line were prescribed metformin-based combination (usually) or insulin-including treatment as third and fourth line.[10] The use of metformin, insulin, DPP4i, and SGLT2i has significantly increased in Asia ($P < 0.001$ for all) over the last few years.[36]

Hence, it was important to assess if metformin-based combinations were effective and safe in Asian patients. Also, it was important to identify the most effective metformin-based combination according to characteristics of the T2D patient population.

Methodology

Aim

To evaluate the efficacy of metformin monotherapy and combination therapy in Asian adults with T2D. Metformin combination therapy included combination or add-on with ADA 2023 recommended GLDs.[21] These included oral GLDs such as sulphonylureas, thiazolidinedione, SGLT2i, and DDP4i, or injectable GLDs (insulin and GLP-1RA) (Box 1).[21]

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The SR also aimed to compare metformin monotherapy/ combination therapy with other ADA 2023 recommended GLDs or one metformin combination therapy with another. Since double and triple combination therapies with metformin are used in real clinical scenarios, various metformin combinations were also explored.

Since lifestyle modification (diet and/or exercise) are also an integral part of ADA 2023 recommended treatment, the SR also aimed to assess the efficacy of metformin monotherapy/ combination therapy versus lifestyle modification. Various metformin combination therapy with lifestyle modification were also explored. Safety and tolerability parameters were captured if available.

Outcomes

Metformin is recommended by the 2023 ADA guidelines[21] for the achievement and maintenance of glycemic and weight goals, either as monotherapy or in combination with other GLDs. Hence, this SR included RCTs that assessed glycemic parameters such as fasting blood glucose (FBS), post-prandial glucose (PPG), and glycosylated hemoglobin (HbA1c) and/or weight parameters such weight loss or weight gain or body mass index (BMI) or anthropometric measures as outcomes. Additionally, proportion of patients achieving ADA target of HbA1c ≤7% or ≤6.5% were also captured.

Protocol

This systematic literature review followed a pre-determined, non-registered protocol and was conducted in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA)[37,38] guidelines. The protocol was modified post-literature search to remove observational, real world, retrospective and cohort studies (as described in methodology).

Inclusion Exclusion Criteria

The systematic review included studies according to a pre-researched and pre-determined inclusion and exclusion criteria as mentioned in (Table 1).

Search Methods and Identification of Studies

Two individuals independently conducted a MEDLINE (PubMed) search on November 1, 2023, to include records published from 2000 until October 31, 2023. The following search string was used by both the individuals: ("Metformin"[MeSH Terms] OR "Metformin"[Text]) AND ("Diabetes Mellitus, Type 2"[MeSH Terms] OR "Type 2 Diabetes"[Text]) AND (("Randomized Controlled Trial"[Publication Type] OR "Quasi-Randomized"[Title/Abstract] OR "Observational Study"[Publication Type] OR "Real-World Study"[Title/Abstract] OR "Cohort Studies"[MeSH Terms])

Table 1 Inclusion/Exclusion Criteria for Study Inclusion

Inclusion Criteria	Exclusion Criteria
≥18 years	<18 years
T2D without comorbidities; (exception: T2D + obesity included)	Type 1 diabetes; Pediatric diabetes; gestational diabetes; drug induced diabetes; T2D with comorbidities except T2D+obesity
Metformin monotherapy/ Metformin plus ADA 2023 recommended therapies for glycemic control and weight[21]	Studies not including metformin or metformin combination as the main therapy
Comparator/combination: ADA 2023 recommended therapies for glycemic and weight control: diet/lifestyle, sulphonylurea, SGLT2i, DDP4i, insulin, GLP-1RA[21]	Comparator/combination not recommended by ADA 2023 for glycemic and weight control such as acarbose
RCTs, quasi randomized, randomized, studies from Asia	RCTs, quasi randomized, randomized, studies not from Asia

(*Continued*)

Table 1 (Continued).

Inclusion Criteria	Exclusion Criteria
Duration of therapy: ≥12 weeks to ≤24 weeks	GLDs other than metformin were the primary study focus, and results were not reported according to metformin use or in comparison with metformin
Trial reporting at least one of the outcomes of this systematic review	Trial reporting an outcome other than included outcomes such as CV mortality, all-cause mortality, pulse pressure, hypertension, malignancy, COPD, tuberculosis, cognition, aortic aneurysms, fractures etc.
Literature published in English language	Literature published and available only in language other than English
Full text of publication available	Full text of publication not available

Abbreviations: ADA, American Diabetes Association; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DDP4i, Dipeptidyl peptidase 4 inhibitors; GLD, glucose lowering drugs; GLP-1RA, Glucagon-like peptide-1 receptor agonist; RCT, randomized controlled trial; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; T2D, Type 2 diabetes.

AND ("2000/01/01"[Date - Publication] : "2023/10/31"[Date - Publication]) AND ("Asia"[MeSH Terms] OR "Asian"[Text])).

A total of 460 records were retrieved. The two researchers then separately reviewed the collected records to identify and eliminate any duplicates utilizing a reference manager. No duplicates were found. They examined the records for inclusion or exclusion criteria based on the study titles and abstracts, and further by going through the full-texts. Of these, 54 records met the inclusion criteria.

Subsequently, after thorough discussion and deliberation, the researchers excluded 24 records of observational, real world, retrospective or cohort studies. There were no records having a quasi-randomized design. This decision to exclude the above studies was taken because there was huge difference in study designs, combinations and outcomes reported. Hence, it was difficult to compare these records amongst themselves, and with the RCTs. However, since real-world data are important to assess the real-world use, efficacy and safety of drugs, the information presented in these records was used to build the introduction and discussion of the SR. The Protocol was then amended accordingly.

In the end, both investigators reached a consensus to include 30 records obtained through the online search. Of these, two studies were of 26 weeks duration viz by Ji et al[39] and VERTIS Asia (2019).[40] However, after mutual discussion, they were included as they the time duration was close to 24 weeks.

Further, one study[41] was conducted in the United States (US), but was included as this was the only the study that compared metformin+sulphonylurea versus sulphonylurea versus metformin and included some Asia-Pacific Islanders. Hence, we also included another multinational study by Bosi et al (2009) where 10.2% of the study population were Asians.

Figure 1 outlines the detailed search and selection criteria of the records through the PRISMA flow chart. The details of the 30 studies included in the systematic review are captured in Figure 2.

Quality of Evidence and Risk of Bias

Metformin is an old drug, and despite limiting the literature to Asia and to T2D without comorbidities, the literature search pulled up 460 records that included studies of many designs. Since we were gathering data from interventional randomized trials comparing metformin mono- or combination therapy versus placebo or other GLDs, we did not include systematic reviews and meta-analyses, even though they are considered high-quality evidence.[42] The Oxford Center for Evidence-based Medicine (OCEBM) – Levels of Evidence[42] considers RCTs as the highest quality interventional study followed by a trial with randomized design of any type. Hence, we included only randomized studies.

Good quality evidence can be extrapolated from randomized trials with low risk bias. The two researchers independently carried out the risk of bias assessment using the Cochrane Collaboration's tool for risk of bias assessment.[43,44] The

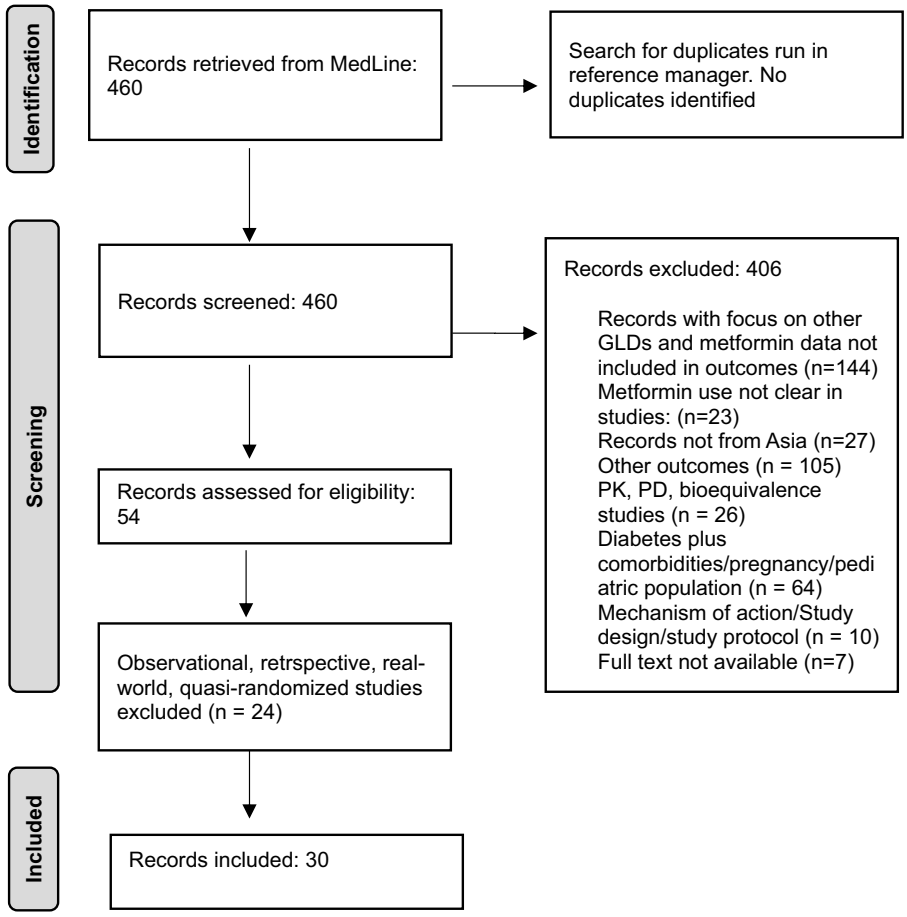

Figure 1 Prisma flow chart.

tool assesses six domains of bias and stratifies the risk of bias as low, high and unclear risk (Figure 2). Any discrepancies in assessment between the two researchers were resolved by mutual discussion and consensus.

The systemic search could not pull out any RCT comparing metformin plus thiazolidinedione versus metformin or versus thiazolidinedione or versus metformin+another GLD that met the inclusion criteria of the SR.

The two researches carried out the risk bias assessment independently. If a record provided the clinical trial identifier number, then information regarding blinding and study design was also taken from the clinical trial website. In general, the risk of bias was low in most of the trials. Blinding of outcome assessment was not clearly outlined in some trials. Other than this, six trials followed a randomized open-label design.

Data Analysis

The data could not be pooled and analyzed statistically because within the same comparative group, the trials had different designs and different patient populations. Therefore, key outcomes were narratively described and due consideration was given to the PRISMA checklist.[37]

Results: Metformin Monotherapy Versus a GLD or Lifestyle Modification

The SR did not retrieve any record comparing metformin against placebo or against lifestyle modification.

Only one record compared metformin extended release (XR) with metformin immediate release (IR) in 532 treatment-naïve Chinese patients with T2D. However, the primary aim of the CONSENT trial[24] was to assess if 16-week treatment with metformin XR had superior gastrointestinal tolerability with non-inferior efficacy as compared to metformin IR. The trial showed that metformin XR was not superior to metformin IR for overall gastrointestinal side

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding participants and personnel (performance bias)	Blinding outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
SUCCESS trial (2023)[65]	+	+*	+*	+*	+	+
Linong Ji et al (2021)[49]	+	+	+	+	+	+
VERTIS Asia (2019)[40]	+	+	+	+	+	+
Shestakova et al (2018)[58]	+	+	+	+	+	+
START study (2018)[53]	+	+	+	+	+	+
CONSENT trial (2018)[24]	+	+*	+*	+*	+	+
Mu et al (2017) [52]	+	+	+	?	+	+
Ji et al (2017)[55]	?	?	?	?	+	+
Kaku et al (2017)[51]	+	+	+	?	+	+
Shankar et al (2017)[67]	+	+	+	+	+	+
INICOM study (2017)[54]	+	+	+	+	+	+
Ba et al (2017) [66]	+	+	+	+	+	+
Suzuki et al (2017)[26]	+	+*	+*	+*	+	+
VISION Study (2016)[50]	+	+*	+*	+*	+	+
Lu et al (2016)[59]	+	+	+	+	+	+
Ji et al (2016) [39]	+	+	+	?	+	+
Wang et al (2016) [2]	+	+	+	?	+	+
Tanaka et al (2015)[61]	+	+*	+*	+*	+	+
Kim et al (2015)[48]	?	+	+	?	+	+
ILLUMINATE study (2015)[57]	+	+	+	+	+	+
Cheng et al (2015) [60]	+	+*	+*	+*	+	+
Moses et al (2014)[64]	+	+	+	+	+	+
Zeng et al (2013)[62]	+	+	+	?	+	+
Yang et al (2012)[47]	+	+	+	+	+	+
Seino et al (2012)[30]	+	+	+	?	+	+
Pan et al (2012)[46]	?	+	+	?	+	+
Owens et al (2011)[63]	+	+	+	?	+	+
Yang et al (2011)[45]	+	+	+	?	+	+
Bosi et al (2009)[56]	?	?	?	?	+	+
Goldstein et al (2003)[41]	+	+	+	+	+	+
Low risk +; high risk -; and unclear risk ?; randomized open-label trial*						

Figure 2 Risk bias assessment of the 30 included studies.

effects (P=0.674) and was non-inferior for change in HbA1c from baseline to week 16 (least square mean difference of 0.03; 95% confidence interval [CI], −0.10, 0.17).[24] The percentage of patients achieving HbA1c <7% at week 16 or experiencing hypoglycemia were similar between groups.

Results: Comparing Metformin with Sulphonylureas

The SR retrieved only one record (multicenter, double-blind, parallel-group, active-controlled study) published in 2003 comparing metformin+SU versus SU or metformin in 247 T2D patients who achieved inadequate glucose control (HbA1C ≥7.5% and ≤12.0%) with at least half the maximum labelled daily SU dose.[41] The trial was conducted at 108 outpatient US clinics and included Hispanic/Latino, Black, and Asian/Pacific Islanders (15.8%, 13.0%, and 1.2%, respectively) with moderate-to-severe hyperglycemia (mean HbA1c, 8.7%) and mean T2D duration of 6.5 years. This study randomized patients into glipizide/metformin (5/500 mg) vs glipizide (30-mg) vs metformin (500-mg) for 18 weeks.

The HBA1c levels reduced significantly more with glipizide/metformin versus glipizide or metformin monotherapies ($P < 0.001$). At the end of the study, HbA1c <7.0% was achieved by 36.3% of patients on glipizide/metformin as compared to 8.9% on glipizide and 9.9% on metformin. Patients on glipizide/metformin also had lower FPG and PPG than glipizide or metformin, with no increase in fasting insulin level. All three treatments were well tolerated with low incidence of hypoglycemia; medical management was not required for hypoglycemia.[41]

As expected, the study showed that metformin+SU was more effective than either metformin or SU in reducing HbA1c, FPG, PPG; achieving target HbA1c of <7%; and had similar safety profile as the monotherapies.[41] However, the results are limited by the fact that Asia-Pacific Islanders constituted only 1.2% of study population, and the study was conducted in the US.

Results: Comparing Metformin with Dipeptidyl Peptidase-4 Inhibitors

The majority of retrieved records were largely designed to study DPP4i and reported DPP4i + metformin versus metformin and/or DPP4i.

Metformin + DPP4i vs Metformin

Seven studies compared DPP4i + metformin versus metformin (stable dose) (Table 2). The DPP4i included in these trials were teneligliptin (two trials each); and vildagliptin, saxagliptin, linagliptin, sitagliptin, and alogliptin (one trial each). The trials usually compared a DPP4i+metformin with placebo+metformin and reported results by DPP4i and placebo groups. However, for the purpose of this SR, we considered the placebo group as the metformin monotherapy control group. Only two trials directly compared DPP4i+metformin with metformin monotherapy, one with alogliptin[30] and another with saxagliptin.[45] Generally, the metformin and DPP4i doses stabilized at the beginning of the study were used throughout the study.

Three trials were from China, one trial each from Japan and Korea, one Asian trial included Chinese, Indian and Korean patients and another included patients from China, Malaysia and Philippines.

The trials demonstrated a significant decrease in HbA1c with linagliptin + metformin at 24 weeks in Asian patients (Chinese, Malaysian, and Filipino) ($P<0.0001$);[2] with alogliptin (12.5 or 25 mg) once daily + metformin at 12 weeks in Japanese patients ($P<0.0001$);[30] with metformin plus vildagliptin 50 mg bid or vildagliptin 50 mg OD versus metformin ($P<0.001$) in Chinese patients at 24 weeks;[48] with saxagliptin + metformin versus metformin ($P\leq0.0052$) in Asian (China, India and South Korea) patients at 24 weeks;[45] sitagliptin +metformin in Chinese patients at 24 weeks ($P<0.001$);[49] teneligliptin plus metformin at 16 weeks in Korean patients ($P<0.0001$)[47] and at 24 weeks in Chinese patients $P<0.0001$).[46] There were significant declines in FPG and PPG as well with DPP4i+metformin (Table 2).

The trial on alogliptin had a 40 week open-label extension period to assess the safety profile of alogliptin + metformin. The total treatment period was 52 weeks and included 12 week randomized treatment period. No safety or tolerability concerns with the combination were observed as compared to metformin.[30]

As expected, the trials demonstrated that DPP4i+metformin combination was more effective than metformin monotherapy in providing glycemic control and achieving glycemic target of HbA1c ≤7% in Asian patients who failed on metformin monotherapy. DPP4i+metformin had similar safety profile (including hypoglycemia) as metformin monotherapy. The trials also showed that DPP4i+metformin was weight neutral in Asian patients (Table 2).

Metformin + DPP4i vs Metformin Uptitration

Two trials compared dpp4i plus metformin against varying doses of metformin.

Table 2 Results Comparing Metformin Plus DPP4i versus Metformin

Trial (year) N (randomization) / Duration of Treatment	Patient Population (including countries and HbA1c defining inadequate glycemic control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (weight)	Adverse Events
Ji et al (2021)[46] 240 (1:1)/ 24 weeks	51 sites in China; T2D inadequately controlled on metformin dose ≥1000 mg/day. HbA1c between 7.0%-<10.0%, FPG <270 mg/dL	20 mg of teneligliptin or a placebo OD	Change in HbA1c (primary), FPG (secondary), from baseline after 24 weeks	Teneligliptin vs placebo after 12 weeks: HbA1c: significant reductions (−0.81%; p < 0.0001) FPG: significant reductions (−22.2 mg/dL; p < 0.0001). HbA1c <7.0% at Week 24,: Teneligliptin (41.7%) significantly more vs placebo (16.1%; p < 0.0001).	Change in body weight from baseline to Week 24	No significant between group differences	Teneligliptin vs placebo: similar incidence of hypoglycemia (3.2% vs 2.4%) and other AEs (URTI, hyperuricaemia, hyperlipidaemia
Wang et al (2016)[2] 305 (2:1) / 24 weeks	Asian patients inadequately controlled on metformin Chinese (n = 265); Malaysian (n = 24); Filipino (n = 17) HbA1c between ≥7.0 and ≤10.0%	Linagliptin 5 mg daily + metformin (LM) (n=205) or placebo + metformin (PM) (n=100)	Change in HbA1c (primary), FPG (secondary), from baseline after 24 weeks Secondary: HbA1c efficacy responses (<7.0% or <6.5%)	Adjusted mean (±SE) HbA1c decrease LM vs PM: by −0.66 ± 0.05 vs −0.14 ± 0.07%, (−0.52 ± 0.09%; P < 0.0001). Higher decrease in patients with baseline HbA1c ≥8.5%: −0.89 ± 0.17% (P < 0.0001) LM significantly reduced FPG vs PM (P = 0.02) In pts. with HbA1c ≥7.0% and LM vs PM: HbA1c of <7.0%: 37.3% vs 10.1% HbA1c of <6.5%: 12.9% vs 3.1%	Change in body weight, BMI, waist circumference (secondary)	No significant between group differences Similar decrease in body weight No increase in BMI/waist circumference	No significant between group differences for AEs No significant differences between groups for hypoglycemia (1% both groups)

(*Continued*)

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Table 2 (Continued).

Trial (year) N (randomization) / Duration of Treatment	Patient Population (including countries and HbA1c defining inadequate glycemic control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (weight)	Adverse Events
Kim et al (2015)[47],204 (2:1) / 16 weeks	Korean patients with T2D inadequately controlled on stable-dose metformin monotherapy (≥1000 mg/day) for at least 8 weeks HbA1c: 7.0–10.0%	20 mg teneligliptin plus metformin (n = 136) vs placebo plus metformin (n = 68).	Change from baseline in HbA1c after 16 weeks of treatment (primary)	Teneligliptin plus metformin vs metformin (placebo) −0.90% vs −0.12% (P < 0.0001)	Body weight: exploratory efficacy endpoint	No between group differences	Percent of participants recording AEs was similar between Teneligliptin + metformin vs metformin (+placebo) 41.2% vs.44.9% (P=0.6076) 2.9% of participants in each group experienced hypoglycemia
Seino et al (2012)[30],288 (1:1:1) / 12 weeks Long-term (40-week), open-label extension	30 Japanese centers; T2D inadequately controlled on metformin (500 or 750mg/day) + diet/ exercise HbA1c between ≥ 6.9 and <10.4%.	12 weeks: 12.5mg alogliptin OD + metformin vs or 25mg alogliptin OD + metformin vs metformin monotherapy Thereafter, 276 patients continued on one of the two alogliptin dosages + metformin in an open-label extension for 40weeks.	Change in HbA1c from baseline to week 12. (primary) HbA1c <6.9% (secondary) HbA1c and FPG at each assessment point, and plasma glucose concentrations during meal tolerance (Secondary endpoints)	Change in HbA1C at 12 weeks: Alogliptin + metformin vs metformin monotherapy (P<0.0001); Alogliptin 12.5mg +metformin: −0.55% ±0.058;alogliptin 25mg +metformin: −0.64% ±0.056; metformin monotherapy: 0.22% ±0.055 Proportion of pt. with HbA1c <6.9%: 28.3 and 27.1% with the 12.5 and 25 mg alogliptin dosages, respectively vs 2% in metformin monotherapy FPG and 2 hour PPG were significantly lower in the two alogliptin groups vs metformin monotherapy	Body weight, at each assessment point	A minor increase in body weight in the alogliptin 12.5 mg +metformin group (mean rise 0.17 ± 1.38 kg) versus minor decreases in the other two groups, the increase was not considered clinically significant.	Extension period: AEs were comparable between groups, with no increases in hypoglycemia. Over 52 weeks, there were no safety or tolerability concerns with alogliptin when added to metformin.

Pan et al (2012)[48] 438 (1:1:1) / 24-weeks	Chinese patients with T2D inadequately controlled on metformin monotherapy HbA1c: 7.0–10.0% at week 2.	Vildagliptin 50 mg bid + metformin vs vildagliptin 50 mg OD + metformin vs placebo + metformin	Change from baseline in the mean HbA1c (primary) and mean FPG. (Secondary) HbA1c <7% (secondary)	Mean change in HbA1c (vidagliptin bid +metformin vs OD + metformin vs metformin: -1.05 ± 0.08% vs -0.92 ± 0.08% vs -0.54 ± 0.08% The between-treatment difference (vildagliptin 50 mg bid–placebo) was 0.51 ± 0.11%, (P < 0.001) Mean FPG vildagliptin 50 mg bid: 0.95 mmol/l (17.1 mg/dl); 50 mg OD: 0.84 mmol/l (15.1 mg/dl) Placebo: 0.26 mmol/l (4.6 8 mg/dl) (P ≤0.001). HbA1c <7%: 53.7% vs 48.9% vs 34.8% (P=0.002 for 50 mg bid and 0.018 for 50 mg OD)	Not reported	AEs reported in vildagliptin 50 mg bid, 50 mg OD or placebo: 34.2, 36.5 and 37.5% respectively.

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Table 2 (Continued).

Trial (year) N (randomization) / Duration of Treatment	Patient Population (including countries and HbA1c defining inadequate glycemic control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (weight)	Adverse Events
Yang et al (2012)[49] 395 (1:1) / 24 weeks	Chinese patients with T2D inadequately controlled on metformin monotherapy (1000 or 1700 mg / day) HbA1c ≥7.5% and ≤ 11.0%	Sitagliptin 100 mg OD + metformin vs placebo + metformin	Change from baseline at Week 24 in HbA1c (Primary) and FPG and 2-hour PPG (secondary) Proportions of patients meeting HbA1c goals (<7.0% and <6.5%) (secondary)	Significant (P < 0.001) changes from baseline in HbA1c: −0.9% Placebo-adjusted changes from baseline in HbA1c for the metformin 1000 and 1700 mg/ day strata: 0.8% and 0.9%, respectively (P < 0.001 for both metformin dose vs placebo) Significantly greater proportion of patients in the Sitagliptin vs placebo groups met the HbA1c goals of <7.0% and <6.5% (P < 0.001 for both) Mean change (sitagliptin vs placebo) FPG: −1.2 mmol / L), and 2-h PPG: −1.9 mmol / L	Change from baseline in body weight	A small decrease from baseline body weight was observed in the placebo group compared with no change in the sitagliptin group (between-group difference 0.5 kg; P = 0.018).	No significant between group differences in the incidence of hypoglycemia or gastrointestinal adverse events.

Yang et al (2011)[45] 530 (1:1) / 24 weeks	40 centers in Asia: China (21 sites), India (7 sites), and South Korea (12 sites) Pts. with T2D inadequately glycaemic controlled with metformin monotherapy (≥1500 mg/day) Regions: China (58.3%), India (25.8%), and South Korea (15.9%) HbA1c 7.0–10.0%	Sitagliptin 5 mg daily plus metformin vs placebo plus metformin	Change from baseline at Week 24 in HbA1c (Primary) and FPG; PPG AUC from 0 to 180 min (Secondary) Proportion of pts. With HbA1c < 7.0% (secondary)	Saxagliptin + metformin vs placebo + metformin: HbA1c (0.78% versus 0.37%), FPG (1.14 mmol/L versus 0.58 mmol/L), and PPG AUC (315 mmol min/L versus 160 mmol min/L), with a P≤ 0.0052. HbA1c < 7.0%: 46.5% vs 30.5%; (P = 0.0001)	BMI, waist circumference, and body weight	Similar between group reductions in body weight, BMI, and waist circumference	Proportion of pts. With AEs (excluding hypoglycemia) was comparable between (42.8% vs 40.8%). Hypoglycemia: 4% in each group

Abbreviations: AEs, adverse events; AUC: area under the curve; bid, twice daily; BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting blood glucose; OD, once daily; PPG, post prandial glucose; pts., patients; SE, standard error; T2D, type 2 diabetes; URTI, upper respiratory tract infection.

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One was a small trial of 50 Japanese patients randomized to vildagliptin + low-dose metformin (control group) versus vildagliptin plus high-dose metformin (intervention group).[26] The vildagliptin dose was the same in both the groups. There were significantly larger decreases in HbA1c ($P < 0.05$), FBG ($P < 0.01$), and BMI ($P < 0.05$) in metformin dose-increase than in low-metformin dose group. At week 24, compared to baseline, the dose-increase group had significantly lower HbA1c than low-dose metformin group ($P < 0.01$). The metformin doses at 24 weeks were 1630 ± 703 mg/day in intervention and 650 ± 125 mg/day in control group.[26] However, since the sample size was very small, the glycemic benefit of increasing metformin dose in DPP4i+metformin combination should be investigated in a larger sample population.

The other trial was the large VISION Study (127 centers) that included 3084 Chinese patients with T2D inadequately controlled with metformin ≤1000 mg/day.[50] The patients were stratified by age and BMI into four equal groups. Each group was randomized 5:1 into vildagliptin and low-dose metformin (VLDM) group (vildagliptin 50 mg twice daily + metformin 500 mg twice daily) or high-dose metformin (HDM) (vildagliptin 50 mg twice daily + metformin uptitration to 1000 mg twice daily). Interestingly, HbA1c reduction at 24 weeks in the VLDM group was non-inferior and statistically superior to HDM group (0.54% vs 0.40%; $P < 0.0001$). The results were replicated in all subgroups, except in subgroup with patients aged <60 years with a BMI of ≥24 kg/m^2. Significantly higher percentage of patients in VLDM group achieved HbA1c ≤6.5% than HDM group, and this was achieved without significant gastrointestinal events. VLDM group had numerically lower FPG at week 24 than HDM group. Safety profile was similar across the two treatment arms.[50]

The trial showed that in T2D patients inadequately controlled on metformin ≤1000 mg/day, vildagliptin 50 mg twice daily + metformin 500 mg twice daily was a better dose combination in achieving glycemic targets than vildagliptin 50 mg twice daily + metformin uptitration to 1000 mg twice daily.

Since both the trials investigated vildagliptin + metformin as the DPP4i+metformin combination, it is reasonable to conclude the metformin uptitration in patients receiving vildagliptin + metformin may not be beneficial.

Metformin + DPP4i versus DDP4i

Only one trial compared DPP4i plus metformin against DPP4i. This was the only trial in the SR that assessed the effect of adding metformin on a background of DPP4i.

One trial randomly assigned 374 Japanese patients (34 sites) with inadequate glycaemic control on alogliptin 25 mg once-daily + diet and exercise into alogliptin/metformin once daily (n = 152) or alogliptin/metformin twice daily (n = 151) versus alogliptin alone (n = 71).[51] The trial showed that alogliptin/metformin once daily was superior to alogliptin alone and non-inferior to alogliptin/metformin twice daily. The least square mean difference in HbA1c from baseline between alogliptin/metformin once daily and alogliptin alone was −0.65% (95% confidence interval [CI] −0.821, −0.480) and between alogliptin/metformin once and twice daily was 0.11% (95% CI −0.026, 0.247). HbA1c <7.0% at week 24 was achieved by 35% on patients on alogliptin/metformin once daily, 34.3% on alogliptin/metformin twice daily and 4.8% on alogliptin alone. Alogliptin/metformin once daily was also well tolerated.[51]

The trial showed that patients inadequately controlled on DPP4i can achieve glycemic control and target HbA1c of <7% by adding metformin in a once daily dose.

Metformin + DPP4i vs Metformin vs DPP4i

Seven trials compared metformin + DPP4i combination with both the individual monotherapies in treatment naïve T2D patients (Table 3). Two trials assessed sitagliptin while one trial each assessed saxagliptin, gemigliptin, linagliptin, alogliptin, and vildagliptin. The trial by Mu et al[52] had a main study group (HbA1c ≥7.5% to <11%) comparing linagliptin + metformin versus individual monotherapies over 24 weeks and a parallel study group with higher baseline HbA1c (≥11%) comparing linagliptin + metformin versus linagliptin over 12 weeks.

All trials were for 24-week duration except the alogliptin trial which was of 26 weeks duration. All the trials compared the efficacy and safety of a DPP4i+ metformin versus individual monotherapies in treatment naïve Asians.

Table 3 Results Comparing Metformin Plus DPP4i versus Metformin versus DPP4i

Trial (year) N (randomization) / duration of treatment	Patient Population (Including Countries and HbA1c Defining Inadequate Glycemic Control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (Weight)	Adverse Events
START Study (2018)[53] 640 (1:1:1) / 24 weeks	Treatment naïve Chinese T2D patients HbA1c 8.0–12.0%	Saxagliptin 5 mg + vs Metformin (combination group), saxagliptin 5 mg + placebo (saxagliptin group) vs or metformin + placebo (metformin group)	Change in HbA1c from baseline (primary); FPG and PPG AUC (secondary) patients with HbA1c ≤6.5% (secondary)	Mean HbA1c reduction Combination vs saxagliptin group (−3.0% vs −2.1%; P < 0.001) or vs metformin group (vs −2.8%; P = 0.034). FPG: combination vs saxagliptin group, (−3.25 mmol/L vs −1.86 mmol/L;P < 0.001); or vs metformin group vs −2.94 mmol/L; P = 0.046) PPG AUC 0–180 combination vs saxagliptin group: (−1027.8 mmol·min/L vs −611.9 mmol·min/L; P < 0.001); vs metformin group (vs −858.5 mmol*min/L; P = 0.001) Proportion of patients with HbA1c ≤6.5% combination vs saxagliptin group (67.0% vs 32.1%, P < 0.001) vs metformin group (vs 55.4%, P = 0.020)	Change in body weight and BMI from baseline to Week 24	**Combination vs saxagliptin group** Significant reductions in BMI (−0.42 kg/m2 vs −0.07 kg/m2, P < 0.001), waist circumference (−1.3 cm vs −0.4 cm, P = 0.030) and total body weight (−1.14 kg vs −0.14 kg, P < 0.001) **Combination vs metformin group** Insignificant reduction in BMI (−0.42 kg/m2 vs −0.58 kg/m2, P = 0.112); waist circumference (−1.3 cm vs −1.1 cm, P = 0.658) and total body weight (−1.14 kg vs −1.56 kg, P = 0.138)	Hypoglycemic events:<2% Similar incidence of AEs between groups (URTI and diarrhea most frequent).

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Table 3 (Continued).

Trial (year) N (randomization) / duration of treatment	Patient Population (Including Countries and HbA1c Defining Inadequate Glycemic Control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (Weight)	Adverse Events
INICOM Study[54] 433 (1:1:1) / 24 weeks	Treatment-naïve Asian patients with T2DM (357 Korean and 76 Thai) HbA1c 7.5% to 11.0% and an FPG <270 mg/dL	Gemigliptin 50 mg OD + metformin 1000 to 2000 mg OD (titrated individually) (combination group) vs gemigliptin 50 mg OD vs metformin 1000 to 2000 mg OD	HbA1c level from baseline to week 24 (primary); FPG (secondary) HbA1c <7% or <6.5% (secondary)	Combination vs gemigliptin vs metformin: Mean HbA1c change:-2.06% vs −1.24% vs −1.47% Adjusted mean treatment differences (HbA1c) of combination vs: gemigliptin (−0.82%; P < 0.001); metformin (−0.62%; P < 0.001) FPG reductions of combination vs: gemigliptin (−26.6 mg/dL); vs metformin (−13.3 mg/dL) HbA1c <7%: 82.4% vs 40.7% vs.50.0%	Mean changes in body weight, waist circumference (secondary)	Body weight decreased significantly by 0.8 kg in the metformin group and insignificantly by 0.4 kg, in combination group but not in the gemigliptin group	Percentages of patients with treatment-related AEs: 17.02%, 7.04% and 14.67% No pt. in gemigliptin group had hypoglycemia Hypoglycemia in combination vs metformin: 2.13% vs 1.33%
Mu et al (2017) **Main group**[52] Total: 876 Main group: 773 (1:1:1:1:1) / 24 weeks	Treatment-naïve Asian patients with T2D from 56 sites (China, 82%; Malaysia, 8.7%; Philippines, 4.9%; Vietnam, 4.5%) HbA1c ≥7.5% (58 mmol/mol) to <11.0% (97 mmol/mol)	Linagliptin 5 mg OD; or metformin 500 mg bid; or metformin 1000 mg bid; or linagliptin 2.5 mg/metformin 500 mg SPC bid; or linagliptin 2.5 mg/metformin 1000 mg SPC bid	HbA1c change from baseline at 24 weeks (primary), and FPG/2-hour PPG (secondary) Proportion of pts. with HbA1c <7.0% (baseline HbA1c ≥7%) or <6.5% (baseline HbA1c levels ≥6.5%)	Mean HbA1c change: Insignificant differences between SPC vs individual monotherapies (*P* = 0.0587) No significant between group differences for FPG and PPG More patients on SPC achieved HbA1c <7.0% or <6.5%	Change in body weight baseline to Week 24	No clinically meaningful changes in body weight over the 24 weeks in all treatment groups	Hypoglycemic AEs were low across the groups.

Mu et al (2017) **Parallel group**[52] Total: 876 Parallel group: 143 (1:1) / 12 weeks	Treatment-naïve Asian patients with T2D from 56 sites (China, 82% of study population) HbA1c ≥11.0% (97 mmol/mol)	Linagliptin 2.5 mg/ metformin 1000 mg SPC bid or linagliptin 5 mg OD*	HbA1c change from baseline at 12 weeks (primary), and FPG/2-hour PPG (secondary) Proportion of pts. with HbA1c <7.0%	Significantly greater for SPC vs monotherapy for mean HbA1c change (*P*=0.0001) and mean FPG change (*P* =0.0002) Proportion of pts. with HbA1c <7.0%: 58.8% vs 27.1% (P = 0.0001)	Change in body weight baseline to Week 12	No clinically meaningful changes in body weight over the 12 weeks in both treatment groups	Hypoglycemic AEs were low across the groups.
Ji et al (2017)[55] 647 (1:1:1:1) / 26 weeks	Treatment naïve T2D Asian (59 sites) (China, Malaysia, Republic of Korea (South Korea) and Taiwan) HbA1c of 7.5%-10.0% and FPG ≤ 275 mg/dL	Placebo vs alogliptin 12.5 mg bid vs metformin 500 mg bid vs alogliptin 12.5 mg/metformin 500 mg SPC bid	Change in HbA1c	Mean HbA1c change: −0.19% with placebo, −0.86% with alogliptin, −1.04% with metformin and −1.53% with alogliptin + metformin SPC. Alogliptin + metformin significantly more effective in lowering HbA1c than either monotherapies (P < 0.0001); and across all time points for lowering HbA1c and FPG (P < 0.02 for HbA1c; P ≤ 0.002 for FPG; both for all comparisons)	Not reported		Frequency of treatment related AEs were similar between groups (URTI was most common AE) Significantly lower proportion of pts in the alogliptin + metformin group required hyperglycemic rescue by Week 26 as compared with the alogliptin group (4.4% vs 14.8%; P = 0.002)

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Table 3 (Continued).

Trial (year) N (randomization) / duration of treatment	Patient Population (Including Countries and HbA1c Defining Inadequate Glycemic Control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (Weight)	Adverse Events
Ji et al (2016)[39] 744 (1:1:1:1:1:1) / 24 weeks	Treatment naïve or washed out from previous therapy Chinese patients HbA1c ≥7.5 and ≤11.0%	Sitagliptin 100 mg OD vs metformin 500 mg bid (M1000) vs metformin 850 mg b.i.d. (M1700) vs sitagliptin 50 mg b.i.d. plus metformin 500 mg b.i.d. (S100/M1000) vs sitagliptin 50 mg b.i.d. plus metformin 850 mg b.i.d. (S100/M1700) vs placebo.	HbA1c change from baseline % of pts with HbA1c goals (<7.0 and <6.5%) at 24 weeks	Mean HbA1c change: Placebo: −0.59%; S100:-0.99%; M1000: −1.29%; M1700: −1.56%; S100/M1000: −1.67%; S100/M1700:-1.83% ($P < 0.05$ for each group vs placebo; for both combinations vs S100, and for S100/M1000 vs M1000). Significant FPG reductions with either combination vs S100 ($P < 0.001$) only and not vs metformin. % of pts. with HbA1c <7% and HbA1c <6.5%: highest in the S100/M1700 group, followed by the S100/M1000 group, and lowest in the placebo group Higher % in coadministration groups vs S100 ($P < 0.001$), and vs metformin dose groups (<7%, $P = 0.007$ for both; <6.5%, $P = 0.005$ for M1000 and $P = 0.002$ for M1700)	Change in body weight from baseline to Week 24	Modest reductions in body weight in placebo, M1000 and M1700	Higher overall incidence of hypoglycemia (symptomatic or asymptomatic) in combination groups vs placebo. The incidence of symptomatic hypoglycemia was low, and similar, across all treatment groups.

Bosi et al (2009)[56] 1179 (1 : 1 : 1 : 1) / 24 weeks	Treatment naïve Caucasian (73.9%), Black (5.1%), Asian (10.2%), Hispanic/Latino (9.2%), others (1.7%) with T2D HbA1c of 7.5–11%	Vildagliptin + metformin high dose (50 mg + 1000 mg) (high dose) bid vs vildagliptin plus low-dose metformin (50 mg + 500 mg bid) vs vildagliptin monotherapy (50 mg bid) vs high-dose metformin monotherapy (1000 mg bid).	Change from baseline at Week 24 in HbA1c (Primary), in FPG (Secondary) % of pts with HbA1c goals (<7.0 and <6.5%) at 24 weeks	Mean HbA1c change: vildagliptin plus high-dose metformin: −1.8%; vildagliptin plus low-dose metformin −1.6%; vildagliptin: −1.1%; and metformin: −1.4% Superior between-group difference with vildagliptin plus high-dose metformin (P < 0.001 vs both monotherapies) and vildagliptin plus low-dose metformin (P < 0.001 and P= 0.004, vs vildagliptin and metformin, respectively) Superior FPG reductions with vildagliptin plus high-dose metformin vs both monotherapies (P < 0.001 for both) Significantly higher proportion of pts in vildagliptin plus high-dose metformin achieved HbA1c <7% and ≤6.5% vs both monotherapies (P < 0.001 for all) and vildagliptin plus low-dose metformin vs vildagliptin and metformin, respectively (<7%: P < 0.001 and P= 0.005, and ≤6.5%: P=0.003 and P=0.012, respectively)	Mean change in body weight from baseline to week 24 endpoint	No weight gain occurred with either combinations; modest weight loss occurred in both combinations Greatest body weight decrease in metformin monotherapy [−1.62 (0.22) kg], but no statistically significant difference vs either combination treatment	No incidence of hypoglycemia with either combination therapy, No between group differences in AE incidence Vildagliptin plus low-dose metformin had a favorable gastrointestinal tolerability profile compared with metformin monotherapy

Notes: pts on inadequate glycemic control after 12 weeks of linagliptin 5 mg OD were switched to linagliptin 2.5 mg/metformin 1000 mg SPC bid for rest of the study.

Abbreviations: AEs, adverse events; AUC: area under the curve; bid, twice daily; BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting blood glucose; OD, once daily; PPG, post prandial glucose; pts., patients; SE, standard error; SPC, single-pill combinations; T2D, type 2 diabetes; URTI, upper respiratory tract infection.

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As expected, the trials demonstrated that DPP4i+metformin combination was more effective than metformin or DPP4i monotherapy in providing glycemic control in treatment naïve Asian patients. DPP4i+metformin had similar safety profile (including hypoglycemia) as individual monotherapies.

However, the DPP4i differed with respect to weight reductions in Asian patients. Metformin monotherapy was superior in reducing BMI, weight and/or waist circumference than saxagliptin + metformin,[53] gemigliptin + metformin,[54] sitagliptin + metformin[55] and vildagliptin + metformin[56] and even as compared to individual DPP4i monotherapies (Table 3). However, the trial by Bosi et al (2009) included patients of various ethnicities, of which only 10.2% were Asians. The linagliptin study[52] showed no significant changes in body weight across the treatment arms, whereas the alogliptin study[55] did not assess weight change.

The results showed that metformin alone may be used in treatment naïve patients with T2D and obesity if the monotherapy is adequate for achieving glycemic control. DPP4i may be added for better glycemic control.

Results: Comparing Metformin with Sodium-Glucose Cotransporter 2 Inhibitors

Metformin+ SGLT2i vs Metformin

Four records compared metformin +SGLT2i with metformin (Table 4). Three trials assessed the efficacy and safety of ipragliflozin while one assessed ertugliflozin as the SGLT2i in combination with metformin. The trials were designed to assess SGLT2i versus placebo on a background metformin therapy, and hence the placebo group was considered the metformin monotherapy group. The trials showed that SGLT2i plus metformin significantly improved glycemic control and reduce weight in Japanese,[57] Chinese,[40] Russian,[58] and Taiwanese and Korean[59] patients with T2D not controlled on metformin therapy. The dose of SGLT2i may be uptitrated to achieve the desired glycemic goal with no additional safety/tolerability concerns, except hypoglycemia which could usually be managed with proper dose adjustment.[40,58]

Results: Comparing Metformin with Insulin

Metformin +GLD Vs Insulin After Short Insulin Period

Only one of the retrieved records compared metformin + oral gld versus insulin therapy.

The investigator-initiated randomized open parallel study showed that metformin-based oral GLD are non-inferior to insulin in providing glycemic control and improving β-cell function in 47 newly diagnosed T2D patients with severe hyperglycemia who were stabilized by a short-term intensive insulin therapy.[60] Severe hyperglycemia was defined as FPG > 11.1 mmol/L or random plasma glucose >16.7 mmol/L. At 24 weeks, HbA1c reductions were significant and similar in metformin + oral GLD (11.7% to 6.2%; $P < 0.001$) and insulin glargine (11.8% to 6.5%; $P < 0.001$) groups. There were no between group differences for hypoglycemic episodes, weight reduction, treatment satisfaction and quality of life. The authors from China concluded that since metformin is safe, cost-effective and convenient (oral) GLD, metformin-based GLDs should be preferred over insulin in newly diagnosed T2D patients with severe hyperglycemia.[60]

However, further research from Asia is necessary to establish conclusive evidence regarding the non-inferiority of using metformin combined with oral GLDs compared to insulin in individuals newly diagnosed T2D and severe hyperglycemia.

Results: Comparing Metformin with Glucagon-Like Peptide 1 receptor Agonists

The SR retrieved only one 24-week study from Japan that compared metformin and GLP-1RA (liraglutide) monotherapies.[61] This open-labelled, randomized controlled study in 46 overweight/obese Japanese patients with T2D demonstrated no between-group differences for HbA1C reductions (−0.95 ± 0.80% [metformin] vs −0.80 ± 0.88% [liraglutide], $p = 0.77$). However, HbA1C reduction was more rapid in liraglutide group. Further, weight reduction, incidence of hypoglycemia, gastrointestinal side effects and treatment satisfaction were similar between groups.[61] However, further research from Asia is necessary to establish conclusive evidence regarding the non-inferiority of using metformin compared to GLP-1RA in overweight/obese individuals with T2D.

Table 4 Results Comparing Metformin Plus SGLT2i Versus Metformin

Trial (year) N (Randomization) / Duration of Treatment	Patient Population (Including countries and HbA1c Defining Inadequate Glycemic Control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (Weight)	Adverse Events
VERTIS Asia (2019)[40] 506 (1:1:1) / 26 weeks	Asian patients with T2D inadequately controlled on metformin Sub-population analysis (Chinese) HbA1c, 7.0–10.5% [53–91 mmol/mol] inclusive	Ertugliflozin 5 mg + metformin vs 15 mg + metformin vs placebo + metformin	Change from baseline in HbA1c at Week 26 (primary) Change from baseline at Week 26 in: FPG, and the proportion of patients with HbA1c <7% or HbA1c ≤6.5% (Secondary)	Mean reduction from baseline in HbA1c *Overall population/Chinese subpopulation* Ertugliflozin 5 mg: –0.8% and ertugliflozin 15 mg: –0.7% (P < 0.001 for both comparisons with placebo) *Overall population* FPG: Ertugliflozin 5 mg vs placebo: –30.4 Ertugliflozin 15 mg vs placebo: –27.8 (similar reductions for FPG in *Chinese sub-population*) Ertugliflozin 5 mg vs 15 mg vs placebo HbA1c <7.0%: *Overall*: (38.2% vs 40.8% vs.16.2%) HbA1c ≤6.5%: 14.7% vs 17.0% vs 3.0% *Chinese sub-population*: 35.3% vs 42.2% vs.18.5%	Change from baseline at Week 26 in body weight	Overall population: Ertugliflozin 5 mg vs placebo: –1.8 kg; Ertugliflozin 15 mg vs placebo: –2.0 kg (similar weight reductions in *Chinese sub-population*)	59.3%, 56.5% and 53.3% of patients experienced adverse events with placebo, ertugliflozin 5- and 15 mg, respectively. Incidence of symptomatic hypoglycemia for ertugliflozin 15 mg vs placebo (4.7% vs 0.6%, P = 0.019)
Shestakova et al. (2018)[58] 165 (2:1) (Period I: Week 0–12) 159 patients (Period 2: Week 12–24*) Total: 24 weeks	Russian patients (14 centers) with T2D inadequately controlled on metformin HbA1c between 7.5% (58 mmol/mol) and 11.0% (97 mmol/mol)	Ipragliflozin (50 mg/day) + metformin vs placebo + metformin Period II: Uptitration to 100 mg/day ipragliflozin	Change in HbA1c from baseline to the end of Period I. (Primary) Change in FPG, during Period I and II, and the change in HbA1c during Period II (Secondary)	Ipragliflozin vs placebo HbA1c at Week 12: −0.3% (3 mmol/mol), P = 0.048. Period II : An additional 13% of patients achieved HbA1c < 7.0% (53 mmol/mol) at Week 24	Change in body weight, and waist circumference during Period I and II	Ipragliflozin vs placebo Period I: _1.34 kg, P < 0.001 Period II: _0.65 kg, P = 0.004) at Week 24	Incidence of AEs was similar between period I and II: (23.7% and 24.6%. Hypoglycemia (ipragliflozin vs placebo: 11.8% vs 10.9%

(*Continued*)

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Table 4 (Continued).

Trial (year) N (Randomization) / Duration of Treatment	Patient Population (Including countries and HbA1c Defining Inadequate Glycemic Control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (Weight)	Adverse Events
Lu et al (2016)[59] 170 (1:1) / 24 weeks	Taiwanese and Korean patients with T2D inadequately controlled on metformin (18 sites in Korea and 12 sites in Taiwan) HbA1c between 7.0 and 10.0%	50 mg ipragliflozin + metformin vs placebo + metformin.	Change from baseline in HbA1c at Week 24 (primary) Change from baseline at Week 24 in: FPG, and the proportion of patients with HbA1c <7% or <6.5% at each visit (Secondary)	Ipragliflozin + metformin vs placebo + metformin Mean HbA1c change: (−0.94% vs −0.47% Between-group difference: −0.46% (P < 0.001). Greater FPG reductions in ipragliflozin; between-group differences: −14.1 mg/dL (P < 0.001). Increase from baseline to Week 24 in proportion of pts with HbA1c <7.0%: Ipragliflozin group: from 11.5% to 69.4% Placebo group: from 3.6% to 44.6% Increase from baseline to Week 24 in proportion of pts with HbA1c <6.5%: Ipragliflozin group: from 1.1% to 25.9% Placebo group: from 0% to 9.6%	Changes in bodyweight from baseline to the end of treatment	Ipragliflozin vs placebo: −1.24 kg (P < 0.001). At Week 24: 33.3% of pts in ipragliflozin and 18.1% in the placebo group achieved a weight reduction of ≥5%.	Most common treatment-emergent AEs (ipragliflozin vs placebo) were URTI (9.2% vs 12.0%) and urinary tract infection (6.9% vs 2.4%). no episodes of hypoglycemia or genital infection in either group
ILLUMINATE trial (2015)[57] 168 (2:1) / 24 weeks	Japanese patients with T2D inadequately controlled on metformin HbA1c level of 7.4–9.9%	50 mg ipragliflozin + metformin vs placebo + metformin OD 28-week open-label extension with 50 or 100 mg ipragliflozin + metformin.	Change from baseline in HbA1c at Week 24 (primary) and FPG (secondary) HbA1c of <7.0% (secondary)	HbA1c decreased by 0.87% in ipragliflozin and increased in placebo group: statistically significant adjusted mean difference of 1.30% between groups Ipragliflozin vs placebo HbA1c <8.0% at week 24: 86.6% vs 17.9% of pts. HbA1c <7.0%: 21.4% vs 0% of pts FPG decrease from baseline significantly greater in the ipragliflozin vs placebo group	Changes in bodyweight and waist circumference from baseline to Week 24	Significantly greater decrease in body weight (P <0.001) and waist circumference (P=0.001) in the ipragliflozin vs placebo group	Overall incidence of TEAE was similar in both groups Pollakiuria and constipation were more common in the ipragliflozin group Total daily dose of metformin did not influence TEAE

Note: *Open-label ipragliflozin (50 mg/day) in addition to the blinded drug.

Abbreviations: BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting blood glucose; OD, once daily; PPG, post prandial glucose; pts., patients; T2D, type 2 diabetes; TEAE, treatment emergent adverse events.

Results: Comparing Various Metformin Combinations

In real-world practice, patients are often prescribed multiple metformin+ GLDs triple combinations to achieve their glycemic targets.

Metformin +SU+DPP4i vs Metformin Plus SU

Three records reported triple-drug combination of metformin+SU+DPP4i versus metformin+SU dual therapy (Table 5). Of these, two records reported results from the same trial.[62,63] The trials were designed to study DPP4i versus placebo. These trials were not specific to Asia, but also included patients from Asian countries. In the study by Moses et al (2014) 54.3% of study population was Asian and 45.7% were Whites. In the study by Owens et al (2011) 53.6% of patients were Asians and 46.4% were lack or African American, Whites or American Indian / Alaska Natives. Zeng et al (2013) reported results for the Chinese population recruited in the study by Owens et al.

The patients were on a stable maximum tolerated dose of metformin plus a sulphonylurea.[62–64] However, none of the studies capture the SUs being used at baseline. In these T2D patients with inadequate glycemic control on metformin +SU, adding a DPP4i such as saxagliptin or linagliptin is effective in achieving glycemic control, and is safe and well tolerated. Hence, this triple combination could be an alternative to initiating insulin in these patients.[63,64] Reducing the SU dose in the triple combination may help reduce the hypoglycemic events.[62] Since, the trials included Asians and non-Asian population, the results of these trials may be extrapolated globally.

Metformin + DPP4i vs DPP4i+ SU vs DPP4i+ Acarbose

This SR retrieved only one 24-week, multicentre, parallel-controlled 1:1:1 randomized study (SUCCESS Study) that compared three DPP4i (saxagliptin) combinations with metformin vs SU (gliclazide) vs acarbose.[65] However, the SR considered only DPP4i + metformin vs DPP4i +SU as acarbose is not an ADA recommended GLD for glycemic control and/or weight loss.

The study included 648 treatment-naive T2DM Chinese patients (n=216 in each arm), aged 18–80 years, with HbA1c >8.0% and ≤11.0%, and body mass index (BMI) 19–40 kg/m^2. The primary outcome was absolute change in HbA1c from baseline while the proportion of patients achieving HbA1c <7.0% and ≤6.5% were the secondary outcomes.[65]

In 583 patients who completed the trial (24 weeks), the mean (95% confidence interval) change in HbA1c from baseline between DPP4i + SU (−2.8% [−2.9, −2.6]) vs DPP4i + Metformin (−2.9% [−3.1, −2.8]) was not significant (p = 0.18). At 24 weeks, HbA1c <7.0% was achieved by 84.9% and 80.3% of participants in DPP4i + Metformin vs DPP4i + SU (overall P = 0.05); and HbA1c ≤6.5% was achieved by 72.6% and 63.3%, of participants, respectively (overall P = 0.10).[65]

Symptomatic hypoglycemia was rare in both combinations. The study concluded that both DPP4i + metformin and DPP4i +SU were effective and safe as initial GLD combination in treatment-naive T2DM patients with high HbA1c. However, DPP-4i + metformin had superior efficacy as compared to DPP4i +SU.[65]

Metformin+DPP4i+SU versus DPP4i+SU

The SR retrieved only one multicenter (32 centers in China) randomized double-blind placebo-controlled study evaluating DPP4i (sitagliptin) in 498 Chinese patients with T2DM inadequately controlled on SU or SU+metformin.[66] Though the study was primarily designed to evaluate the efficacy and safety of DPP4i/placebo in 1:1 ratio (n=249 in each group) as an add-on therapy to SU±metformin, the study reported the efficacy and safety results by metformin use.

At week 24, the addition of DPP4i (sitagliptin) to SU+metformin showed greater reductions from baseline in HbA1c, FPG and PPG than those on placebo in each metformin stratum (Box 1; P < 0.001). Patients on DPP4i achieved similar least squares mean (LSM) HbA1c change from baseline across each metformin stratum. However, for patients on placebo, the LSM change was higher in patients on metformin compared to patients not on metformin.

Significantly higher number of patients on DPP4i + metformin achieved HbA1c values < 0.7% than placebo+ metformin (27.9% vs 13.4%; P = 0.007). However, more patients on DPP4i reported symptomatic or asymptomatic hypoglycemia than those in the placebo group; but none of the hypoglycemia events needed medical assistance.[66]

Table 5 Results Comparing Metformin +SU+DPP4i Vs Metformin Plus SU

Trial (year) N (randomization) / duration of treatment	Patient population (including countries and HbA1c defining inadequate glycemic control)	Comparators	Glycemic Endpoints	Results (Glycemic)	Weight Endpoints	Results (Weight)	Adverse Events
Moses et al (2014)[64] 257 (1:1) / 24 weeks	T2D with BMI ≤40 kg/m (2) from 35 centers in Australia, Canada, India, Korea, Thailand and the UK Inadequate glycaemic control on metformin+SU (≥50% of the maximum recommended dose) HbA1c, 7.0–10.0% (53–86 mmol/mol)	Saxagliptin 5 mg + metformin ((≥1500 mg IR or XR) + SU vs placebo + metformin + SU	Change in HbA1c from baseline to week 24 (Primary); FPG, PPG and proportion of patients with HbA1c < 7% (secondary)	Triple had higher HbA1c adjusted mean change from baseline Between-group difference (triple [saxagliptin] minus dual [placebo]) of −0.66% [95% CI, –0.86 to −0.47 (7.2 mmol/mol, −9.4 to −5.1); P<0.0001 Significant 2-h PPG change from baseline to week 24: P=0.0301 No statistically significant reduction in FPG at week 24: P=0.0868 Proportion of patients who achieved HbA1c<7% with triple vs dual: 30.7% vs 9.4% (P<0.0001) 6.2% on triple and 5.5% on dual discontinued due to worsening glycemic control (P=0.8022)	Change in weight (secondary)	No clinically significant weight change Mean change in weight at week 24: 0.2 vs −0.6 (P=0.0272)	Low discontinuation rates due to AEs: saxagliptin, 0.8%; placebo, 2.3%; P=0.3701 Proportion of patients reporting ≥1 AE: triple vs dual: 62.8% vs 71.7% Confirmed hypoglycemia: 1.6% vs 0

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Owens et al (2011)[63] 1049 / 24 weeks	T2D patients from 100 centers in 11 countries: Argentina, Belgium, Canada, China, Germany, Korea, the Philippines, Russia, Taiwan, Turkey and the UK Inadequate glycaemic control on metformin ‡ 1500 mg metformin (or the maximum tolerated dose, if lower) +SU (maximum tolerated dose) HbA1c ≥53 mmol/mol (≥7.0%) and ≤86 mmol / mol (≤10.0%) stratified by HbA1c value [< 69 vs ≥69 mmol/ mol (< 8.5 vs ≥ 8.5%)]	Linagliptin+metformin +SU vs placebo + metformin + SU	Change in HbA1c from baseline to week 24 (Primary); FPG, proportion of patients with HbA1c <6.5% or < 7% (secondary)	Triple vs dual HbA1c adjusted mean change: −7 mmol/mol to −6 mmol/mol; P < 0.0001]. More participants with baseline HbA1c ≥ 7.0% achieved an HbA1c <7.0%: 29.2% vs 8.1%, P< 0.0001. FPG reduction higher with triple: P<0.0001	Weight	No significant weight changes	SAE: 2.4% vs.1.5% Symptomatic hypoglycemia: 16.7% vs 10.3% Severe hypoglycemia: 2.7% vs 4.8% of patients experiencing hypoglycemia
Zeng et al (2013)[62] Sub analysis of study by Owens et al (2011)[63] 192 / 24 weeks	Chinese patients with T2D from study by Owens et al (2011) Same as study by Owens et al (2011)	Linagliptin + metformin + SU vs placebo + metformin + SU	Same as study by Owens et al (2011)	Triple vs dual Placebo corrected mean HbA1c change: −0.68% (P<0.0001) Placebo corrected mean FPG change: −18.8 (P=0.0044)	Weight	No significant weight changes	Drug-related AEs: 12.5% vs 2.1% Hypoglycemia: 10.4% vs 0

Abbreviations: AEs, adverse events; AUC: area under the curve; bid, twice daily; BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting blood glucose; OD, once daily;PPG, post prandial glucose; pts., patients; SE, standard error; SPC, single-pill combinations; T2D, type 2 diabetes; URTI, upper respiratory tract infection.

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DPP4i + Insulin + Metformin vs DPP4i + Insulin

Another study too evaluated the same DPP4i (sitagliptin) as add-on therapy in 467 Chinese patients with inadequate glycemic control on stable dose of insulin± metformin and reported the results by metformin use (Box 2).[67] During the study, insulin dose was modified to meet the glycemic targets or to avoid hypoglycemia.

After 24 weeks, there was a significant reduction in HbA1c and PPG in the DPP4i group; and the HbA1c reductions were similar for patients on metformin and those not on metformin. The LSM difference in FPG was appreciable but not significant both in patients on metformin and those not on metformin.[67]

Though a significantly higher number of patients on DPP4i achieved HbA1c <7.0% at 24 weeks compared to placebo, the results were not reported by metformin use (16% vs 8%; P = 0.013).[67]

Discussion

This is probably the first SR from Asia demonstrating the efficacy of metformin in various combinations in Asian patients with T2D. Since T2D is characterized by insulin resistance with a decline in pancreatic insulin secretion, drugs that improve insulin sensitivity (metformin) and insulin secretagogues (SU) are widely used to treat T2D along with lifestyle modification.

The SR did not retrieve any record comparing metformin against placebo or against lifestyle modification. Metformin is an old drug and therefore randomized trials comparing metformin against placebo/LSM would have been conducted during the initial drug trajectory. However, metformin and lifestyle modification are independently beneficial in the Asian population in reducing the risk of prediabetes converting to diabetes.[68]

One trial[24] showed that metformin XR had a similar efficacy and safety profile as metformin IR. In line with this finding, a large study in 3556 patients with T2D from six Asian countries (Hong Kong, Indonesia, Malaysia, the Philippines, Singapore, and South Korea) demonstrated that metformin XR was well tolerated, provided adequate glycemic control and had few gastrointestinal side effects with good adherence in Asian population.[69]

Metformin+sulphonylurea is the most popular combination used in Asia in patients who failed on metformin monotherapy.[11,34,35] Despite known efficacy and safety of this combination,[41] the SR failed to retrieve any study comparing metformin + sulphonylurea with either sulphonylurea or metformin monotherapy that was conducted in Asia.

Box 2 HbA1c, FPG and PPG Reductions from Baseline in Patients on metformin+DPP4i+insulin vs Those Not on Metformin (Taking Placebo+insulin)

	All Sub-Group of Patients on Metformin*+Insulin				**Patients not on Metformin (Only on Insulin)**			
	LSM change from baseline (95% CI)				LSM change from baseline (95% CI)			
Efficacy parameter	DPP4i (Sitagliptin 100 mg QD)	Placebo	LSM difference (95% CI)	P value	DPP4i (Sitagliptin 100 mg QD)	Placebo	LSM difference (95% CI)	P value
HbA1c (%)	−0.7 (−0.9, −0.6)	−0.3 (−0.5, −0.2)	−0.4 (−0.6, −0.1	P < 0.01	−0.6 (−0.8, −0.4)	−0.3 (−0.5, 0.2)	−0.3 (−0.5, −0.1)	P < 0.05
FPG (mg/dL)	−13.0 (−21.4, −4.6)	−9.1 (−17.4, −0.7)	−3.9 (−15.4, 7.5	Not significant	−16.4 (−25.8, −7.0)	−13.5 (−22.9, −4.1)	−2.9 (−14.5, 8.7)	Not significant
2-hour PPG (mg/dL)	−49.8 (−62.5, −37.1)	−21.5 (−34.2, −8.9)	−28.2 (−45.5, −11.0)	P ≤ 0.001	−46.6 (−60.0, −33.2)	−22.1 (−35.4, −8.8)	−24.4 (−40.9, −8.0)	P < 0.01

Notes: Data from Shankar et al.[67] *Patients were on different metformin doses, but doses were kept constant throughout the study.
Abbreviations: CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitors; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; LSM, least square mean; PPG, post-prandial glucose.

This SR showed that DPP4i was the most common add-on therapy with metformin investigated compared to metformin or DPP4i. DPP4i was also investigated as an add-on therapy to metformin+ sulphonylurea and metformin +insulin. DPP4is and metformin are the most frequently prescribed first-line drugs for T2D patients in Japan.[70] Metformin use in patients receiving first-line DPP4i is suggested to have the ability to reduce the risk of death.[70]

In Asia, patients with inadequate glycemic control on metformin+ sulphonylurea are often co-prescribed a DPP4i as a triple regimen.[71] Evidence from SR/MAs showed that DPP4is have better glucose lowering effect in Asians than in non-Asians (higher HbA1c reduction by −0.26% (95% CI: −0.36% to −0.17%, P<0.001) but produced similar weight changes in both populations.[72]

Ba et al (2017) compared DPP4i (sitagliptin) +sulphonylurea±metformin vs placebo+ sulphonylurea±metformin and noted that the results of the study were consistent with that of sitagliptin monotherapy[73] or combination therapy with metformin[49] in Chinese patients. In these patients, sustained glycemic control was also dependent on the dose metformin and sulphonylurea.[71] Incidence of hypoglycemia was more in patients on sulphonylurea, than those on metformin. Hypoglycemia seen with use of triple therapy (DPP4i+sulphonylurea+metformin) can be managed by reducing the dose of sulphonylurea.[62]

Metformin +DPP4i has been found to be effective in significantly reducing HbA1c, FPG and PPG (P < 0.0001 for all) in Indian patients with T2D.[74] Patients on early combination therapy (DPP4i) with metformin (VERIFY study from Korea) consistently achieve lower HbA1c levels over 5-years.[29] DPP4i+metformin was weight neutral in Asian patients, an important finding given that T2D occurs at a lower BMI in Asians.[2–5] Further, DPP-4i+metformin is also associated with a lower risk of severe hypoglycemia, cardiovascular events, and all-cause mortality compared with metformin +sulphonylurea.[25]

Evidence shows that SGLT2i produces similar glycemic control and weight reductions in Asians and non-Asians (p>0.05 for both).[75] The use of a SGLT2i (ipragliflozin) or metformin in combination with DPP4i is widely used in Japan and may have beneficial effects in reducing multiple cardiovascular risk factors.[76] Further, the dose of SGLT2i may be uptitrated in a combination therapy to achieve the desired glycemic goal with no additional safety/tolerability concerns, except hypoglycemia which is usually managed well with proper dose adjustment.[40,58] However, there were no SGLT2i and DPP4i combination trials retrieved from this region.

Only one study in this SR compared metformin+oral GLD versus insulin glargine.[60] The study showed that though HbA1c reductions were significant in both the groups, they were similar in metformin + oral GLD and insulin groups (11.7% to 6.2%; P < 0.001 vs 11.8% to 6.5%; P < 0.001). Evidence consistently shows that insulin use in Asians is associated with a lower HbA1c reduction than in Caucasians/non-Asians, and less likely to achieve HbA1c<7%.[77,78] However, Asians had lower weight gain than non-Asians. Hence, the authors concluded that metformin-based oral GLDs should be preferred over insulin in newly diagnosed T2D patients with severe hyperglycemia as they are cost-effective and convenient (oral).[60]

Metformin is often combined with a GLP-1RA in overweight/obese individuals with T2D. The only trial in this SR comparing GLP-1RA with metformin reported similar reduction in weight, and incidence of hypoglycemia, gastrointestinal side effects and treatment satisfaction between groups.[61] Evidence from a SR/MA showed that GLP-1RA produced greater reductions in HbA1c in Asians than non-Asians, but similar weight reductions in the two populations.[79] A 52 week study comparing metformin+ GLP-1RA vs metformin+ oral GLD too reported similar reduction in weight, and incidence of hypoglycemia and other AEs between the two groups.[80] Hence, overweight/obese Asian patients with T2D may preferably be managed with metformin over a GLP-1RA since it is much cheaper than a GLP-1RA, has the convenience of oral dosing.

Literature shows that metformin treatment is associated with gastrointestinal adverse events (AEs) in ≤30% of patients, and though transient, associated with treatment discontinuation in ≤5% of patients.[24,81] This SR showed that metformin monotherapy and combination therapy were associated with minimal gastrointestinal AEs. However, none of the AEs were serious enough to require treatment discontinuations. Also, gastrointestinal AEs were adequately managed without treatment. This may be possible by titrating the metformin dose over several weeks and concurrently administrating metformin with food.[24]

Strength and Limitations

To the best of our knowledge, this is the first systematic review assessing metformin monotherapy and combination therapies in Asian patients with T2D. The systemic search could not retrieve any RCT comparing metformin plus thiazolidinedione versus metformin or versus thiazolidinedione or versus metformin+another GLD. We do note that thiazolidinediones are one of the recommended GLDs for the management of T2D by the ADA and Asian guidelines.[21,31] However, lack of thiazolidinedione RCTs in Asian patients have been reported by other SR/MAs as well.[82] However, there is not enough evidence of long-term safety of thiazolidinediones in Asians and there have been concerns regarding increasing risk of heart failure.[82,83] Moreover, currently, metformin plus thiazolidinedione is not commonly used in T2D, both globally and in Asians.[10,83]

The SR could not include observational, real-world, retrospective and cohort studies in the analysis due to appreciable differences in their design and outcomes. However, data from these studies was used to build up the discussion session. Also, T2D patients with comorbidities, paediatric patients, and women with gestational diabetes mellitus were excluded from the SR.

Research Gaps

There were many trials which compared GLDs as add-ons to metformin, but reported the outcomes for GLD monotherapies or GLD combinations with metformin. These trials did not compare the effect of add -on therapy with metformin therapy (there was no placebo+ metformin group) nor reported results stratified by metformin dose. Some examples of these trials include DIVERSITY-CVR/Japan,[84] RCT ipragliflozin as an add-on therapy to sitagliptin and metformin/Korea,[85] the TROICA study,[86] and the SUPER study (results were not affected by metformin use).[87] RCTs from several Asian countries such as India, Pakistan, Afghanistan, Bhutan, Nepal, Sri Lanka, Myanmar, etc were largely lacking. Also, some important trials from these countries such as the Xrise Study,[88] multicenter START study from India (SU+metformin vs DPP4i+ metformin),[89] and the EVOLUTION INDIA study (evogliptin versus sitagliptin as an add-on therapy to metformin)[90] did not meet the inclusion criteria because the results were not stratified by metformin use.

Further, there were no randomized trials comparing metformin monotherapy/combination therapy versus diet/exercise, metformin monotherapy versus SU, DPP4i, SGLT2i, or insulin monotherapies; metformin + insulin versus insulin, and metformin + GLP-1RA versus GLP-1RA.

Since, physicians in real-world scenario treat T2D patients with multiple comorbidities, there is need to identify and report literature in this patient population from Asia. Further, since T2D starts early in Asia, literature focused on T2D prevention, literature on management of T2D in paediatric and adolescent population should be prioritized and published.

Conclusion

Metformin is an old oral cheap GLD that produces glycemic and weight control. The drug is effective and safe for long-term control of T2D in Asians. Metformin monotherapy may be initiated and continued in treatment naïve Asian patients with T2D and/or obesity if the monotherapy is adequate for achieving glycemic control. Sulphonylurea, DPP4i, SGLT2i, insulin and GLP-1RA may be added for better glycemic control for those who fail on monotherapy. Patients inadequately controlled on first-line DPP4i or another GLD can achieve glycemic control and target HbA1c of <7% by adding metformin in a once daily dose. The use of metformin reduces the risk of hypoglycemia, and its gastrointestinal side effects are mild and manageable in Asians.

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