# The Ability of Combination Sulfonylurea and Metformin in Reducing Morbidity and Mortality in Type 2 Diabetes

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## Abstract

### Background Literature
*Type 2 diabetes is a health concern worldwide, and treatment with oral antidiabetic medicines presents a clinical challenge. This systematic review aims to assess the ability of combination sulfonylurea and metformin in reducing morbidity and mortality in type 2 diabetes.*

### Methods
*A search of the databases NU Search, PubMed, Ovid, Embase, CINAHL and Medline was conducted by the author, using key search terms.*
*11 studies were included, 6 RCT's, and 5 cohort studies with a combined number of 168,138 participants.*

### Results
*Cardiovascular risk: Atherosclerotic Cardiovascular Disease (ASCVD) risk score DPP4i and metformin: -1.5 versus -1.1 for SU and metformin. Six studies found no difference for MI, CVD, stroke across groups for SU, DPP4i, or SGLT2i. DPP4i combination was superior, with better protective effects than SU combined for, Heart failure (HF) HR 0.86 DPP4i versus 1.0 SU, Cerebrovascular disease HR 0.72 versus 1.0 Myocardial Infarction (MI), DPP4i= 340, HR 1.0, versus SU =402, HR 0.84. HbA1c reductions across groups: SU -1.59, DPP4i -2.43 versus -2.91 with SGLT2i. More rapid reduction with SU and metformin versus SGLT2i and DPP4i from 0- week 18. Weight changes across groups: weight gain with SU 5.72kg, versus – 4.27kg for DPP4i and – 20.7kg for SGLT2i.*

### Conclusion
*Cardiovascular risk was inconclusive. SU's were shown to be associated with a rapid reduction of HbA1c and weight gain. More robust research is needed to examine further combination oral antidiabetic treatments and cardiovascular risk, as a high level of heterogeneity ($I^2$) and bias between the studies existed.*

## 1. Introduction

The World Health Organisation (WHO) (2022) estimated that between 1980 to 2014, the prevalence of diabetes increased from 108 million to 422 million worldwide. Diabetes takes many different forms, such as type 1, type 2, gestational, type 3, Maturity Onset Diabetes of the Young (MODY), and Latent Autoimmune Diabetes in Adults (LADA) (Diabetes UK, 2019). Type 2 diabetes accounts for around 85% of the diabetic population, making it the most prevalent type [1]. During normal physiological conditions, blood glucose level is maintained and regulated by the islets of Langerhans located in the pancreas; insulin is secreted in response to elevated glycaemic levels and facilitates the transfer of glucose into muscle and fat cells for energy utilisation [1].

Under abnormal conditions in type 2 diabetes, however, the pancreas fails to produce sufficient insulin, or the insulin produced is deficient. This progressive autoimmune disease is linked to genetic causes, obesity and/or poor diet [2]. Metformin, a common treatment for type 2 diabetes, is part of the biguanide class of medicines and functions in reducing hepatic glucose output by suppressing gluconeogenesis. In contrast, sulfonylureas act by stimulating the pancreatic beta cells to increase the amount of

insulin released and efficiency [3]. Here, the authors examined if combinatorial Sulfonylurea and Metformin therapy had the ability to reduce morbidity and mortality in Type 2 Diabetes.

## 2. Methodology
A comprehensive search of the databases NU Search, PubMed, Ovid, Embase, CINAHL and Medline was undertaken to identify studies for inclusion. The inclusion criteria were patients with type 2 diabetes, aged >18, taking metformin and/or sulfonylureas, assessing the safety and efficacy of combination therapy. The exclusion criteria were participants with other types of diabetes, patients aged <18, and patients taking insulin or other subcutaneous injection anti-diabetes medications. The following key search terms were entered into the selected online databases: type 2 diabetes + oral + metformin + sulfonylurea + adults + morbidity + mortality.

The search returned a total of 1057 studies. After reviewing each study manually, and assessing against inclusion and exclusion criteria, 1045 studies were excluded. A total of 11 studies met the inclusion criteria and were included in this review. A Critical Appraisal Skills Programme (CASP, 2020) was utilised for data extraction and assess the risk of bias. Each study was read, synthesized and the main outcomes described.

## 3. Results and Discussion
### 3.1 Theme one - Cardiovascular risk
Cardiovascular risk and diabetes have a well-documented association, and Diabetes UK (2019) states that the risk is increased by 2 and a half times for stroke or heart attack, which highlights the importance of reducing the risk. Ten of the eleven studies by Gillani et al. (2022), Wang, Wua, and Chiena, (2021), Douros et al. (2018), Chang et al. (2015), Leiter et al. (2015), Nauck et al. (2014), Del Prato et al. (2014), Hassan and Abd-Allah (2015), Pantalone et al. (2012), and Nauck et al. (2011) reported cardiovascular risk/mortality for 166,767 participants [4 -13]

### 3.2 Dpp4i Versus Sulfonylurea and Metformin
Of the ten studies, two of the studies by Gillani et al. (2022) and Wang et al. (2021) revealed that combination metformin and DPP4i versus SU and metformin, concurred that DPP4i combination had better cardioprotective effects [4,5]. Assessed Atherosclerotic Cardiovascular Disease (ASCVD) risk and identified a significant mean reduction -1.1 % from baseline for sulfonylureas plus metformin combined, and DPP4i and metformin – 1.56%. SU and DPP4i were both found to reduce ASCVD risk score, however DPP4i's were superior. The study also found gliclazide exhibited an enhanced cardiovascular profile to glimepiride. The results of Wang et al. (2021) found that DPP4i combination was superior, with better protective effects than SU combined for, Heart failure (HF) HR 0.86 DPP4i versus 1.0 SU, Cerebrovascular disease HR 0.72 versus 1.0 Myocardial Infarction (MI), DPP4i= 340, HR 1.0, versus SU =402, HR 0.84 [5].

### 3.4 Metformin and Sulfonylurea Combinations
Of the ten studies, two by Hassan and Abd-Allah (2015) and Pantalone et al [11,12]. Assessed different combinations of SU and metformin. Assessed lipid profiles, and found Low density lipoprotein (LDL) improved from baseline, but suggested greater reduction of cardiovascular risk with glimepiride and metformin 142+7, versus gliclazide and metformin 146+7. Pantalone et al. (2012) found no significant difference in mortality across groups with metformin plus, glimepiride, versus metformin and glipizide HR 1.03, or metformin plus glimepiride HR 1.03 or glipizide and metformin versus metformin plus glibenclamide, HR 1.05. there were 636 deaths in the cohort [12].

### 3.5 Sulfonylurea and Metformin Versus SGLT2i
Leiter et al. (2015) assessed high density lipoprotein (HDL) and was found to be reduced in patients that received metformin and sulfonylurea combination 0.06 versus SGLT2i 0.38, however this was not statistically significant. Nauck et al. (2011), also reported results concomitant with Leiter et al. (2015) that HDL was increased in the SGLT2i group and reduced in the SU group. The 156-week extension study Nauck et al. (2014) did not report outcomes HDL. The extension study by Nauck et al. (2014) reported the additional cardiac outcomes, coronary artery occlusion (CAO) and aortic aneurysm (AA) but no differences were identified across groups [8,13]

### 3.6 Sulfonylurea and Metformin Vs Glinides and A- Glucosidase
Chang et al. (2015) identified that the metformin and glinides, N=9 or alpha glucosidase inhibitor N=13, Versus N=323 in SU and metformin group. significantly reduced the risk of MI, but showed no variance in risk of stroke or HF.

### 3.7 Sulfonylureas and Metformin Versus Sglt2i, Dpp4i And Su Combinations
Six of the ten studies by Douros (2018), Chang et al. (2015), Del Prato et al. (2014), Nauck et al. (2014), Pantalone et al. (2012) and Nauck et al. (2011) found no substantial difference between the study groups for cardiovascular risk of different events, including cardiovascular death, MI, CVD, stroke and heart failure, between combination SU with metformin, versus SGLT2i, DPP4i, and SU combinations. Though it would be important to note Nauck et al. (2011) suggested that persistent reduction in systolic blood pressure and weight with SGLT2i may exert a favourable effect on cardiovascular risk, but not a significant finding [6,7,9, 10,12,13].

After reviewing the results from all ten studies assessing cardiovascular risk and mortality, the studies confirm that combination metformin and sulfonylurea reduced cardiovascular risk to a degree, and some SU's might be associated with a further reduced risk than others. However, the evidence is not strong enough to form a sound conclusion on the different types of SU. When comparing the performance of metformin and sulfonylureas to other anti-diabetic medicines, the results were inconclusive. Six out of ten, did not show a meaningful reduction of cardiovascular risk. More robust research is needed to further investigate this

points out that SGLT2i combination with metformin may provide beneficial cardioprotective effects, which is supported by the current guidance by the National Institute for health and Care Excellence (2015) which advocates the use of SGLT2i for patients with cardiovascular risk or existing cardiac disease, rather than SU which is in keeping with the findings from the studies included in this review [4,5,11]. conducted their studies in settings that were vastly different, Malaysia, Egypt and Taiwan which limits the generalisations that can be made from this research. Two of the studies by Gillani et al. (2022) and Wang et.al. (2021) indicated enhanced cardioprotective effects of DPP4i in comparison to SU, however both had risk of bias. Gillani et al. (2022) may have introduced selection bias, as participants self-referred or were recommended by study sites [2,5]. Wang et al. (2021) had a large sample size which increases the validity. However, the retrospective cohort study design, reduces the strength of the results [5]. Additionally, the information was taken from an insurance database where there was potential for data to be missing. In the initial study by Nauck et al. (2011) HDL was reported as increased with the SGLT2i group and reduced in the SU groups [13]. The extension study Nauck et al. (2014), did not report outcomes for HDL, this could indicate reporting bias [14].

## 4. Theme Two - HbA1c Reduction
The second theme emerging from the results was HbA1C levels. Chen et al. (2015) explained that macrovascular complications in diabetes are associated with poor control of HbA1c and is linked to the pathophysiology of vascular damage.
Eight of the eleven studies by Gillani et al. (2022), Muskiet et al. (2020), Hollander et al. (2017) Hassan and Abd-Allah (2015), Leiter et al. (2015), Del Prato et al. (2014), Nauck et al. (2014) Nauck et al. (2011) assessed outcome for HbA1c levels in 8925 participants.

## 5. Sulfonylurea and Metformin Versus Dpp4i and Metformin
Two of the eight studies by Gillani et al. (2022) and Del Prato et al. (2014) found whilst HbA1c was improved with SU's and metformin 7.93 +1.69, there was a greater improvement with DPP4i 7.86 + 1.92 at end point [2,10]. Gillani et al. (2022) and Del Prato et al. (2014) found that HBA1c was reduced with SU's but noted a greater reduction with DPP4i and metformin over 24 and 104 weeks. 6.73 -2.65 metformin and SU, versus 6.22- 2.07 with metformin and DPP4i, a 0.72% mean change for DDP4i, versus 0.59%, for metformin and SU respectively.
One of the eight studies by Muskiet et al. (2020) found similar reductions for DPP4i linagliptin and SU glimepiride across both groups - 0.10% and -0.09% respectively from baseline to endpoint assessment after 8 weeks.

## 6. Sulfonylurea and Metformin Versus Sglt2i and Metformin
Four of the Eight studies Hollander et al. (2017), Leiter et al. (2015) Nauck et al and Nauck et al. (2011), assessed SGLT2i's. Two of which, by Hollander et al. (2017) and Leiter et al. (2015) concurred that there was a sharp fall in HbA1c with SU at 6 -18 weeks. Both SGLT2i's, ertugliflozin and canagliflozin,

demonstrated an advantage in results over SU's. Hollander et al. (2017) showed a reduction of -1.2 for ertugliflozin and metformin, versus -0.7 glimepiride and metformin. The results for Leiter et al. (2015) showed a reduction of -1.39 SGLT2i and metformin, versus metformin and SU -0.55. Both trials established non-inferiority between SGLT2i and SU [14,8].

Nauck et al. (2011) and Nauck et al. (2014) assessed SU versus SGLT2i, and found that glipizide had an earlier reduction in HbA1c in from baseline to week 18. At week 52, Nauck et al. (2011) found no difference between the groups. SU -0.52%, and SGLT2i -0.52%. However, at 104 weeks dapagliflozin showed a greater and sustained reduction in HbA1c, with a reduction of -0.32 for metformin and SGLT2i, and -0.14 for SU and metformin [13,9].

## 7. Different Combinations of Sulfonylurea with Metformin
Hassan and Abd-Allah (2015) compared different combinations of SU with metformin and found that glimepiride performed superior to gliclazide at 3months in reducing HbA1c. The results were Glimepiride and metformin 7±0.1, compared to 7.1±0 for Gliclazide and metformin [11].

The results here indicated a consensus towards sulfonylureas being effective in reducing HbA1c. All eight recorded a significant reduction from baseline.
A combined loss of -1.59 for SU and metformin, versus DPP4i and metformin -2.43 versus -2.91 for SGLT2i and metformin. However, four of the eight studies and the extension study by Nauck et al. (2011) found that HbA1c had a more rapid reduction in the early stages of the studies with SU and metformin. However, SGLT2i's had a longer sustained lowering than SU at endpoint. Chen and Li (2019) also supported this finding in their systematic review, as SGLT2i's were shown to be more effective over longer periods of time than SU's and have similar effects in the short term [8,9,13-15].

Similar to SGLT2i, DPP4i also demonstrated better efficacy long term in comparison to SU. A review conducted by Deacon and Lebovitz (2016), also supports this finding. Current guidance from National Institute for Health and Care Excellence (NICE) (2022) recommends the use of SU's as rescue therapy, and advise to review the treatment, once glucose levels are under control. This correlates with its ability to rapidly reduce HbA1c in the studies above. The evidence confirms the efficacy of sulfonylurea in reducing HbA1c but suggest DPP4i and SGLT2i are an effective alternative treatment to SU [16]. Although eight of the 11 studies agreed that SU's reduce HbA1c, there were some limitations in their design. Of the eight, seven studies Muskiet et al. (2020), Hollander et al. (2017) Hassan and Abd-Allah (2015, Leiter et al. (2015), Del Prato et al. (2014), Nauck et al. (2014) and Nauck et al. (2011) used a randomised control trial design (RCT). One study by Gillani et al. (2022) used a cohort study design. Using a Robust RCT design, enhances the validity of the results by providing a rigorous tool to test relationships between intervention, the design reduces the play

of external factors influencing the outcome [4,9,11,10,13,14,18].

Muskiet et al. (2020) and Hassan and Abd-Allah (2015) used small sample sizes N=46 and N=180 respectively. Both studies also used short study periods, Muskiet et al. (2020) only eight weeks, and Abd-Allah (2015) assessed outcome at 3 months. Additionally, the sample only included males, meaning that the sample was not representative, which limits the generalisations that can be made from the results. Larger sample sizes and longer study periods could have been utilised to increase the validity and reliability [11,17]. The study by Gillani et al. (2022) may have introduced bias, as there was no mention of dosage of each medication used. Potentially, the interventions may have been different which could have introduced performance bias. Additionally, confounders may have had a role to play, as compliance with trial medication may have affected the results [4].

## 8. Theme Three – Changes in Body Weight
Of the eleven studies, seven by Gillani et al. (2022), Muskiet et al. (2020), Hollander et al [4,14,17]. Assessed body mass/weight in 8,745 participants. All established that SU and metformin combination was associated with weight gain [8,9,10,13].

## 9. Metformin and Su Combination
All seven studies established that SU and metformin combination was associated with weight gain. Gillani et al. (2022) found an increase of + 0.87kg, Muskiet et al. (2020) +0.8 increase with glimepiride, Hollander et al. (2017) + 0.9kg with glipizide, Leiter et al. (2015) + 0.8kg with glimepiride, Del Prato et al. (2014) + 0.95 kg for glipizide, Nauck et al. (2014) and Nauck et al. (2011) found a 1.4kg increase glipizide. A combined weight gain of 5.72kg for SU and metformin [4,8,13,17].

## 10. Metformin and DPP4i
Of the seven studies, three compared SU and metformin to DPP4i. All 3 studies concurred that DPP4i was linked to weight loss. Gillani et al. (2022) found a -2.2kg weight loss with DPP4i, Muskiet et al. (2020) a 0.5kg weight loss with Linagliptin and Del Prato et al. (2014) -0.68 and -0.89 loss with Alogliptin. A combined weight loss of -4.27kg for DPP4i [4,17].

## 10.1 Metformin and SGLT2i
Four of the seven studies measuring weight/body mass, assessed the performance of SU's and metformin against SGLT2i. Hollander et al. (2017) found in the two ertugliflozin groups, a loss of - 3.4kg and -3.0kg. Leiter et al. (2015) found a loss of 3.6kg and 3.6kg in both canagliflozin groups. Nauck et al. (2014) and Nauck et al. (2011) demonstrated a -3.4kg and -3.7kg at the end of the studies [14,8,9,13].

A combined loss of -20.7kg. Here, all seven studies agreed that SU's

are associated with weight gain, with a combined weight gain of over 5.72kg. In contrast, SGLT2i' and DPP4i's showed significant weight reduction versus SU, -20.7kg and 4.27kg respectively. Overall SGLT2i's provided a greater weight reduction than DPP4i's. The findings are parallel to those of a systematic review and meta-analysis by Storgaard et al. (2016). They concluded that SGLT2i's had a greater weight loss when compared to DPP4i and Sulfonylurea. In their study, sulfonylurea was also shown to cause increased weight gain. Storgaard et al. (2016) suggests SGLT2's is a safe and effective alternative to SU's, and that the reduction in body weight, lipid profiles and systolic blood pressure identified from the findings, may have a positive impact on the reduction of cardiovascular risk [18].

Gillani et al. (2022), included only newly diabetic patients, this means patients with more advanced disease were excluded [4]. This limits the generalisations that could be made from the results and indicates potential selection bias. Including patients with different stages of the disease would have increased the representativeness of the sample. Hollander et al. (2017) and Del Prato et al. (2014) performed a power calculation, which was met, thus adding validity to the study. In contrast, Leiter et al. (2015) did not. A power calculation would ensure enough participants were enrolled to see a true effect [14,10,8].

Seven of the studies by Gillani et al. (2022), Muskiet et al. (2020), Hollander et al. (2017), Leiter et al. (2015), Del Prato et al. (2014), Nauck et al. (2014) and Nauck et al. (2011) did not monitor the participants calorie intake or diet which could have impacted the outcomes [4,17,14,8,10,9,13]. Nauck et al. (2014) Nauck et al. (2011) conducted the studies internationally, including 16 UK centres, making the results more applicable and increases generalisability [9,19].

## 11. Conclusion
Whilst metformin and sulfonylureas remain an effective second line treatment option for type 2 diabetes by reducing HbA1c levels. The review emphasized that SU's are associated with weight gain, and cardiovascular risk remains unclear. SGLT2i's are concomitant with a reduction in body weight, with a more sustained lowering of HbA1c over time and blood pressure lowering. SGLT2i's are a safe and effective alternative to SU as they may provide cardiovascular protection. An individualised holistic assessment of patients should be carried out to determine the cardiovascular risk, and regular reviews of antidiabetic medication should be carried out to ensure they are updated to suit the patient's needs. More robust research is needed to further examine combination oral antidiabetic treatments and cardiovascular risk, as there was a high level of heterogeneity (I2) and bias between the studies [20-30].
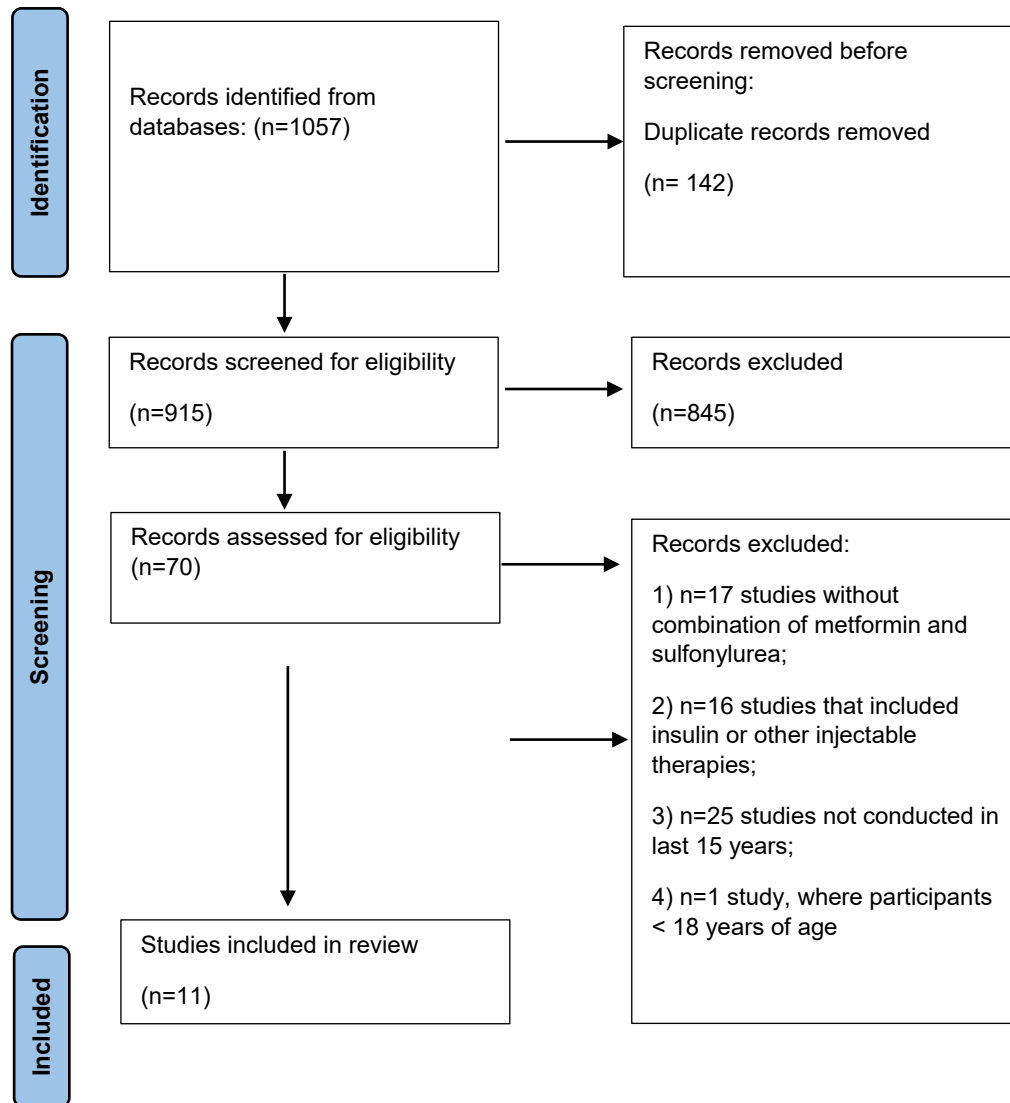
**Figure 1:** Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. 2021.

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

## Table 1: Characteristics of included studies

| Study Number | Author/ Year | Study Design | Participants/ Location/ sample age range | Intervention | Clinical Outcomes | Results |
|---|---|---|---|---|---|---|
| 1 | Gillani et.al, 2022 | Prospective multicentre, observational cohort study. | -N= 1657 -New diagnosis T2DM less than 5 years. -age > 18 years - No other serious comorbidities -5 different primary or tertiary healthcare centres Penang, Malaysia. - Above 6 mmol and Hb1Ac above 6% | Over 24 months (2 years) 3monthly f/u centres monitored by research team. Baseline Measures: lipid profile, renal function, risk ASCVD, glucose profile, BMI, BP then 3monthly N=513 G1 metformin, N=217, G2 metformin + glimepiride N=231, G3 metformin + gliclazide N=384, G4 metformin +sitagliptin N= 312, G5 metformin+ saxagliptin DPP4i or SU | Increased body weight: metformin + gliclazide =0.87 increase, metformin + saxagliptin = 2.2 decrease. ASCVD: differences from baseline to end of trial significant mean reduction -1.1% 95% CI: -1.69 to 0.89, p = 0.041 ASCVD risk for Su's combined. Significant mean reduction -1.56% 95% CI: -2.18 to 1.02 risk score for DPP4i combined. -Hospitalisation: significantly higher frequency of hospitalization from -Hba1c SU+ met =6.732.65, DPP4i+ met =6.222.07 -Hyperglycaemia metformin alone 78.16% and 30.8% SU 70.1% and 28.3%, and DPP-4 56.6% + 20.4% Hypoglycaemia SU + metformin 294 (65.6) Vs DPP4i + metformin 259 (37.2) HBA1c 6.73 – 2.65 SU+met 6.22 -2.07DPP4i +met | Increased body weight: metformin + gliclazide =0.87 increase, metformin + saxagliptin = 2.2 decrease. ASCVD: differences from baseline to end of trial significant mean reduction -1.1% 95% CI: -1.69 to 0.89, p = 0.041 ASCVD risk for Su's combined. Significant mean reduction -1.56% 95% CI: -2.18 to 1.02 risk score for DPP4i combined. -Hospitalisation: significantly higher frequency of hospitalization from -Hba1c SU+ met =6.732.65, DPP4i+ met =6.222.07 -Hyperglycaemia metformin alone 78.16% and 30.8% SU 70.1% and 28.3%, and DPP-4 56.6% + 20.4% Hypoglycaemia SU + metformin 294 (65.6) Vs DPP4i + metformin 259 (37.2) HBA1c 6.73 – 2.65 SU+met 6.22 -2.07DPP4i +met |
| 2 | Wanga, Wua and Chiena, (2021) | Cohort study | N=68,591 aged >20 years Taiwanese Insurance health data | Compared DPP4i vs SU for Major Adverse Cardiovascular Events (MACEs) From health claims on a national insurance database - Patients who received metformin + DPP4i and metformin + SU. 2yr 3month period | -Primary outcome: hospitalisation for MACE's -Secondary outcome: hospitalisation for, MI, CVA, HF & hospitalisation for hypoglycaemia. Comparison of SU &, DPP4i: DPP4i Significantly reduced hospitalisation risk for MACE Hazard ratio (HR) adjusted IRR 0.80 0.770.83 (HF) HR 0.86 DPP4i, versus 1.0 SU. Cerebrovascular disease HR 0.72 versus 1.0 Myocardial Infarction (MI), DPP4i= 340, HR 1.0, versus SU =402, HR 0.84. hypoglycaemia HR 0.46 0.41-0.52 Large reduction risk of hospitalisation for MACE Sitagliptin = 0.89 0.850.94 vildagliptin =0.77 0.60-0.99. saxagliptin borderline meaningful higher risk of HF | DPP4i more effective protective results than Sulfonylurea for MACE, HF, acute MI, CVD, and hypoglycaemia. DPP4i shows cardioprotective effects with +/-hx of CVD. Sitagliptin +vildagliptin superior cardioprotective effect. saxagliptin may increase risk of HF. Compared SU, all 3 DPP4i's lowered the risk of hypoglycaemia in patients T2DM |
| 3 | Muskiet, et.al, 2020 RENALIS | Double-blind RCT | DPP-4i Linagliptin vs sulfonylurea on renal functioning in T2DM patients already on metformin -46 overweight T2DM Caucasian, women and men aged 35 to 75 years, on metformin alone HbA1c 6.5–9.0, BMI >25kg | Linagliptin 5mg vs glimepiride 1mg for 8 weeks. (GFR) effective renal plasma flow (ERPF) determined by Fractional excretions, urinary damage markers, inulin, -and paraMino hippuric acid clearance, glucagon-like peptide 1SC derived factor-1α and DPP4i substrata | GFR=Linagliptin- no effect from baseline ERPF= Linagliptin- no effect from baseline - HBA1c= reductions similar: Glimepiride –0.65 6 0.10%. -Linagliptin mean 6 SEM – 0.45 6 0.09% -BMI: glimepiride vs linagliptin caused increased body weight +0.8 kg, -0.5kg for DPP4i. BP & HR - No changes noted for heart rate and BP -Fractional excretion of sodium was increased with linagliptin Hypoglycaemia: Linagliptin 4% vs 25% Glimepiride | Renal function not affected by linagliptin. Linagliptin increased vs glimepiride patients. -DPP-4 inhibition promotes Na excretion -SU associated with increased weight gain and more hypoglycaemic events |

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|---|---|---|---|---|---|---|
| 4 | Douros et. al, 2018 | Cohort study | N=47,184 Patients T2DM started on metformin alone between 1998 - 2013. UK CPRD database | Does adding or switching to SU increases risk severe hypoglycaemia ischaemic stroke, MI, cardiovascular death, mortality vs remaining on metformin alone for second line treatment SU N=23, 592 Metformin N=23, 592 | 25,699 added or switched to SU Mean f/u 1.1 years. SU linked to higher risk of MI =incidence 7.8 v 6.2, HR 1.26, 95% CI 1.01 - 1.56 -Mortality= 27.3 v 21.5, 1.281.15 - 1.44. -Hypoglycaemia= 0.7 v 5.5, 7.60, 4.64 to 12.44 vs remaining on metformin only. -Increased risk of cardiovascular death 8.1 v 9.4, 1.18, 0.98 - 1.43. and stroke 6.7 v 5.5, 1.24 0.99 - 1.56 Vs adding SU. switching to SU concomitant with higher risk of MI HR 1.51, 95% CI 1.03 - 2.24 and mortality 1.23, 1.00 - 1.50. No difference for, cardiovascular death ischaemic stroke, or severe hypoglycaemia adding SU= N39, CI 95% 3.4 2.5 - 4.7 | SU alone linked with a higher risk of MI, severe hypoglycaemia, and mortality, vs staying on metformin alone. When introducing SU it is safer to add metformin than to switch |
| 5 | Study Hollander et. al, 2017 VERTIS | RCT, double blind, Non- inferiority trial Phase 3 | N =1325,18+ years + T2DM 232 sites, 16 countries: Taiwan, Canada, Republic, Poland, South Korea, Hungary, Argentina, Mexico, Lithuania, Romania, Slovakia, South Africa, Czech, Ukraine, USA, Philippines, Russia, | -Measure effects and safety of glimepiride compared with ertugliflozin. Patients with T2DM - Poor control on metformin -Over 104 weeks. First 52 weeks (A phase) Second 52 weeks (B phase) to measure long-term effectiveness and of ertugliflozin -HbA1c between 7 and 9 percent, taking metformin 1500 mg per day to, glimepiride titrated from 1 mg, or ertugliflozin 15mg/5mg once daily. | Participants were similar, a minimum of 1 AE through the groups. Trial drug related AEs = GMI. SAE's in ertugliflozin 5mg group higher vs glimepiride and ertugliflozin 15mg. - Spread across classes, 2 Pneumonia: Ertugliflozin 5mg N=2 Glimepiride N=1 CVA: ertugliflozin 5mg N= 2 compared to glimepiride N=1 AE's resulting in discontinuation across groups. 7 deaths: glimepiride N=1 ertugliflozin 15mg N=1, ertugliflozin 5mg N=5 and Hypoglycaemia reduced with ertugliflozin vs with glimepiride. Severe hypoglycaemia reported in N=1 with ertugliflozin 15mg, N=1 ertugliflozin 5mg, and N=10 glimepiride. Weight loss -6.4 with ertugliflozin HBA1c – ertugliflozin 1.1mmol difference. SU greater reduction – sharp fall 6-12 weeks | -More SAEs in ertugliflozin groups not considered related to medication - Safety for use of ertugliflozin acceptable - non-inferiority of Ertugliflozin 15 mg + metformin to glimepiride confirmed inHbA1c reduction. - Ertugliflozin provides, better weight loss, glucose control, and lowering BP relative to Glimepiride. -Ertugliflozin reduced the occurrence of hypo, but increased incidence of Genital mycotic infections. Results: Ertugliflozin safe alternative to SU for insufficient glycaemic control on metformin. |
| 6 | Chang et. al, (2015) | Retrospective cohort study | N=36,118 Taiwanese, National Health Insurance database 1 year study | -Hospitalisations for any cardiovascular event: MI, ischaemic stroke congestive cardiac failure (CCF) and - Over 1 year until outcome, death, or disenrollment. 5 categories: metformin, Aglucosidase inhibitors, sulfonylureas and metformin, metformin and glinides, metformin and DPP4i and metformin and pioglitazone | -ITT analysis results: No variance in risk of cardiovascular events across treatment groups. -Significantly reduced risk of acute MI found in glinides and metformin group, crude HR 0.52 Adjusted HR 0.39; 95% CI 0.20 to 0.75 and -A- glucosidase- I + metformin, HR (crude) 0.63, -Adjusted HR 0.54; 95% CI 0.31 to 0.95. Risk of stroke or CCF on change observed | -No alteration to overall cardiovascular risk linked with sulfonylureas vs other second-line agents. - Potentially lower risk of MI with glinides + metformin compared with sulfonylureas +metformin |

| 7 | Leiter, et.al, 2015 | RCT Phase 3 Study | N = 1,450) 52- weeks followed by 52-week extension. 157 centres, 19 countries Study conducted 28 August 2009 - January 2013. Age >18 and <80 years | Canagliflozin 100 or 300 mg + Metformin Vs N=968 Glimepiride -titrated to 6 or 8mg daily + Metformin N=482 | 104-week HBA1C reductions 100mg -0.65%, -300mg 0.74%, and Glimepiride -0.55% -7.1, 8.1, and -6.0 mmol. Reduced body weight - 0.68kg, -0.89, Canagliflozin and +0.95, Glimepiride. SBP (-2.0 100mg -3.1 300mg and +1.7 Glimepiride. Adverse Events 73.3%, 100mg 77.9%, 300mg and 78.4% Glimepirides GMI, UTI, increased urination related AEs increased for canagliflozin vs glimepiride Hypoglycaemia significantly higher with Glimepiride 40.9% for canagliflozin 100mg 6.8 % and 300mg 8.2 % glimepiride 6.8% reduction, in GFR with canagliflozin. This attenuated over the trial. SAEs =9.7%, 100mg 9.7% 300mg and 14.3%, Glimepiride. Canagliflozin associated increased HDL-C 0.21 and 22, stable at 26 and remained | Canagliflozin provides more reduced body weight, durable glycaemic effect vs Glimepiride More hypoglycaemic events and SAEs with Glimepiride. AE's similar across groups More UTIs and GMI's in canagliflozin group Reduce systolic BP and weight observed with canagliflozin versus glimepiride. Reduced eGFR observed in 3 groups but was higher for Glimepiride |
| 8 | Nauck et.al, (2014) | Double blind multicentre RCT – extension study | 52 weeks with a 156- week extension – N=814 DAP & Metformin = n 406 GLIP& Metformin = n 408 | Initial 52-week study once completed, entered longer extension double-blind period. -52 additional treatment weeks One chance for up titration permitted. – If HbA1c was above 7, if not on max dose. Down titration allowed if hypoglycaemia happens on more than one occasion. | HbA1c mean decrease: at 52 weeks. Dapagliflozin vs glipizide changes at 104 wks −0.18% 2.0 mmol 95% CI: −0.33 −3.6, −0.03−0.3. FPG than decrease at 104 weeks −1.12 mmol 95% CI: −1.32, −0.92, glipizide −0.68 mmol 95% CI: −0.89, −0.47 0 deaths with dapagliflozin. 4 deaths with glipizide. -7 cancers, across both groups Weight: − 3.7 dapagliflozin + met vs + 1.4 glipizide + met Hypoglycaemia less in dapagliflozin 4.2 % vs glipizide 45.8% No significant difference for cardiovascular risk between groups AA: SGLTi2+met=0 SU+met=1 MI: SGLTi2+met=1 SU+met=1 CAO: SGLTi2+met=0 SU+met=1 | Glycaemic durability significantly better over 24mnths with dapagliflozin vs glipizide, -UTIs and GMI most prevalent side effects linked to dapagliflozin. incidence reduced during assessment period. -Persistent weight loss +SBP, may provide a beneficial result for cardiovascular risk – but no significant difference. |
| 9 | Del Prato et.al, (2014) | RCT- Multi centre, double blind, | N=2639 Participants aged 18–80. With T2DM Research sites: 310 Australia, America North + South, Europe, South, New Zealand, and South Africa | Treatment for 104 weeks. N=880 metformin +alogliptin 12.5mg OD N=885 alogliptin25 mg OD N=874 Glipizide 5 mg OD. Max titration of 20 mg | Primary results: Mean HbA1c and Fasting plasma glucose FPG at the end of 104 weeks from start 104: −0.68% alogliptin 12.5 −0.59% glipizide and −0.72% alogliptin 25 mg FPG: reduced by 0.05 + 0.18 mmol for alogliptin 12.5/25mg, glipizide increased 0.30 mmol - Safety for MACE (cardiovascular death, Ml or stroke) alogliptin 12.5mg = 6, alogliptin 25mg = 8, glipizide =11. Safety results for hypoglycaemia: Glipizide 23.2, alogliptin 25 mg 1.4%, alogliptin12.5mg 2.5% Mean weight difference: −0.68, alogliptin 12.5, −0.89 25mg and +0.95 glipizide. ss | Significantly increased risk of hypoglycaemia in Glipizide group. Risk for MACE Cardiovascular death, stroke or MI and risk of pancreatitis comparable across the 3 groups |

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| 10 | Hassan and Abd-Allah, 2015 | RCT | N=180 Recruited from Alzahra Hospital, by staff, Cairo, Egypt. Male, age 30-75 3month period T2DM | Randomised 6 groups, N30 in each: Placebo Control group - calorie-restricted diet, active lifestyle Gliclazide 80mg Metformin 500mg BD, Glimepiride 3 mg OD, Gliclazide + Metformin or Glimepiride + Metformin Outcome measures: FPG, PPG, plasma glucose, change in Hcy and HbA1c from 0-3mnths secondary outcomes: vitamin B12 level | HBA1c: met + gliclazide 7.1±0 Vs glimepiride 7±0.1 from baseline change FPG reduction -26.1% gliclazide + met ±3.7 vs. glimepiride + met 28.9±3.1PPG gliclazide + Met-42.4%±3.3 vs Glimepiride + Met -46±2 HbA1C gliclazide +Met 21.1±1.5 vs. -21.3±1.6% Glimepiride +Met Gliclazide or glimepiride + Met improved induced disruption of Hcy. glimepiride +met 10.3±0.3 vs gliclazide + met 11±0.3 Hypoglycaemic events patients 6.6%, Gliclazide alone n=2, glimepiride alone n=2 Metformin=0, 3/30 met =gliclazide, 5/30 (16.6%) met + glimepiride 16.6% LDL: met + gliclazide 146±7 met + glimepiride 142±7 Cholesterol: met 235±8 212±12b | |
| 11 | Pantalone et. al, (2012) | Retrospective cohort study | N= (7320) Pts >18 yrs. using academic health centre electronic health record system, Cleveland, OH, USA | 3768 glibenclamide + metformin 2277 glipizide + metformin 1275 Glimepiride and metformin, assessed for outcome of mortality by Social Security Death Index. And electronic health record From 1998 and 12 October 2006(8 years) follow up median (2.4 years) | Metformin plus glipizide or glimepiride plus metformin: HR 1.03; 95% CI 0.89– 1.20, -Metformin plus glimepiride plus versus Metformin plus glibenclamide:1.08; 95% CI 0.90–1.30, or metformin plus glipizide vs. metformin plus glibenclamide: HR 1.05; 95% CI 0.95–1.15. 636 deaths occurred in the cohort | No identification of higher risk for mortality with variation of metformin in addition to sulfonylureas, indicating total mortality is not significantly impacted by selection of sulfonylurea. |

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