Glinides and Glitazones for Type 2 Diabetes Mellitus

Short Report

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Acronyms and Abbreviations

Abbreviation or Acronym	Full Term
ADA	American Diabetes Association
CHF	Swiss Franc
DPP-4	dipeptidyl peptidase-4
f/u	follow-up
GLP-1	glucagon-like peptide-1
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HTA	Health Technology Assessment
MACE	major adverse cardiovascular events
NR	not reported
NS	no statistically significant difference
PICO	population, intervention, comparators, outcomes
RCT(s)	randomised controlled trial(s)
SGLT2	sodium-glucose cotransporter-2
T2DM	type 2 diabetes mellitus

Executive Summary

Introduction	*Policy Context:* This short report is a focused assessment of the effectiveness and safety of glinides (repaglinide and nateglinide), and glitazones (pioglitazone) for treatment of type 2 diabetes mellitus (T2DM) to inform whether their reimbursement should continue or be limited in Switzerland.
	Technology Description: Glinides and glitazones are oral glycaemic control medications for patients with T2DM. Although evidence suggests that glinides and glitazones are associated with improved glycaemic control, questions remain regarding safety and other clinical benefits, especially with regard to long-term effects on mortality and morbidity.
	Health Problem: T2DM is a common form of diabetes characterised by insulin resistance, impaired insulin secretion, and other abnormal metabolic or inflammatory changes. T2DM increases risk of microvascular and macrovascular complications. The prevalence of T2DM is rising and is projected to affect more than 500 million adults worldwide by 2030.
Review Methods	Methods of systematic review were employed for this short report, including definition of scope by a population, intervention, comparator, and outcomes (PICO) statement and key questions; multimodal systematic literature searches; objective literature selection criteria; narrative synthesis; and critical appraisal of the evidence. The last search for evidence for this report was conducted on December 19, 2019, in PubMed and Embase.
Key Question 1: *What is the comparative effectiveness and safety of repaglinide, alone or in combination with metformin, pioglitazone, or insulin?*	
Evidence	Evidence for this question comprised eight randomised controlled trials (RCTs). Sample sizes ranged from 100 to 576 patients, and follow up was one year in all studies. All studies compared repaglinide monotherapy using heterogeneous dosing schedules with sulfonylurea or metformin monotherapy. The strength of the evidence for individual outcomes ranged from insufficient to moderate.
Findings and Conclusions	Evidence does not suggest treatment-related differences in hypoglycaemia, blood pressure, weight changes, cardiovascular morbidity, or adverse events between repaglinide monotherapy and comparators. Evidence regarding mortality was presented in only one study and therefore insufficient to inform conclusions. Limitations include clinical heterogeneity (which precluded quantitative analyses of the findings), and a lack of statistical analyses within studies for many outcomes. Additionally, the evidence was limited because none of the studies were specifically designed to address effectiveness and safety outcomes of interest, and therefore they generally lacked sufficient statistical power and length of follow-up.
Key Question 2: *What is the comparative effectiveness and safety of nateglinide, alone or in combination with metformin or pioglitazone?*	
Evidence	Seven RCTs described in eight publications met inclusion criteria. Sample sizes ranged from 78 to 701 patients, and follow-up ranged from 12 weeks to 104 weeks. Nateglinide was administered with or without metformin using a variety of dosing schedules. Comparators varied across studies and included placebo or no treatment, metformin, and metformin plus a sulfonylurea. The strength of the evidence for individual outcomes was very low to moderate.
Findings and Conclusions	Evidence does not suggest that nateglinide administered with or without metformin is associated with differences in all-cause mortality, episodes of confirmed hypoglycaemia, study drop-out due to adverse events, or substantive changes in weight, compared with comparator groups. Evidence on cardiovascular morbidity was not identified. Limitations include clinical

	heterogeneity across studies (which precluded quantitative analyses of the findings) and a lack of statistical analyses within studies for many outcomes The evidence was additionally limited because none of the studies were specifically designed to address effectiveness and safety outcomes of interest, and therefore generally lacked sufficient statistical power and length of follow-up.
Key Question 3: *What is the comparative effectiveness and safety of pioglitazone, alone or in combination with metformin, sulfonylureas, or insulin?*	
Evidence	The body of included evidence comprised 13 RCTs presented in 28 publications. Sample sizes ranged from 522 to 5238 patients, and follow-up ranged from 1 to 10.7 years. Across studies, pioglitazone was administered differently, including as an add-on to existing treatments, sulfonylureas, and/or metformin. Comparators varied across studies and included placebo or no treatment, sulfonylurea or metformin monotherapy, sulfonylureas and metformin as add-on therapies, and vildagliptin as an add-on to metformin. The strength of the evidence for individual outcomes ranged from low to moderate.
Findings and Conclusions	Evidence does not suggest that pioglitazone is associated with differences in all-cause mortality or most individual macrovascular events versus comparators. Limited evidence from one large study suggests that major adverse cardiovascular events (MACE) may occur at a lower rate in patients receiving pioglitazone than placebo (in addition to other medications); however, this finding was not replicated in three other placebo-controlled studies and two active controlled studies, which found no treatment-related differences in MACE and other related composite measures. Pioglitazone may be associated with an increased risk of heart failure, oedema, and weight gain compared with controls. Pioglitazone may be associated with fewer episodes of hypoglycaemia compared with sulfonylurea regimens and may be associated with improvements in blood pressure relative to comparators. Limitations include clinical heterogeneity across studies (which precluded quantitative analyses of the findings) and a lack of statistical analyses within studies for many outcomes. The evidence suggests few differences between pioglitazone versus comparators in improving health outcomes, and the apparent risks associated with pioglitazone should be considered in treatment and coverage decisions.

Zusammenfassung

Einleitung	*Politischer Kontext:* Der Fokus dieses kurzen Berichts liegt auf der Bewertung der Wirksamkeit und Sicherheit von Gliniden (Repaglinid und Nateglinid) und Glitazonen (Pioglitazon) zur Behandlung von Typ-2-Diabetes mellitus (T2DM) im Hinblick auf die Entscheidung, ob deren Rückerstattung in der Schweiz fortgesetzt oder beschränkt werden soll.
	Beschreibung der Technologie: Glinide und Glitazone sind oral angewendete Wirkstoffe für die Blutzuckerkontrolle bei Patienten mit T2DM. Obwohl die Daten vermuten lassen, dass sich Glinide und Glitazone für eine verbesserte Blutzuckerkontrolle einsetzen lassen, bleiben Fragen im Zusammenhang mit der Sicherheit und weiteren klinischen Vorteilen offen, insbesondere bezüglich langfristigen Wirkungen auf die Mortalität und Morbidität.

	Gesundheitliches Problem: T2DM ist eine verbreitete Form von Diabetes mellitus, die gekennzeichnet ist durch Insulinresistenz, eine beeinträchtigte Insulinsekretion und weitere abnorme metabolische und entzündliche Veränderungen. T2DM erhöht das Risiko für mikro- und makrovaskuläre Komplikationen. Die Prävalenz von T2DM nimmt zu und es wird prognostiziert, dass 2030 weltweit mehr als 500 Millionen Erwachsene betroffen sein werden.
Review-Methoden	Es wurden für diesen Kurzbericht verschiedene Methoden für systematische Übersichtsarbeiten angewendet, einschliesslich der Festlegung des Untersuchungsbereichs mithilfe des PICO-Modells (Population Intervention Comparison Outcome) und Schlüsselfragen, multimodale systematische Literaturrecherche, objektive Literatur-Auswahlkriterien, narrative Synthese und kritische Evidenzbewertung. Die letzte Suche nach Daten für diesen Bericht wurde am 19. Dezember 2019 auf PubMed und Embase durchgeführt.
Schlüsselfrage 1: *Was ist die vergleichende Wirksamkeit und Sicherheit von Repaglinid, allein angewendet oder in Kombination mit Metformin, Pioglitazon oder Insulin?*	
Evidenz	Für diese Frage wurden acht randomisierte kontrollierte Studien (RCT) ausgewertet. Die Populationsgrösse lag bei 100 bis 576 Patienten. Das Follow-up dauerte bei allen Studien ein Jahr. In allen Studien wurde eine Repaglinid-Monotherapie bei unterschiedlichen Dosierungsschemata mit einer Sulfonylharnstoff- oder Metformin-Monotherapie verglichen. Die Evidenzstärke bezüglich einzelner Outcomes reichte von ungenügend bis mässig.
Ergebnisse und Schluss-folgerungen	Die Daten deuten nicht auf Unterschiede bezüglich Hypoglykämie, Blutdruck, Gewichtsveränderung, kardiovaskuläre Morbidität oder unerwünschte Wirkungen bei der Repaglinid-Monotherapie gegenüber den Vergleichsbehandlungen. Da nur in einer Studie Daten zur Mortalität vorgelegt wurden, lassen sich dazu keine Schlussfolgerungen ziehen. Zu den Begrenzungen gehören die klinische Heterogenität zwischen den Studien (die quantitative Analysen der Ergebnisse verhinderte) und fehlende statistische Analysen innerhalb der Studien für viele Outcomes. Ausserdem war die Evidenz beschränkt, da das Design keiner Studie spezifisch darauf ausgelegt war, die hier analysierten Outcomes zur Wirksamkeit und Sicherheit zu untersuchen, und deshalb die statistische Aussagekraft im Allgemeinen begrenzt und die Follow-up-Dauer zu kurz war.
Schlüsselfrage 2: *Was ist die vergleichende Wirksamkeit und Sicherheit von Nateglinid, allein angewendet oder in Kombination mit Metformin oder Pioglitazon?*	
Evidenz	Sieben RCT, die in acht Publikationen beschrieben wurden, erfüllten die Einschlusskriterien. Die Populationsgrössen lagen zwischen 78 und 701 Patienten, die Follow-up-Dauer betrug zwischen 12 Wochen und 104 Wochen. Nateglinid wurde mit oder ohne Metformin unter Anwendung unterschiedlicher Dosierungsschemata verabreicht. In den Studien wurden unterschiedliche Vergleichsbehandlungen verwendet, darunter Placebo oder keine Behandlung, Metformin sowie Metformin plus ein Sulfonylharnstoff. Die Evidenzstärke bezüglich der einzelnen Outcomes reichte von sehr tief bis mässig.
Ergebnisse und Schluss-folgerungen	Die Daten deuten nicht auf Unterschiede bezüglich Gesamtsterblichkeit, Episoden bestätigter Hypoglykämie, Studienausschluss aufgrund unerwünschter Wirkungen oder erheblicher Gewichtsveränderungen bei der Verabreichung von Nateglinid mit oder ohne Metformin gegenüber den Vergleichsgruppen. Es wurden keine Daten gefunden, die auf die kardiovaskuläre Morbidität schliessen lassen. Zu den Begrenzungen gehören die klinische Heterogenität zwischen den Studien (die quantitative Analysen der Ergebnisse verhinderte) und fehlende statistische Analysen innerhalb der Studien für viele Outcomes. Ausserdem war die Evidenz beschränkt, da das Design keiner Studie spezifisch darauf ausgelegt war, die hier

	analysierten Outcomes zur Wirksamkeit und Sicherheit zu untersuchen, und deshalb die statistische Aussagekraft beschränkt und die Follow-up-Dauer zu kurz war.
Schlüsselfrage 3: *Was ist die vergleichende Wirksamkeit und Sicherheit von Repaglinid, allein angewendet oder in Kombination mit Metformin, Sulfonylharnstoffen oder Insulin?*	
Evidenz	In die Auswertung eingeschlossen wurden die Daten aus 28 Publikationen zu 13 RCT. Die Populationsgrösse lag zwischen 522 und 5238 Patienten, die Follow-up-Dauer betrug zwischen 1 und 10,7 Jahren. In den Studien erfolgte die Pioglitazon-Behandlung in unterschiedlicher Weise, darunter als Add-on zu bestehenden Behandlungen mit Sulfonylharnstoffen und/oder Metformin. Als Vergleichsbehandlung wurde je nach Studie Placebo, keine Behandlung, eine Sulfonylharnstoff- oder Metformin-Monotherapie, Sulfonylharnstoffe und Metformin als Add-on-Therapie oder Vildagliptin als Add-on zu Metformin eingesetzt. Die Evidenzstärke bezüglich der einzelnen Outcomes reichte von gering bis mässig.
Ergebnisse und Schluss-folgerungen	Die Daten deuten nicht auf Unterschiede bezüglich Gesamtmortalität und den meisten makrovaskulären Ereignissen bei der Pioglitazon-Behandlung gegenüber den Vergleichsbehandlungen. In einer umfassenden Studie deuten die Daten mit begrenzter Evidenz darauf hin, dass schwerwiegende unerwünschte kardiovaskuläre Ereignisse (MACE) bei Patienten mit Pioglitazon-Behandlung mit geringerer Häufigkeit auftreten als bei der Gruppe mit Placebo (zusätzlich zu anderen Medikationen). Dieses Ergebnis konnte jedoch in drei weiteren Placebo-kontrollierten und zwei aktiv kontrollierten Studien nicht wiederholt werden, die keine behandlungsbedingten Unterschiede bezüglich MACE und anderen verwandten zusammengesetzten Messgrössen ergaben. Im Vergleich zu den Kontrollen kann Pioglitazon mit einem erhöhten Risiko für Herzinsuffizienz, Ödeme und Gewichtszunahme verbunden sein. Pioglitazon kann im Vergleich zu Sulfonylharnstoff-Behandlungen mit selteneren Hypoglykämie-Episoden und im Vergleich zu den Kontrollen mit Verbesserungen des Bluthochdrucks verbunden sein. Zu den Begrenzungen gehören die klinische Heterogenität zwischen den Studien (die quantitative Analysen der Ergebnisse verhinderte) und fehlende statistische Analysen innerhalb der Studien für viele Outcomes. Die Daten zeigen geringe Unterschiede von Pioglitazon im Vergleich zu Kontrollbehandlungen bezüglich verbesserter Gesundheitsoutcomes und die erkennbaren Risiken im Zusammenhang mit Pioglitazon sollten bei Entscheiden zur Behandlung und Rückerstattung berücksichtigt werden.

Synthèse

Introduction	*Contexte:* ce bref rapport évalue de manière ciblée l'efficacité et de la sécurité des glinides (répaglinide et natéglinide), et des glitazones (pioglitazone) pour le traitement du diabète de type 2 (DT2) afin de déterminer si leur remboursement doit continuer ou être limité en Suisse.
	Description de la technologie : les glinides et les glitazones sont des médicaments oraux qui permettent de contrôler la glycémie chez les patients atteints de DT2. Bien que des données suggèrent que les glinides et les glitazones sont associés à un meilleur contrôle de la glycémie, des questions subsistent concernant la sécurité et d'autres avantages cliniques, notamment en ce qui concerne les effets à long terme sur la mortalité et la morbidité.

	Problème de santé : le DT2 est une forme courante de diabète caractérisée par une résistance à l'insuline, une altération de la sécrétion d'insuline et d'autres changements métaboliques ou inflammatoires anormaux. Le DT2 augmente le risque de complications microvasculaires et macrovasculaires. La prévalence du DT2 est en hausse et devrait toucher plus de 500 millions d'adultes dans le monde d'ici 2030.
Méthodes d'examen	Des méthodes d'examen systématique ont été utilisées pour le présent rapport, notamment la définition de la portée (scope) sur la population, l'intervention, le comparateur et les résultats (PICO) et des questions clés, des recherches bibliographiques systématiques multimodales, des critères objectifs de sélection de la littérature, une synthèse narrative et une évaluation critique des preuves. La dernière recherche de preuves pour ce rapport a été menée le 19 décembre 2019, dans PubMed et Embase.
Question clé 1 : *Quelle est l'efficacité et la sécurité comparées du répaglinide, seul ou en combinaison avec la metformine, la pioglitazone ou l'insuline ?*	
Preuve	Les données probantes pour répondre à cette question comprennent huit essais contrôlés randomisés (ECR). La taille des échantillons variait de 100 à 576 patients, et le suivi était d'un an dans toutes les études. Toutes les études ont comparé le répaglinide en monothérapie à l'aide de schémas posologiques hétérogènes avec la sulfonylurée ou la metformine en monothérapie. La solidité des preuves concernant les résultats individuels varie, d'insuffisante à modérée.
Résultats et conclusions	Les preuves n'indiquent pas de différences liées au traitement en termes d'hypoglycémie, de pression artérielle, de changements de poids, de morbidité cardiovasculaire ou d'événements indésirables entre le répaglinide en monothérapie et les comparateurs. Les preuves concernant la mortalité n'ont été présentées que dans une seule étude et sont donc insuffisantes pour étayer les conclusions. Les limites incluent l'hétérogénéité clinique (qui a empêché des analyses quantitatives des résultats), et un manque d'analyses statistiques au sein des études pour de nombreux résultats. En outre, les preuves étaient limitées car aucune des études n'était spécifiquement conçue pour traiter des résultats d'intérêt en matière d'efficacité et de sécurité, et elles n'avaient donc généralement pas une puissance statistique et une durée de suivi suffisantes.
Question clé 2 : *Quelle est l'efficacité et la sécurité comparatives du natéglinide, seul ou en combinaison avec la metformine ou la pioglitazone ?*	
Preuve	Sept ECR décrits dans huit publications ont satisfait aux critères d'inclusion. La taille des échantillons varie de 78 à 701 patients, et le suivi varie de 12 à 104 semaines. Le natéglinide a été administré avec ou sans metformine selon divers schémas posologiques. Les comparateurs varient selon les études et comprennent un placebo ou aucun traitement, la metformine, et la metformine plus une sulfonylurée. La pertinence des preuves concernant les résultats individuels était très faible à modérée.
Résultats et conclusions	Les preuves n'indiquent pas que le natéglinide administré avec ou sans metformine soit associé à des différences de mortalité toutes causes confondues, à des épisodes d'hypoglycémie confirmée, à des abandons d'études en raison d'événements indésirables, ou à des changements importants de poids, par rapport aux groupes de comparaison. Aucune preuve de morbidité cardiovasculaire n'a été identifiée. Les limites comprennent l'hétérogénéité clinique entre les études (qui a empêché des analyses quantitatives des résultats) et un manque d'analyses statistiques au sein des études pour de nombreux résultats. Les preuves étaient en outre limitées parce qu'aucune des études n'était spécifiquement conçue pour traiter des résultats d'intérêt en matière d'efficacité et de

	sécurité, et n'avait donc généralement pas une puissance statistique et une durée de suivi suffisantes.
Question clé 3 : *Quelle est l'efficacité et la sécurité comparées de la pioglitazone, seule ou en combinaison avec la metformine, les sulfonylurées ou l'insuline ?*	
Preuve	L'ensemble des preuves incluses comprenait 13 ECR présentés dans 28 publications. La taille des échantillons varie de 522 à 5238 patients, et le suivi varie de 1 à 10,7 ans. Dans toutes les études, la pioglitazone a été administrée différemment, notamment en complément de traitements existants, de sulfonylurées et/ou de metformine. Les comparateurs varient selon les études et comprennent un placebo ou aucun traitement, une sulfonylurée ou la metformine en monothérapie, des sulfonylurées et la metformine comme thérapies d'appoint, et la vildagliptine en complément de la metformine. La pertinence des preuves concernant les résultats individuels varie, de faible à modérée.
Résultats et conclusions	Les preuves n'indiquent pas que la pioglitazone soit associée à des différences de mortalité toutes causes confondues ou à la plupart des événements macrovasculaires individuels par rapport aux comparateurs. Les preuves limitées d'une grande étude suggèrent que les événements cardiovasculaires majeurs (MACE) peuvent se produire à un taux plus faible chez les patients recevant de la pioglitazone que chez ceux recevant un placebo (en plus d'autres médicaments) ; cependant, cette conclusion n'a pas été reproduite dans trois autres études contrôlées par placebo et deux études contrôlées actives, qui n'ont trouvé aucune différence liée au traitement dans les MACE et autres mesures composites connexes. La pioglitazone peut être associée à un risque accru d'insuffisance cardiaque, d'œdème et de prise de poids par rapport aux contrôles. La pioglitazone peut être associée à moins d'épisodes d'hypoglycémie par rapport aux schémas de sulfonylurées et peut être associée à des améliorations de la pression artérielle par rapport aux comparateurs. Les limites comprennent l'hétérogénéité clinique entre les études (qui a empêché des analyses quantitatives des résultats) et un manque d'analyses statistiques au sein des études pour de nombreux résultats. Les preuves suggèrent peu de différences entre la pioglitazone et les comparateurs dans l'amélioration des résultats de santé, et les risques apparents associés à la pioglitazone devraient être pris en compte dans les décisions relatives au traitement et à la prise en charge des coûts.

Short Report

1 POLICY CONTEXT

Purpose and Scope: This short report provides a focused assessment of the comparative effectiveness and safety of two glinides (repaglinide and nateglinide) and one glitazone (pioglitazone) for treatment of type 2 diabetes mellitus (T2DM). It summarizes and critically appraises eligible full-text, peer-reviewed, published evidence with the intent of drawing evidence-based conclusions.

This short report is intended to summarize evidence for patient-centered clinical outcomes related to direct health benefits and safety concerns for the drugs of interest, and intermediate or surrogate outcomes are outside of the intended scope. The rationale for this is that commonly evaluated surrogate measures (e.g. HbA1c) may not correlate well with patient-centered outcomes of interest such as cardiovascular risk [1]. Further, while evidence suggests that glinides and glitazones are associated with improved glycaemic control as measured by intermediate outcomes, their impact on direct health outcomes such as mortality or macrovascular morbidity is uncertain [2-5].

Policy Question: An up-to-date assessment of the comparative effectiveness and safety of the specified glinides and glitazone is needed to inform whether reimbursement should continue or be limited in Switzerland, given concerns described in the following text.

Glinides: A Health Technology Assessment (HTA) report by the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) issued in 2009 reported that no studies were found to determine mortality outcomes or cardiovascular benefits of glinides [6]. In 2016, the Gemeinsamer Bundesausschuss (G-BA) reduced the use of glinides to patients having a creatinine clearance below 25 millilitres (mL) per minute [7].

Glitazones: Pioglitazone is used to treat patients with T2DM. Since 2010, pioglitazone is no longer reimbursed in Germany due to safety concerns [8]. In France, pioglitazone lost market authorisation because reviewed evidence showed an increased risk of bladder cancer [9].

Current Service Provision: The following information was provided via personal communication from the Section of Health Technology Assessment, Division of Health Care Services in the Federal Department of Home Affairs in Switzerland.

As of July 2019, the following antidiabetics (mono substances only; fixed-dose combinations are not mentioned) are approved and reimbursed in Switzerland:

- Biguanides: metformin
- Sulfonylureas: glibenclamide (glyburide), gliclazide, glimepiride
- Glinides: repaglinide, nateglinide
- Glitazones: pioglitazone
- Gliptins (dipeptidylpeptidase-4-inhibitors [DPP-4]): alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin
- glucagon-like peptide-1 (GLP-1)-receptor-agonists: dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin

A summary of total sales in Swiss Franc (CHF) for 2017 and 2018 for each drug of interest is provided in Table 1. Following that, Table 2 provides a summary of current retail prices in CHF.

Table 1. Volume of Sales by Retail Price in CHF (Source: SASIS Tarifpool, processed by COGE GmbH accessed 10.01.2020)

Drug	2017	2018
Repaglinide (original and generics)	1'041'427	779'510
Nateglinide (original, no generic available)	294'278	207'377
Pioglitazone (original and generics)	2'629'250	1'925'757
Pioglitazone and metformin fixed dose combination (original, no generic available)	893'056	678'846

Table 2. Retail Price of Currently Available Packages in CHF

Drug	Current Retail Price in CHF (20.08.2019), only of original products
Repaglinide	Novonorm, 0.5 mg, 90 tablets: 20.3 Novonorm 1 mg, 90 tablets: 27.00 Novonorm 2 mg, 90 tablets: 33.65
Nateglinide	Starlix mite 60 mg, 84 tablets: 48.55 Starlix 120 mg, 84 tablets: 48.55
Pioglitazone	Actos 15 mg, 28 tablets: 41.70 Actos 15 mg, 98 tablets: 104.70 Actos 30 mg, 28 tablets: 50.70 Actos 30 mg, 98 tablets: 135.85 Actos 45 mg, 28 tablets: 57.55 Actos 45 mg, 98 tablets: 159.65
Pioglitazone and metformin	Competact 15/850 mg, 28 tablets: 23.40 Competact 15/850 mg, 98 tablets: 69.60

The indications for repaglinide, nateglinide, and pioglitazone are as follows [10]:

- Repaglinide is indicated for treatment of adults with T2DM if blood sugar levels are not adequately controlled by nutritional therapy, physical activity, or reduction in body weight. If repaglinide monotherapy does not sufficiently control blood sugar levels, it can be used in combination with metformin or a glitazone. A combination therapy of repaglinide with insulin is indicated in T2DM patients

if the blood sugar level cannot be controlled sufficiently by a combination of a sulfonylurea or repaglinide alone.

- Nateglinide is indicated to treat patients with T2DM if hyperglycaemia cannot be controlled via nutritional therapy or physical activity. It can be used as monotherapy or in combination with metformin or a glitazone.
- Pioglitazone is indicated as a second-line therapy for T2DM if blood sugar levels are inadequately controlled via nutritional therapy or physical activity. Pioglitazone as monotherapy is only indicated when metformin is contraindicated or not tolerated. Pioglitazone can be combined with metformin, if the maximum daily dose of metformin cannot control blood sugar levels sufficiently. Pioglitazone can also be combined with sulfonylurea, if the maximum dose of sulfonylurea alone cannot control the blood sugar level sufficiently. Pioglitazone may also be combined with both metformin and sulfonylurea, if the latter two cannot control the blood sugar level sufficiently. Pioglitazone can be combined with insulin, if insulin cannot sufficiently control the blood sugar and if metformin is not tolerated or is contraindicated.

2 BACKGROUND

2.1 GLINIDES AND GLITAZONES

Rationale: In patients with T2DM who have inadequate disease management despite comprehensive dietary and behavioral interventions, pharmacological interventions may be required [11]. Treatment selection is based on patient characteristics, clinical factors, and comorbidities [11].

Technology Description: Glinides and glitazones are oral medications that provide glycaemic control through different mechanisms.

Glinides (repaglinide and nateglinide) work by stimulating insulin secretion. They are short-acting insulin secretagogues that are administered before each meal [12]. Repaglinide was the first glinide approved for clinical use in T2DM. Both repaglinide and nateglinide are approved and reimbursed for the treatment of T2DM in Switzerland as monotherapy or in combination with metformin, pioglitazone, or insulin (repaglinide only). Evidence suggests that glinides are associated with improved glycaemic control, although their impact on health outcomes such as mortality or cardiovascular morbidity is uncertain [2 3 13 14]. Hypoglycaemia may be a risk for glinides, and other safety concerns are not well-characterised [15].

Glitazones enhance insulin sensitivity and decrease insulin resistance by binding directly to a transcription factor identified as Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) [16]. Glitazones are administered orally once daily. At present, only pioglitazone and its fixed-dose combination with metformin are approved and reimbursed for second-line treatment of T2DM in Switzerland. Pioglitazone can be combined with metformin, sulfonylurea, or insulin. Evidence suggests that pioglitazone is associated with improved glycaemic control that is comparable with other medications [4 5 17 18]. However, safety concerns exist. Pioglitazone is suspected to increase the risk of bladder cancer in a time- and dose-dependent manner [12 19-21], and clinical recommendations suggest that it should not be used for longer than two years. Other potential adverse effects may include weight gain, as well as more serious side effects such as an increased risk of congestive heart failure [15].

Clinical Application and Alternatives: The first-line treatment for T2DM is lifestyle modification, followed by addition of metformin. Other drugs, including glitazones or glinides, may be added or substituted as appropriate, with treatment selections based on patient characteristics, clinical factors, and comorbidities [11]. Alternatives to glinide and glitazone drugs may include sulfonylureas, alpha-glucosidase inhibitors, gliptins, GLP-1-receptor-agonists, and SGLT2 inhibitors alone or in combination.

2.2 TYPE 2 DIABETES MELLITUS (T2DM)

Health Problem: Type 2 diabetes mellitus (T2DM) is by far the most common form of diabetes, accounting for 90% to 95% of all cases. T2DM is generally characterised by insulin resistance, impaired insulin secretion, or both; as well as abnormalities in other metabolic or inflammatory processes originating from various pathophysiological pathways [22]. A primary feature of T2DM is the body's inability to effectively use insulin, a hormone that regulates blood sugar, causing hyperglycaemia (also referred to as high blood sugar). The body may compensate with increased insulin production; although over time, the beta cells of the pancreas become unable to maintain adequate production levels [23]. Individuals with T2DM have relative (rather than complete) insulin deficiency, as well as peripheral insulin resistance [24]. T2DM is associated with an increased risk for macrovascular complications (e.g. myocardial infarction, stroke, peripheral arterial disease) and microvascular complications (e.g. nephropathy, renal failure, neuropathy, retinopathy, blindness) [22 2423].

Epidemiology: The prevalence of T2DM is projected to affect more than 500 million adults worldwide by 2030 [9]. The disease caused four million deaths worldwide in 2017. An estimate of 500'000 people suffer from diabetes in Switzerland, of which 460'000 are affected by T2DM [25].

Clinical Presentation: Signs and symptoms of T2DM may include thirst, frequent urination, delayed healing, fatigue, and blurred vision [11]. However, these signs may be subtle, delaying diagnosis. T2DM can lead to damage, dysfunction, and failure of macrovascular systems (leading potentially to major cardiac events or stroke), and microvascular systems (leading potentially to blurred vision, neuropathy, or nephropathy) [26].

Diagnosis: Based on American Diabetes Association (ADA) guidelines, criteria for diagnosis of T2DM include fasting plasma glucose (FPG) ≥7.0 mmol/L, or two-hour plasma glucose tolerance of ≥11.1 mmol/L during a 75-g oral glucose tolerance test, or random plasma glucose of >11.1 mmol/L in patients with symptoms of T2DM. Glycated hemoglobin (HbA1c) ≥6.5% may also be considered, though controversy remains whether it should be a primary or optional diagnostic criterion [27].

Treatments: Initial treatments for T2DM may include lifestyle and behavioral modifications, including medical nutrition therapy and exercise. First line pharmacological therapy of T2DM typically consists of metformin in combination with comprehensive lifestyle changes. The choice of drug for the add-on therapy is made based upon drug-specific effects and patient factors, as well as comorbidities [11]. Individuals with T2DM may not require insulin treatment for survival, especially in the early phases of the disease [27].

3 METHODS

The principles of systematic review guided the development of this short report. A protocol was developed and approved by the Swiss Federal Office of Public Health, Section of Health Technology Assessment. Methods are intended to yield a report that is transparent, rigorous, and reproducible. Key methods included designation of

and adherence to a PICO (population, intervention, comparators, outcomes) statement, use of key questions, systematic literature search strategies, objective literature selection criteria, and synthesis using narrative methods, as described in the following text.

3.1 PICO STATEMENT

The scope of this short report is defined using the PICO statement—to define **p**opulation, **i**nterventions, **c**omparators, and **o**utcomes of interest.

Population and Setting: Individuals diagnosed with T2DM. Studies of individuals with diagnoses other than T2DM (e.g. gestational diabetes, pre-diabetes, metabolic syndrome without diabetes, or polycystic ovary syndrome) were excluded. Studies of mixed populations with analyses that do not stratify by specific diagnoses were also excluded.

Interventions: The interventions of interest are:

- Key Question 1: repaglinide alone or in combination with metformin, pioglitazone, or insulin
- Key Question 2: nateglinide alone or in combination with metformin or pioglitazone
- Key Question 3: pioglitazone alone or in combination with metformin, a sulfonylurea, or insulin

Note that the glitazones class includes rosiglitazone and pioglitazone; however, only pioglitazone is addressed in this short report since rosiglitazone lost market authorisation in Switzerland in October 2010.

Studies evaluating repaglinide, nateglinide, or pioglitazone in combination with drugs that are not available or reimbursed in Switzerland are excluded. Studies in which individual patients receive different drugs or drug combinations, and the analyses do not stratify by type of drug will also be excluded. For example, a study of patients who received thiazolidinediones but did not stratify based on those who received pioglitazone and those who received rosiglitazone would not meet inclusion criteria.

Comparators: Eligible studies directly compare the medications of interest with other alternative antidiabetics licensed and reimbursed in Switzerland. Comparisons may include the listed medications from the following classes of drugs:

- Sulfonylureas: glibenclamide (glyburide), gliclazide, glimepiride
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors: dapagliflozin, empagliflozin, ertugliflozin
- Biguanides: metformin
- Alpha-glucosidase inhibitors: acarbose
- Gliptins (dipeptidyl peptidase-4 [DPP-4] inhibitors): alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin
- glucagon-like peptide-1 (GLP-1) receptor agonists and GLP-1 analogs: dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide

Studies comparing a drug of interest provided as monotherapy versus the same drug provided as part of a combination therapy (e.g. pioglitazone alone versus pioglitazone plus metformin) were included for adverse events outcomes. In addition, studies comparing an intervention of interest with placebo, no treatment, or lifestyle changes (e.g. nutrition therapy and exercise) were eligible for inclusion. Studies comparing a drug of interest with placebo or no treatment shall be considered for adverse events outcomes.

Studies comparing only glinides with glitazones were not included. Comparisons with other treatments that are not listed are outside the scope of this report. Studies without a comparison group were not included.

Outcomes: This short report is intended to focus on patient-centered outcomes related to safety and effectiveness. Outcomes of interest include all-cause mortality; all-cause and disease-related morbidity, such as microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (including, but not limited to, individual and composite rates of major adverse cardiac events [MACE]; coronary artery, peripheral artery, or cerebrovascular disease; coronary artery bypass surgery or percutaneous coronary intervention; stroke); and treatment-related harms (including, but not limited to, blood pressure changes, weight changes, oedema, and incidence of hypoglycaemia).

Change in HbA1c, an intermediate outcome that is often assessed in studies of T2DM drugs, is not an outcome of interest for this short report. This decision was made in response to controversy regarding whether HbA1c reductions are an appropriate surrogate outcome for macrovascular events and mortality risk [1]. While the majority of studies evaluating T2DM drugs report outcomes related to HbA1c, far fewer provide data for key patient-centered outcomes of interest. This short report was scoped to include the best-available, direct evidence for safety and effectiveness outcomes and did not assess surrogate outcomes such as HbA1c. A discussion of HbA1c reductions as reported in identified systematic reviews and meta-analyses is presented for each key question.

3.2 KEY QUESTIONS

Key questions unite the PICO statement into a conceptual framework. This short report addresses the following key questions.

For individuals with T2DM, what is the comparative evidence for effectiveness and safety for:

1. Repaglinide, alone or in combination with metformin, pioglitazone, or insulin?
2. Nateglinide, alone or in combination with metformin, or pioglitazone?
3. Pioglitazone, alone or in combination with metformin, sulfonylureas, or insulin?

3.3 LITERATURE SEARCH STRATEGIES

A comprehensive multimodal literature search was performed to identify primary peer-reviewed clinical studies addressing the key questions. Systematic search strategies were designed for PubMed and Embase databases to optimize sensitivity and specificity, with inclusion of Medical Subject Headings (MeSH) and Emtree preferred terms. Search terms were keywords related to the population, interventions, and outcomes of interest.

No date limits were employed, and databases were searched from inception. PubMed was searched without the use of filters. In Embase, searches were performed using the advanced search function and terms were searched as free text in all fields. Ineligible publication types were filtered in Embase by unselecting all publication types other than articles and articles in press.

Due to a large body of literature for Key Question 3 (pioglitazone), terms related to the desired study design (RCTs) were also introduced into the search string. A smaller body of evidence was available for Key Questions 1 and 2 (repaglinide and nateglinide), and the search strategy was expanded to include studies without randomised designs; this was accomplished by omitting terms related to RCTs from the search string for glinides.

Bibliographic database search strategies are summarised in Table 3, and results represent the yield on the date of the last search, December 19, 2019. For additional search details, see Appendix I.

Table 3. Summary of Literature Search Strategies (Performed December 19, 2019)

Key Question	Database	Terms	Results (December 19, 2019)
Key Question 1 and 2 (glinides)	PubMed	(glinide OR glinides OR meglitinide OR meglitinides OR repaglinide OR nateglinide OR prandin OR GlucoNorm OR Surepost OR EIPICO OR NovoNorm OR starlix) AND (diabetes mellitus OR type 2 diabetes OR type ii diabetes) AND (mortality OR morbidity OR cardiac OR heart OR cardiovascular OR fracture OR malignancy OR cancer OR stroke OR renal OR kidney OR microvascular OR macrovascular OR retinopathy OR nephropathy OR neuropathy OR myocardial infarction OR adverse event OR adverse events OR safety OR death OR blood pressure OR weight)	791
	Embase	(glinide OR glinides OR meglitinide OR meglitinides OR repaglinide OR nateglinide OR prandin OR GlucoNorm OR Surepost OR EIPICO OR NovoNorm OR starlix) AND ('diabetes mellitus' OR 'type 2 diabetes' OR 'type ii diabetes') AND (mortality OR morbidity OR cardiac OR heart OR cardiovascular OR fracture OR malignancy OR cancer OR stroke OR renal OR kidney OR microvascular OR macrovascular OR retinopathy OR nephropathy OR neuropathy OR 'myocardial infarction' OR 'adverse event' OR 'adverse events' OR safety OR death OR blood pressure OR weight) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	463
Key Question 3 (pioglitazone)	PubMed	(pioglitazone OR Actos OR Glustin OR Glizone OR Pioz OR Zactos OR thiazolidinedione OR thiazolidinediones OR glitazone OR glitazones) AND (diabetes mellitus OR type 2 diabetes OR type ii diabetes) AND (mortality OR morbidity OR cardiac OR heart OR cardiovascular OR fracture OR malignancy OR cancer OR stroke OR renal OR kidney OR microvascular OR macrovascular OR retinopathy OR nephropathy OR neuropathy OR myocardial infarction OR adverse event OR adverse events OR safety OR death OR blood pressure OR hypoglycemia OR weight) AND (randomized controlled trial OR random*)	1485
	Embase	(pioglitazone OR thiazolidinedione OR thiazolidinediones OR glitazone OR glitazones OR actos OR glustin OR glizone OR pioz OR zactos) AND ('diabetes mellitus' OR 'type 2 diabetes' OR 'type ii diabetes') AND (mortality OR morbidity OR cardiac OR heart OR cardiovascular OR fracture OR malignancy OR cancer OR stroke OR renal OR kidney OR microvascular OR macrovascular OR retinopathy OR nephropathy OR neuropathy OR 'myocardial infarction' OR 'adverse event' OR 'adverse events' OR safety OR death OR 'blood pressure' OR weight) AND 'randomized controlled trial' AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	197

To verify that all relevant primary studies were identified, we performed supplementary searches of the grey literature and manual searches of the bibliographies of relevant systematic reviews, primary studies, regulatory documents, evidence-based clinical practice guidelines, and published abstracts from professional society conferences. Publications that were manually searched are listed in Appendix I.

In addition to primary clinical studies, relevant, recent systematic reviews and meta-analyses were identified to provide supplementary information and context to the evidence included in the current short report. These publications were identified during the literature search using combinations of terms related to the population and intervention of interest, combined with terms related to systematic review and meta-analyses. Searches were conducted in PubMed and Embase, and supplementary internet searches were also performed.

3.4 LITERATURE SELECTION CRITERIA

All primary clinical studies were required to meet the following criteria to be included as evidence in this short report:

- *PICO:* Study must address the PICO and one or more key question. Specifically, study must evaluate repaglinide, nateglinide, or pioglitazone (as monotherapy or in specified combinations), compared with specified drugs of interest, and report one or more outcomes of interest.
- *Publication type:* Study must be original research in a full-length peer-reviewed publication. Other publication types, such as editorials, letters, conference proceedings, and stand-alone abstracts were excluded. Duplicate accounts of data sets were excluded to avoid double-counting data. Where there was more than one published account of a data set, the more comprehensive publication was selected.
- *Language:* Abstracts from all studies were reviewed for potential inclusion, regardless of language. English, French, and German language publications were eligible for inclusion; publications in other languages were not eligible. All identified studies meeting inclusion criteria were published in the English language.
- *Study Design:* RCTs were the primary study design of interest for this report. Observational studies were considered for inclusion for key questions with a small body of evidence from RCTs.
    - Observational studies were required to meet study design criteria to inform comparative effectiveness and safety without excessive risk of bias. Specifically, observational studies must compare outcomes of interest between two or more groups of individuals with T2DM with similar baseline characteristics (in particular, HbA1c and co-morbidity) treated with a pharmaceutical and comparator of interest contemporaneously and followed for the same duration of follow-up.
    - Early scoping for this short report revealed that key question 1 and 2 (glinides) had smaller bodies of evidence than key question 3 (pioglitazone). Based on this observation, the decision was made to review observational studies for key question 1 (repaglinide) and 2 (nateglinide), but not for key question 3 (pioglitazone).
- *Sample Size and Follow-up:* Studies with large sample sizes and long durations of follow-up are most likely to provide accurate information regarding effectiveness and safety outcomes such as mortality and cardiac events, which are likely to be rare. Detecting them requires large groups of treated patients and long-term follow-up periods. Sample size and duration of follow-up criteria were employed to objectively select studies and for the pragmatic purpose of rendering an evidence base that could be evaluated within the scope, budget, and timeline of a short report. Thresholds were influenced by the overall volume of available studies related to each key question. Key question 3 (pioglitazone) had a large body of associated evidence from studies with low risk of bias with large sample sizes and long follow-up durations. Key question 2 had a smaller body of associated evidence, and key question 1 had an even smaller body of associated evidence. The following minimum study size and length of follow-up criteria were applied for RCTs for each key question:
    - Key Question 1 (repaglinide): RCTs enrolling ≥100 individuals with ≥6 months follow-up
    - Key Question 2 (nateglinide): RCTs enrolling ≥25 individuals with ≥3 months follow-up
    - Key Question 3 (pioglitazone): RCTs enroll ≥500 individuals with ≥1 year follow-up

Study size thresholds were initially considered for observational studies and proposed during protocol development in order to ensure that the best available evidence was evaluated within the scope of a short report. A post hoc decision was made to remove the study sizes limits for observational studies during the literature review phase, and ultimately, all identified observational studies were screened for key questions 1 and 2 regardless of study size. However, none of them met the methodological standards (described above in *Study Design*), which were set to ensure that studies with the most potential to exhibit the lowest risk of bias were included for evidence.

During the title and abstract screening phase, all studies clearly meeting the PICO criteria or with uncertain eligibility were flagged for full text review and assessment of study design elements such as study size, length of follow-up, and random or nonrandom allocation. Full-text articles were evaluated using the above study selection criteria by a senior analyst and were verified by a senior scientist. Disagreements between reviewers were resolved through discussion in all cases without third-party adjudication. Studies evaluated in full-length and not found to meet inclusion criteria are documented in the key exclusions table in Appendix II.

The study selection criteria are summarised in Table 4. Criteria specific to individual key questions are noted; otherwise, the same inclusion and exclusion criteria applied across key questions.

Table 4. Study Selection Criteria

Key: MACE, major adverse cardiovascular events; RCTs, randomised controlled trials; T2DM, type 2 diabetes mellitus

PICO	Inclusion Criteria	Exclusion Criteria
Population	• Individuals diagnosed with T2DM.	• Gestational diabetes • Pre-diabetes orimpaired glucose tolerance • Metabolic syndrome without diabetes • Polycystic ovary syndrome • Studies with mixed populations and the analyses do not stratify by specific diagnosis.
Interventions	• Key Question 1: Repaglinide as monotherapy or as part of a combination therapy with metformin, pioglitazone, or insulin • Key Question 2: Nateglinide as monotherapy or as part of a combination therapy with metformin or pioglitazone • Key Question 3: Pioglitazone as a monotherapy or as part of a combination therapy with metformin, a sulfonylurea, or insulin.	• Glinides or glitazones that are not available or reimbursed in Switzerland (e.g. mitiglinide, rosiglitazone) or given in combinations that are not approved and reimbursed in Switzerland • Studies in which individual patients receive different drugs or drug combinations and the analyses do not stratify by type of drug.
Comparators	• Antidiabetics available in Switzerland (used as monotherapy or as part an approved/reimbursed combination therapy) • Lifestyle changes (e.g. nutrition therapy and exercise) • Placebo or no treatment.	• No comparison group • Comparisons between glinides vs. glitazones • Comparison with a drug that is not available or reimbursed in Switzerland for the treatment of T2DM. • Studies comparing different doses of the same drug.
Outcomes	• All-cause mortality • Morbidity (all-cause and disease related)	• Intermediate outcomes (e.g. HbA1c, fasting plasma glucose levels, lipid levels, imaging outcomes).

PICO	Inclusion Criteria	Exclusion Criteria
	○ macrovascular complications (including but not limited to diseases of the coronary arteries, peripheral arteries, cerebrovasculature; stroke, myocardial infarction) ○ microvascular complications (retinopathy, nephropathy, and neuropathy) • Composite outcomes of mortality and/or macrovascular morbidity (e.g. MACE) • Adverse events (including but not limited to overall events, major adverse events, withdrawals due to adverse events, specific adverse events including but not limited to weight gain, hypoglycaemia, oedema, and blood pressure).	
Study Types	• Key Question 1 (repaglinide) ○ RCTs with ≥100 patients and ≥6 months follow-up ○ Observational studies meeting study design criteria[†] • Key Question 2 (nateglinide) ○ RCTs ≥25 patients with ≥3 months follow-up ○ Observational studies meeting study design criteria[†] • Key Question 3 (pioglitazone) ○ RCTs with ≥500 patients and follow-up ≥1 year.	• Case reports, uncontrolled studies, preclinical studies, reviews, editorials.

[†]A post hoc decision was made to remove sample size restrictions for observational studies, as described in the *Sample Size and Follow-up* subsection of 3.4 Literature Selection Criteria.

3.5 METHODS FOR EVIDENCE EVALUATION

Comprehensive methods for reviewing effectiveness and safety evidence were employed as follows, consistent with guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [28].

Data Extraction Strategies: All data were extracted onto standardised forms by a single senior-level scientific analyst and audited in full by a senior scientist. Discrepancies not resolved through discussion were presented to and adjudicated by a third party. No discrepancies were unresolvable through discussion or required third-party adjudication.

Methods for Data Analysis: Although quantitative synthesis was contemplated at early stages in protocol development for this short report, it was ultimately not used for multiple reasons. First, after study selection steps were completed, the considerable clinical heterogeneity of the evidence base was recognised. Sources of clinical heterogeneity included patient population (i.e. treatment-naive and treatment-resistant patients were studied),

differences in interventions (e.g. co-interventions, monotherapy versus dual therapy), differences in comparators, and differences in durations of follow-up. Given these differences, the true intervention effect can reasonably be expected to differ across studies [29]. For this reason, combining studies with considerable variability in meta-analysis can be misleading [29]. This is because meta-analysis renders pooled effect and may not accurately represent actual outcomes where there is clinical variability that can be expected to render different true effect sizes [29 30]. In this particular evidence base, subdividing the studies addressing each PICO to reduce clinical heterogeneity rendered study sets too small to justify meta-analysis.

While meta-analytic tools such as meta-regression provide objective and statistically rigorous methods to investigate the association between potential moderators and covariates (e.g. sources of clinical heterogeneity) and outcomes and provide potentially informative exploratory analyses [29], in the evidence base for this short report there were too few studies reporting statistically compatible data addressing each PICO to adequately power such an analysis.

Data were therefore analysed using methods of narrative synthesis. Narrative synthesis is an analysis method used within the context of systematic review to summarize information across studies [31]. It is differentiated from narrative review, which refers to literature reviews that do not use systematic methods to identify, select, and analyse studies [30].

Narrative synthesis is a form of descriptive data synthesis that employs tabular presentation of data and textual presentation of findings, presented by outcome [30]. Narrative synthesis employs logic, organisation, and exploration of relationships among studies (including consistency) to inform conclusions. When using narrative synthesis, we consider the effect sizes and precision of findings of individual studies, not just *p* values, which only inform statistical significance and are influenced by population size. Commentary on the evidence base will include the precision and size of effect of individual study findings; whether the effect sizes appear large enough to be clinically important; consistency of findings among studies; and, where identified, possible sources of heterogeneity.

Methods for Quality Assessment. To assess the quality of the evidence, we used widely accepted instruments developed by international panels of methodology experts. For individual study quality, the Cochrane Collaboration's tool for assessing risk of bias in randomised trials was used to assess quality in RCTs [32]. The Newcastle-Ottawa Scale (NOS) was intended to be employed to assess the quality of nonrandomised studies (using the coding manual for cohort studies) [33]; however, no observational studies meeting inclusion criteria were identified, as described in the Literature Selection Criteria. In consideration of study design and findings from the risk of bias assessments, individual studies were determined to be of good, fair, poor, or very poor quality. The overall quality of the evidence addressing each outcome (i.e. or strength of evidence) was assessed based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system [34 35]. Using GRADE, the strength of the evidence for each outcome is determined to be high, moderate, low, very low, or insufficient, representing a level of confidence in the conclusion for each outcome [35].

For detailed descriptions of methods for evidence evaluation, see Appendix III.

4 EVIDENCE EVALUATION

4.1 EVIDENCE BASE

During the title and abstract screening phase of the literature review for this report, all abstracts from clinical studies with the potential to meet the PICO statement were flagged for further review, regardless of sample size or follow-up duration. During the title and abstract screening phase, disparities in the volume of comparative evidence available for each key question were evident. Searches demonstrated that the largest body of evidence was available for key question 3 (pioglitazone) and smaller bodies of evidence were available for key questions 1 (repaglinide) and 2 (nateglinide). In order to remain within the scope of a short report and ensure the focus remained on the effectiveness and safety outcomes of interest, it was necessary to identify study design criteria that would allow for the inclusion and evaluation of the most applicable and robust evidence within each of the bodies of evidence. The most salient study design criteria for this phase of the selection process were deemed to be study size and length of follow-up because the outcomes of interest are rare and detecting them requires long-term follow-up periods. The overall volume of available studies influenced the number of studies of sufficient size and duration for each key question; therefore, different cut-off points for study size and length of follow-up were selected for each key question. Minimum thresholds were lower for key questions 1 and 2 than for key question 3. Because of the disparities in the number of available comparative studies, observational studies were considered for inclusion for key question 1 and key question 2, but not for key question 3, if they demonstrated specified study characteristics. However, upon review, none of the screened observational studies met the predefined criteria. Consequently, the body of evidence for this report derives entirely from RCTs for all three key questions. Figure 1 presents the number of publications identified, screened, excluded, and included.

Following full-text review and the application of all inclusion and exclusion criteria, 28 RCTs (in 44 publications) and 0 observational studies were identified as eligible for this short report.

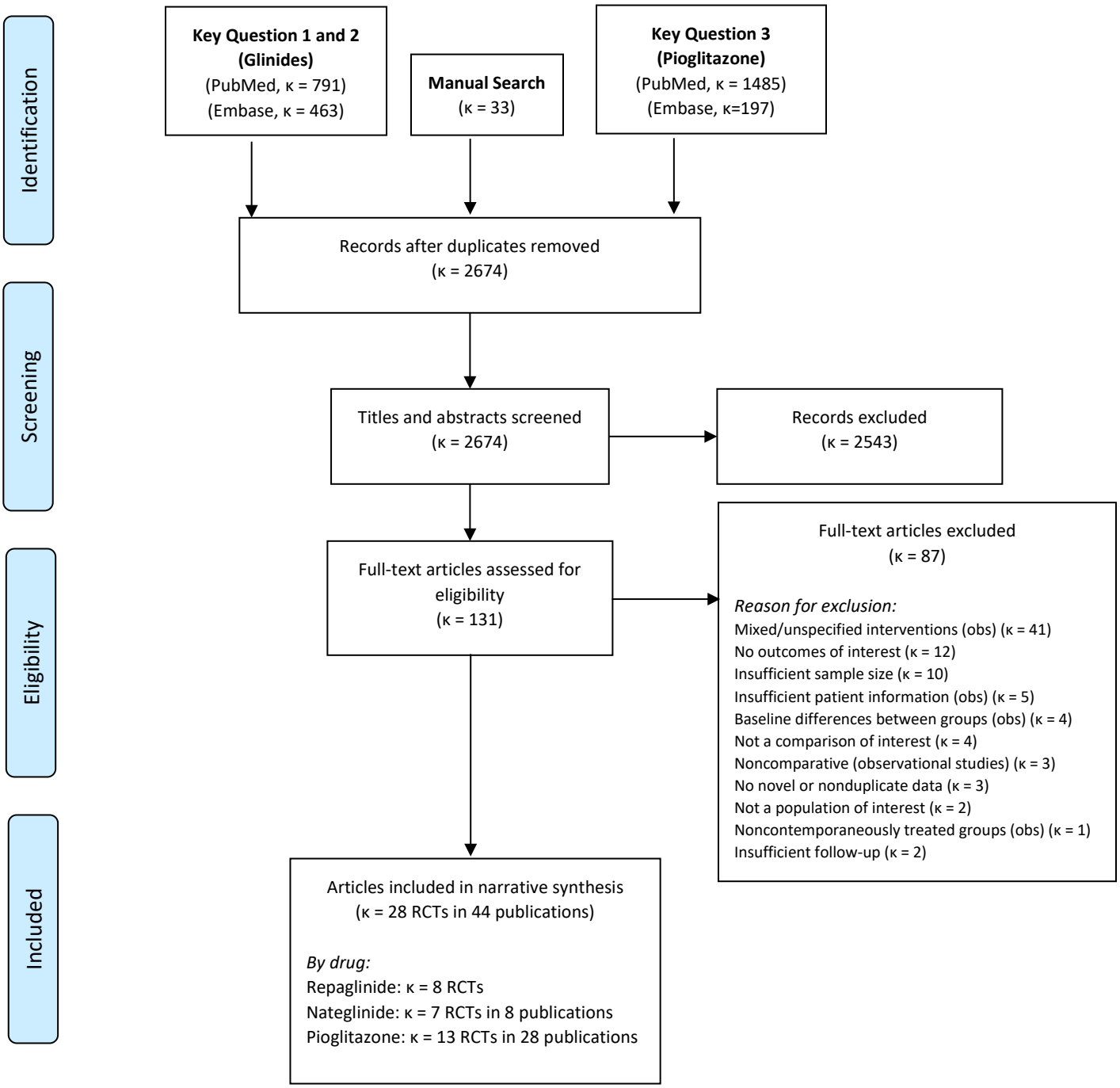
The evidence base for each drug is presented in the following text.

Key Question 1 (repaglinide): The body of included evidence for the use of repaglinide to treat T2DM comprised eight RCTs [36-43]. No observational studies meeting methodological standards were identified for inclusion. Sample sizes ranged from 100 to 576 patients, and follow-up was 1 year in all of the studies.

Key Question 2 (nateglinide): The body of included evidence for the use of nateglinide to treat T2DM comprised seven RCTs described in eight publications [44-51]. No observational studies meeting methodological standards were identified for inclusion. Sample sizes ranged from 78 to 701 patients, and the duration of follow-up ranged from 12 weeks to 104 weeks.

Key Question 3 (pioglitazone): The body of included evidence for the use of pioglitazone to treat T2DM comprised 13 RCTs [52-64]. Several companion publications were available for one of the included RCTs (the PROactive [PROspective pioglitAzone Clinical Trial In macroVascular Events] study) [55]. These included two longer-term follow-up publications [65 66] and 12 post hoc analysis publications [67-78]. Due to a large body of evidence from RCTs, observational studies were not considered for inclusion as evidence. Sample sizes ranged from 522 to 5238 patients, and follow-up ranged from 1 to 10.7 years.

Figure 1. Modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart of study selection [28]



Key: obs, observational studies; RCTs, randomised controlled trials

4.2 KEY QUESTION 1. WHAT IS THE COMPARATIVE EFFECTIVENESS AND SAFETY OF REPAGLINIDE, ALONE OR IN COMBINATION WITH METFORMIN, PIOGLITAZONE, OR INSULIN?

Evidence Base

The body of included evidence for repaglinide for treatment of T2DM comprised 8 RCTs (n = 100 to 576 patients, follow-up was one year in all studies) [36-43].

Study Characteristics

The following text presents a summary of study characteristics. For more information about each study, refer to Appendix Table 3 in Appendix IV.

Patient Characteristics: Across studies, patients were diagnosed with T2DM with mean HbA1c levels >6.5%. Males and females were enrolled at similar rates across studies, with some studies enrolling more males or more females. Mean ages ranged from 46 to 74 years across studies, with the majority of studies enrolling patients in their mid to late 50s or early 60s. All studies excluded patients with cardiovascular disorders or impaired liver or kidney function. With regard to treatment history, 6 studies enrolled patients with newly diagnosed T2DM or T2DM that was not currently treated with oral medications [36-40 42]. Two studies permitted prior use of oral anti-diabetic medications, though all non-study medications were discontinued for the duration of the study [41 43].

Treatment Characteristics: Across studies, patients received repaglinide as a monotherapy. Repaglinide doses varied across studies from 1.5 mg to 12 mg per day, typically divided into 2 or 3 doses before meals.

- Three studies had a maximum dose of 12 mg per day, provided in 3 doses of 4 mg each [39 41 43]
- Two studies had a maximum daily dose of 6 mg [40 42]
- One study provided a maximum dose of 4 mg per day [37]
- One study provided a maximum dose of 2.5 mg per day [38]
- One study did not report the maximum daily dose but started patients with 5 mg per day in 2 doses [36]

Comparison groups received the following treatments. Seven of the eight included studies compared repaglinide monotherapy with a sulfonylurea, and one compared repaglinide monotherapy with metformin. Specifically:

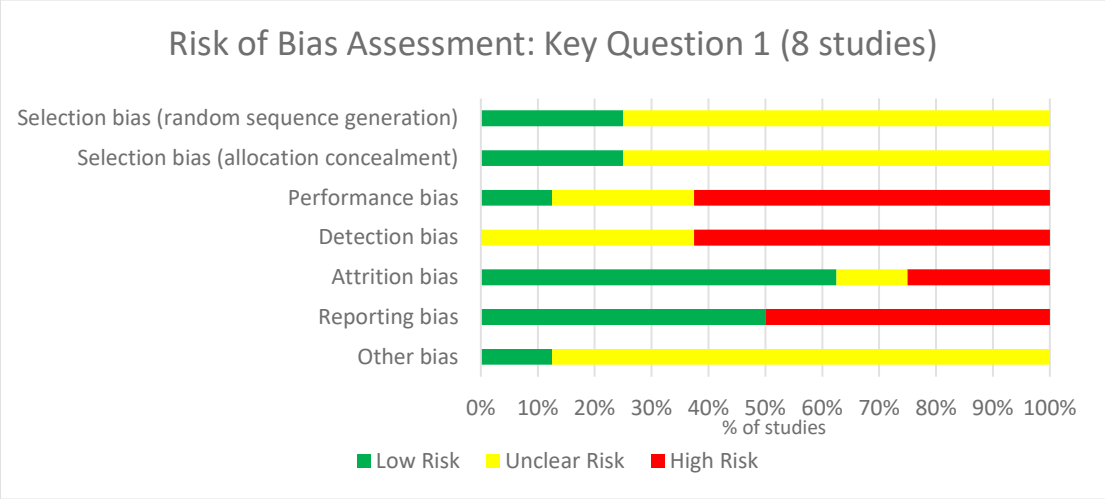
- Six studies provided glyburide monotherapy, most commonly with a maximum daily dose of 15 mg provided twice daily before meals (maximum dose range: 0 mg to 20 mg) [36 39-43]
- One study provided glimepiride monotherapy with a mean final dose of 3 mg per day [38]
- One study provided metformin monotherapy with a mean final dose of 1000 mg per day [37]

Study Quality and Risk of Bias Assessment:

The quality of the individual studies was fair or poor, based on an assessment of risk of bias and other quality issues. Appraisals of key types of common risks of biases across studies are depicted in Figure 2. For an itemised account of the risk of bias assessment for each study, refer to

Appendix Table 4 of Appendix IV. For summaries of study limitations and quality, refer to Appendix Table 3 of Appendix IV.

Figure 2. Risk of Bias Assessment for Studies Evaluating Repaglinide



Overview of Studies

Table 5 provides an overview of the characteristics and key outcomes of interest of the included studies. Unless otherwise specified, data for each outcome are reported as % of patients in the intervention group, % of patients in the comparison group. When provided in the publication, confidence intervals and other statistical analyses are also summarised. A narrative synthesis of the findings by outcome follows Table 5.

Table 5. Overview of Evidence Evaluating Repaglinide

Key: BMI, body mass index; Gly, glyburide; grp(s), group(s); Met, metformin; NR, not reported; NS, no statistically significant differences; pt(s), patient(s); Repa, repaglinide; Sulf, sulfonylurea; T2DM, type 2 diabetes; tx, treatment

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Mortality	Cardiovascular Events	Hypo-glycaemia	Blood Pressure	Weight Change	Other Adverse events
Marbury et al. (1999)[41] RCT 1 yr n = 576	**P:** T2DM **I:** Repa monotherapy **C:** Gly (Sulf) monotherapy	0.8% (3 pts), 0.5% (1 pt) No deaths were tx related.	5%, 2%	15%, 19%	No clinically significant changes in either grp, data NR.	0.22 kg loss, 0.05 gain; NS between grps	**Any tx-related adverse event:** 30%, 28% **Any serious adverse**

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Mortality	Cardiovascular Events	Hypo-glycaemia	Blood Pressure	Weight Change	Other Adverse events
Poor							**event:** 10%, 6% **Withdrawals for adverse events:** 10%, 10%
Wolffenbuttel et al. (1999) RCT 1 yr n = 425 Poor	**P:** T2DM **I:** Repa monotherapy **C:** Gly (Sulf) monotherapy	NR	Occurred at similar frequency between grps. Data NR.	9%, 9%	Both grps had small statistically significant decreases; NS between grps.	0 kg change, 0.7 kg gain; NS between grps	NR
Derosa et al. (2003)[38] RCT 1 yr n = 132 Fair	**P:** T2DM **I:** Repa monotherapy **C:** Glimepiride (Sulf) monotherapy	NR	NR	NR	No changes within grps or differences between grps.	0.1 kg gain, 0.5 kg loss; NS between grps	NR
Derosa et al. (2003)[37] RCT 1 yr n = 112 Poor	**P:** T2DM **I:** Repa monotherapy **C:** Met monotherapy	NR	NR	0%, 0%	No changes within grps or differences between grps.	0.4 kg loss (95% CI -0.8 to 0.28), 2 kg loss (95% CI -6 to 5); *p*=-0.14	No serious adverse events occurred in either grp.
Esposito et al. (2004)[39] RCT 1 yr n = 175 Fair	**P:** T2DM **I:** Repa monotherapy **C:** Gly (Sulf) monotherapy	NR	NR	9%, 13%	No changes within grps or differences between grps.	Mean BMI change, kg/m^2: 0.3, 0.4; NS between grps	NR

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Mortality	Cardiovascular Events	Hypo-glycaemia	Blood Pressure	Weight Change	Other Adverse events
Abbatecola et al. (2006)[36] RCT 1 yr n = 156 Poor	**P:** T2DM **I:** Repa monotherapy **C:** Gly (Sulf) monotherapy	NR	NR	NR	NR	Mean BMI: no difference within or between grps; data NR.	NR
Jibran et al. (2006)[40] RCT 1 yr n = 100 Poor	**P:** T2DM **I:** Repa monotherapy **C:** Gly (Sulf) monotherapy	NR	NR	None in either grp.	NR	Mean body weight change, kg: 0.2, -1.0. Difference was not statistically significant.	NR
Shah et al. (2011)[42] RCT 1 yr n = 200 Poor	**P:** T2DM **I:** Repa monotherapy **C:** Gly (Sulf) monotherapy	NR	NR	NS between grps. Data NR.	NR	Mean body weight change, kg: -1.8, 0.2. Difference was not statistically significant.	Adverse events: NS between grps; details and data NR.

Findings

Studies included in the body of evidence for repaglinide reported the following outcomes of interest: all-cause mortality, cardiovascular events, hypoglycaemia, blood pressure, and body weight changes. Follow-up was 1 year across studies. Evidence for all-cause mortality was derived from one study and was insufficient to evaluate. Evidence for macrovascular morbidity and adverse events was also limited, deriving from two to three studies. Overall, there is no evidence for treatment-related differences between repaglinide as a monotherapy and comparator groups (sulfonylurea or metformin) for clinical outcomes of interest. However, none of the studies of repaglinide were powered to detect differences in adverse event rates, and statistical analyses were not consistently reported.

Findings for each outcome are summarised below. For more detailed Evidence Tables and Strength of the Evidence (SOE) summary tables, refer to Appendix Table 3 and Appendix Table 5 of Appendix IV.

All-Cause Mortality (One study): One study (n = 576) reported that there were three deaths (0.8%) among patients receiving repaglinide monotherapy, and one death (0.5%) among patients receiving

glyburide monotherapy. No statistical analyses were performed, and none of the deaths were thought to be treatment related [41]. None of the remaining studies reported mortality rates. The evidence is insufficient to draw conclusions regarding any mortality-related outcomes for repaglinide. The strength of the evidence was downgraded due the paucity of studies reporting all-cause mortality, individual study limitations, and lack of statistical analyses.

Cardiovascular Events (Two studies): Two studies reported overall rates of cardiovascular events, without providing details on the nature or incidence of individual events. Among 576 patients, 5% of those receiving repaglinide, and 2% of those receiving glyburide had a cardiovascular event in the year following treatment. Statistical analyses were not performed [41]. In a second study (n = 424), authors report that the incidence of cardiovascular events was similar between groups without providing further details [43]. The strength of the evidence was downgraded to low due to a paucity of studies reporting the outcome, individual study limitations, and a lack of statistical analyses.

Adverse Events (any event, severe event, withdrawals) (Three studies): Three studies (n = 576, 200, and 112) reported outcomes related to the overall rates of adverse events. One study comparing repaglinide with glyburide among 576 patients reported that overall adverse event rates were 30% and 28%, serious adverse event rates were 6% and 10%, and withdrawals due to adverse events were 10% and 10%, respectively. Statistical analyses were not reported. [41]. One study reported that adverse events occurred at similar rates between repaglinide and glyburide groups, without providing additional details [42], and 1 study reported that no serious adverse events were reported for either repaglinide or metformin groups [37]. The strength of the evidence was downgraded to low due to individual study limitations and a lack of statistical analyses.

Hypoglycaemia (Six studies): Six studies (n = 576, 424, 200, 175, 112, and 100) reported the incidence of hypoglycaemia [37 39-43]. All studies evaluated patient-reported hypoglycaemic events, and patients were instructed to provide blood glucose measurements at the time of symptoms, if possible, though events were not clinically confirmed. Evidence does not suggest that rates differed by treatment types. Across studies, 0% to 15% of patients receiving repaglinide monotherapy experienced hypoglycaemia, compared with 0% to 19% of patients across comparator groups. Two studies reported that there were no statistically significant differences between the repaglinide and glyburide groups [39 42], and four studies did not report statistical comparisons between repaglinide versus glyburide [40 41 43] or metformin [37]. The body of evidence for hypoglycaemia was relatively large in size and fairly consistent across studies. The strength of the evidence was downgraded to moderate due to individual study limitations and lack of statistical analyses.

Blood Pressure (Five studies): Outcomes related to blood pressure were reported in five studies (n = 576, 434, 175, 132, and 112) [37-39 41 43]. There were no differences between groups across studies. Four studies reported that there were no changes in blood pressure following treatment for repaglinide or comparator groups, and one study reported small but statistically significant improvements for both repaglinide and glyburide groups [43]. Limited details were reported across studies. The body of evidence for blood pressure was relatively large in size and findings were consistent across studies. The strength of the evidence was downgraded to moderate due to individual study limitations and lack of statistical analyses.

Weight Change (Eight studies): All of the included studies reported changes in body weight [36-43]. Studies consistently reported that there were no statistically significant differences between treatment groups.

Across repaglinide groups, mean weight changes ranged from a 1.8 kg loss to a 0.3 kg gain. Across comparator groups, mean weight changes ranged from 2 kg loss to a 0.7 kg gain. The body of evidence for changes in body weight was large in size and findings were consistent across studies. The strength of the evidence was downgraded to moderate due to individual study limitations.

Findings from Systematic Reviews

Few relevant recent systematic reviews (published within the preceding 3 years) were identified that addressed the effectiveness and safety of repaglinide for patients with T2DM. Findings from identified systematic reviews and meta-analyses are summarised below.

HbA1c

A 2019 network meta-analysis of RCTs evaluated oral hypoglycaemic drugs as monotherapies in patients with T2DM. Authors report that repaglinide is associated with greater mean reductions in HbA1c compared with placebo (mean difference [MD] -1.61%; 95% CI -2.57% to -0.65%; p<0.0001) and metformin (MD 0.37%; 95% CI 0.11% to 0.62%), and similar mean reductions compared with sulfonylureas (MD -0.1% to 0.01%) [2].

An archived report from the Agency for Healthcare Research and Quality (AHRQ) published in 2011 evaluated meglitinides for treatment of T2DM, in addition to a variety of other anti-diabetic medications [3]. With regard to differences in HbA1c, evidence suggested that there were no between-group differences for meglitinides (repaglinide or nateglinide, without stratification) versus metformin, or between repaglinide versus sulfonylurea therapy (MD 0.1%; 95% CI -0.2 to 0.3%).

A 2019 systematic review and meta-analysis evaluated the short term (≤12 weeks) efficacy and safety of glimepiride (a sulfonylurea) versus repaglinide as add-ons to metformin [14]. None of the included studies met the inclusion criteria for the current report due to the abbreviated follow-up period. The authors report that compared with glimepiride, repaglinide was associated with no significant difference in HbA1c (MD -0.06; 95% CI -0.27 to 0.15).

Other Clinical Outcomes

In the 2011 AHRQ review, the majority of analyses for other clinical outcomes did not stratify by meglitinide type. Authors concluded that the evidence for mortality and cardiovascular morbidity outcomes is insufficient to draw conclusions. One analysis noted that changes in body weight throughout treatment were negligible and were similar between repaglinide and sulfonylurea groups (0.01 kg MD; 95% CI −1.0 kg to 1.0 kg). Overall conclusions are in line with those of the current report. Notably, the AHRQ review was updated in 2016, and the authors excluded analyses of meglitinides from the update due to their infrequent use in clinical practice in the US [79].

In the 2019 systematic review and meta-analysis of short-term outcomes for glimepiride plus metformin versus repaglinide plus metformin, there were no differences between groups for the risk of overall adverse events (odds ratio [OR] 0.55; 95% CI 0.26 to 1.16), or hypoglycaemia (OR 0.64; 95% CI 0.22 to 1.88). Intermediate outcomes were also reported, (e.g. HbA1c, as described above), and based on these outcomes the authors conclude that repaglinide plus metformin may have short-term benefits compared with glimepiride plus metformin [14].

In slight contrast to the findings of the current report, several outdated systematic reviews and meta-analyses (not summarised further) [80-82] were cited in a 2019 narrative review [83] suggesting that glinides are associated with weight gain. Full-text review of the cited systematic reviews and meta-analyses revealed that few glinides studies were analysed (two to four studies per systematic review), and analyses were not stratified by glinides type (i.e. findings from studies of nateglinide and repaglinide were analysed together). Although limited evidence suggested glinides were associated with weight gains, confidence intervals were large. These reviews conclude that sulfonylurea treatment is also associated with weight gain, which may explain the lack of weight differences between treatment groups in the current report, given that seven of eight studies compared repaglinide with sulfonylureas.

Evidence-based Conclusions

The evidence base addressing repaglinide for treatment of T2DM is composed of a small number of RCTs addressing each outcome. Findings from these studies with follow-up up to 1 year suggest that there are no treatment-related differences in hypoglycaemia, blood pressure, weight changes, cardiovascular morbidity, or adverse events related to repaglinide monotherapy versus comparators (sulfonylurea in seven of eight studies). Evidence for outcomes related to mortality was insufficient to draw conclusions. It is unlikely that the follow-up duration was sufficient to meaningfully inform all outcomes of interest, and none of the studies were explicitly designed or powered to evaluate the risk of adverse events. Although RCTs with smaller sample sizes and/or shorter follow-up periods were available and excluded from this report, these are unlikely to provide meaningful data that would change overall conclusions.

4.3 KEY QUESTION 2. WHAT IS THE COMPARATIVE EFFECTIVENESS AND SAFETY OF NATEGLINIDE, ALONE OR IN COMBINATION WITH METFORMIN OR PIOGLITAZONE?

Evidence Base

Seven RCTs described in eight publications addressing the use of nateglinide to treat T2DM were identified and are included in this report [44-51]. Sample sizes ranged from 78 patients to 701 patients, and follow-up ranged from 12 weeks to 104 weeks.

Study Characteristics

Patient characteristics and treatment characteristics were heterogeneous. The following text presents a summary of study characteristics. For more information about each study, refer to Appendix Table 6 in Appendix IV.

Patient Characteristics: All patients were diagnosed as having T2DM. Mean age was in the mid-late 50's or early 60's. Women comprised approximately a third to a half of each study's population. Mean HbA1c at the start of the studies varied from 6% to over 8%. The mean duration of diabetes prior to study enrollment ranged from less than 2 years to over 7 years. Some studies enrolled patients who were drug naïve, while others enrolled patients whose T2DM was not adequately managed with metformin monotherapy. The studies that enrolled drug-naïve patients typically had populations with lower HbA1c and a shorter duration of T2DM [44-46 48 51].

Treatment Characteristics: A variety of treatment protocols and comparators were employed across studies. With the exception of two studies that included a comparison of nateglinide alone versus placebo alone [46 51], no other studies administered nateglinide in the same way, nor made the same

comparisons.

Studies evaluated nateglinide provided as a monotherapy or in combination with metformin. Doses of nateglinide and administration schedules varied. Schedules included:

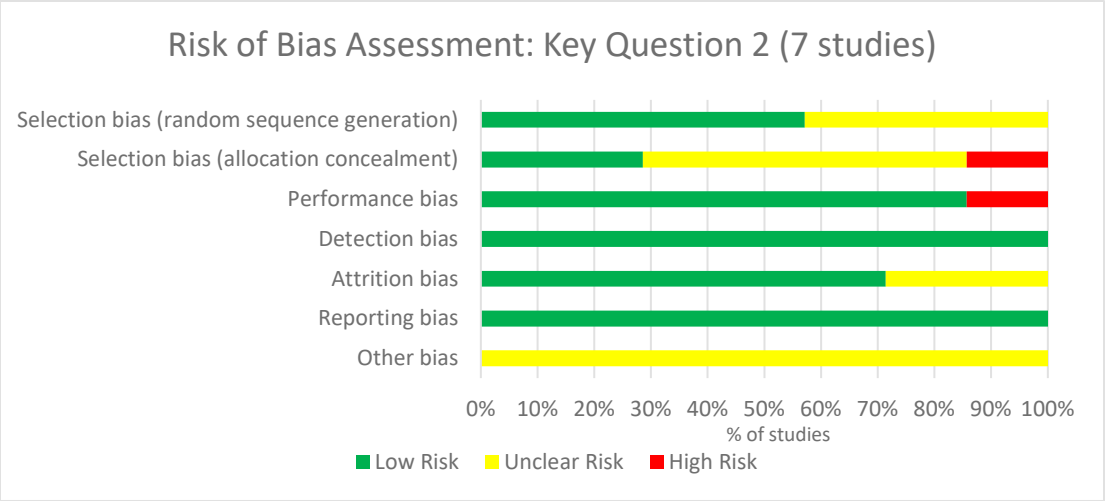
- 60 mg 3 times/day, titrated to maximum 240 mg/day total [49 50]
- 60 mg *or* 120 mg 3 times daily, plus 1000 mg metformin twice daily [47]
- 90 mg 3 times/day [48]
- 120 mg 3 times/day alone [46 51]
- 120 mg 3 times/day with metformin 500 mg 3 times/day [46]
- 120 mg 3 times/day with metformin 500 mg 4 times/day [45]
- 180 mg/day titrated to 300±60 mg/day, plus 1500 mg/day metformin titrated to mean 2500±500 mg/day[44]

Comparisons also varied. Active comparators included metformin alone or in combination with a sulfonylurea. Placebo and no treatment-controlled studies were also included. Comparators included:

- Metformin alone [46]
- Metformin with placebo [47]
- Metformin plus glyburide [45]
- Metformin plus gliclazide [49 50]
- Metformin plus glibenclamide[44]
- Placebo [46 51]
- No treatment [48]

Study Quality and Risk of Bias Assessment: The quality of the individual studies was fair or good based on an assessment of risk of bias and other quality issues. Appraisals of key types of common biases across individual studies are depicted in Figure 3. For an itemised account of the risk of bias assessment for each study, refer to Appendix Table 7 of Appendix IV. For summaries of individual study limitations and quality, refer to Appendix Table 6 of Appendix IV.

Figure 3. Risk of Bias Assessment for Studies Evaluating Nateglinde



Overview of Studies

Table 6 provides an overview of the included studies, including the patients, interventions, and comparators, and the key outcomes of interest reported in those studies. Additional outcomes reported by the studies are presented in

Table 7. We present these as additional reported outcomes, the majority of which were adverse events reported by one study, or by two studies in inconsistent ways, thus providing an insufficient amount of evidence to enable synthesis across studies or to support an evidence-based conclusion (due to insufficient quantity of evidence and lack of demonstration of establishment of consistency). In addition, total proportion of patients reporting at least one adverse event are included. These data are provided but not further analysed due to the lack of association between the drug and most events and possible variation among studies in methods of collecting this outcome (suggested by considerable variability in data among studies); however, the proportion of patients who discontinued treatment due to adverse events is analysed. Other outcomes of interest for this short report, as listed in the PICO statement, were not presented in these studies; therefore, there was insufficient evidence available to evaluate those outcomes.

Table **6** and

Table **7** provide summaries only. For full study extraction, refer to Appendix Table 6 of Appendix IV.

Table 6. Overview of Evidence Evaluating Nateglinide

Key: AE(s), adverse event(s); BL, baseline; Gli, gliclazide; Glib, glibenclamide; Gly, glyburide; grp, group; MD, mean difference; Met; metformin; Nat, nateglinide; NR, not reported; NS, not statistically significantly different; PBO, placebo; RCT, randomised controlled trial; SD, standard deviation; T2DM, type 2 diabetes mellitus; tx, treatment

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Mortality (all-cause)	Confirmed Hypoglycaemia	Weight Change	Discontinuation Due to Adverse Events
Horton et al. (2000)[46] RCT 24 wks n = 701 Fair	**P:** T2DM, drug naïve **I:** Nat + Met **C:** Met; PBO	Met: n=1	Nat n=3 (1.7%) Nat + Met n=5 (2.9%) Met n=1 (0.5%) PBO n=0 (0%) *p* values NR	Authors note "no significant changes" from BL for any grp, data NR	Nat n=5 (2.7%) Nat + Met n=16 (9.3%) Met n=12 (6.7%) PBO n=9 (5.2%) *p* values NR
Marre et al. (2002)[47] RCT 24 wks n = 467 Good	**P:** T2DM, Met-resistant **I:** Nat 60 mg + Met, Nat 120 mg + Met **C:** PBO + Met	Nate: n=2	Nat 60 mg n=0 (0%) Nat 120 mg n=5 (3.1%) PBO n=1 (0.7%) *p* values NR	Nat 120 mg vs. PBO: MD 0.9 (95% CI 0.0 to 1.4), *p*>0.05 Nat 60 mg vs. PBO: MD 0.3 (95% CI -0.2 to 0.8), *p*=NS	Nat 60 mg n=8 (5%) Nat 120 mg n=6 (3.9%) PBO n=5 (3.2%) *p* values NR
Gerich et al. (2005)[45] RCT 104 wks n = 428 Fair	**P:** T2DM, drug naïve **I:** Nat + Met **C:** Gly + Met	n=1/grp	Nat + Met 8.2% Gly + Met 17.7% *p*=0.003	Nat + Met -0.4±0.4 kg Gly + Met+0.8±0.5 kg *p*=0.01	NR
Ristic et al. (2006)[50]**; Ristic et al. (2007)**[49] RCT 24 wks (2006) 52 wks (2007) n = 262 Good	**P:** T2DM, Met-resistant **I:** Nat + Met **C:** Gli + Met	n=0/grp	24 wks: Nat + Met n=28 (21.5%) Gli + Met: n=28 (22.2%) *p*=NR 52 wks: Nat + Met n=17 (15.2%) Gli + Met: n=15 (14.9%) *p*=NR	52 wks: Gli + Met: 0.91 kg mean increase from BL (*p*=0.009) Nat+Met: 0.42 kg mean change increase (*p*=0.201)	52 wks: Nat + Met n=1 (0.8%) Gli + Met n=2 (1.6%), *p*=NR
Mita et al.	**P:** T2DM, drug	NR	0/grp	NR	Nat n=1 (2.6%)

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Mortality (all-cause)	Confirmed Hypoglycaemia	Weight Change	Discontinuation Due to Adverse Events
(2007)[48] RCT 52 wks n = 78 Fair	naïve **I:** Nat **C:** No tx				No tx n=2 (5%) *p* values NR
Gonzalez-Clemente and the Spanish Nateglinide Study Group (2008) [51]	**P:** T2DM, drug naïve **I:** Nat **C:** PBO	NR	None in either grp	*p*=0.737 for change from BL between grps	Nat n=1 (1.8%) PBO n=1 (1.9%), *p*=NR
Derosa et al. (2009)[44] RCT 52 wks n = 248 Good	**P:** T2DM, drug naïve **I:** Nat + Met **C:** Glib + Met	NR	NR	BMI at BL, 6 mos, 12 mos, mean kg/m^2±SD: Nat + Met: 26.4±1.4, 26.6±1.3, 26.8±1.6 Glib + Met: 26.5±1.5, 26.7±1.6, 26.9±1.7 *p* value of comparison NR but both NS vs. BL	NR

Table 7. Overview of Additional Outcomes Reported for Nateglinide (Insufficient for Synthesis)

Key: AE(s), adverse event(s); BL, baseline; btwn, between; Gli, gliclazide; Glib, glibenclamide; Gly, glyburide; grp(s), group(s); Met; metformin; mm Hg, millimeter of mercury; Nat, nateglinide; NR, not reported; PBO, placebo; RCT, randomised controlled trial; SD, standard deviation; tx, treatment; URI, upper respiratory infection

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Other Outcomes of Interest (insufficient for synthesis)
Horton et al. (2000)[46] RCT 24 wks n = 701	**P:** T2DM, drug naïve **I:** Nat; Nat + Met **C:** Met; PBO	*ECG abnormalities*: Nat+Met: n=1 PBO: n=1 *p*=NR *Diarrhoea*: Met 19.7% Nat + Met 14.5% Data NR for other tx grps

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Other Outcomes of Interest (insufficient for synthesis)
Fair		*p* values NR *Any AE*: Nat 77.7% Nat + Met 83.1% Met 79.2% PBO 68.6% *p* values NR Other AEs reported as similar between grps (data NR): URI, headache, abdominal pain, nausea, fatigue, sinusitis
Marre et al. (2002)[47] RCT 24 wks n = 467 Good	**P:** T2DM, Met-resistant **I:** Nat 60 mg + Met; Nat 120 mg + Met **C:** PBO+Met	Data reported as Nat 60 mg + Met; Nat 120 mg + MET, PBO + Met: Diarrhoea: 5.6%, 7.9%, 5.8% URI: 8.1%, 4.6%, 9.7% Any AE: 54.6%, 60.0%, 58.8% *p* values NR for all outcomes
Gerich et al. (2005)[45] RCT 104 wks n = 428 Fair	**P:** T2DM, initial drug tx **I:** Nat + Met **C:** Gly + Met	Data reported for Nat + Met, Gly + Met: Hypertension: 8.7%, 14.8% Influenza: 12.3%, 10.0% Headache: 16.4%, 17.7% Arthralgia: 10.5%, 10.5% Any AE: 91.8, 90.9% *p* values NR for all
Ristic et al. (2006)[50]; Ristic et al. (2007)[49] RCT 24 wks (2006) 52 wks (2007) n = 262 Good	**P:** T2DM, Met-resistant **I:** Nat + Met **C:** Gli + Met	At 24 wks: the authors stated that no clinically relevant difference for any AE between tx grps was observed; full data NR
Mita et al. (2007)[48] RCT 52 wks	**P:** T2DM, drug naïve **I:** Nat **C:** No tx	Mild liver dysfunction: Nat: n=1 No tx: n=0 The authors note no changes in metabolic parameters (other than HabA1c and triglycerides) were observed.

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Other Outcomes of Interest (insufficient for synthesis)
n = 78 Fair		
Gonzalez-Clemente and the Spanish Nateglinide Study Group (2008) [51 84]	**P:** T2DM, drug naïve **I:** Nat **C:** PBO	Blood pressure, mean±SD mm Hg (Nat, PBO): Systolic: 125.3±15.4, 129.3±18.7, *p*=0.015 btwn grps *p*=0.007 for change from BL btwn grps Diastolic: 75.3±10.4, 75.0±9.7, *p*=0.921 btwn grps *p*=0.561 change from BL btwn grps
Derosa et al. (2009)[44] RCT 52 wks n = 248 Good	**P:** T2DM, drug naïve **I:** Nat + Met **C:** Glib + Met	Blood pressure, systolic (BL, 6 mos, 12 mos), mean±SD mm Hg: Nat+Met: 136.8±4.4, 135.3±4.0, 134.5±3.6 Glib+Met: 137.4±4.6, 136.2±4.3, 135.4±3.8 Blood pressure, diastolic (BL, 6 mos, 12 mos), mean±SD: Nat + Met: 87.3±3.8, 86.1±3.5, 85.4±3.4 Glib + Met: 88.1±3.5, 88.3±3.6, 86.8±3.5 Neither grp had statistically significant changes from BL. Outcomes between grps were not directly compared by study authors but appear similar.

Findings

Findings are organised by outcome and type of comparator in the following text and summarised below. For a more detailed account of the considerations used to determine the strength of evidence for each outcome using the GRADE methodology, refer to Appendix Table 8 of Appendix IV.

Mortality (Four studies): There is no evidence suggesting that nateglinide is associated with an increased risk of all-cause mortality, though studies are limited in size and follow-up duration and are unlikely to accurately inform this outcome.

Although each study made a different comparison, rates of all-cause mortality were low, and when RCTs are considered collectively, did not appear to vary by study group assignment. Studies typically reported no more than 1 or 2 deaths each, and none compared the incidence of mortality between groups. This is presumably because the incidence was low and studies were not statistically powered to detect rare events (and therefore imprecise). Due to the imprecision and individual study limitations, the strength of evidence was rated as low.

Horton et al. (2000) reported 1 death in the metformin group (n=178), due to arteriosclerotic and hypertensive heart disease, and no deaths among patients taking nateglinide during the study's 24-week follow-up.

Marre et al. (2002) reported 1 death among 120 patients receiving 120 mg nateglinide plus metformin, and 1 death among 155 patients receiving 60 mg nateglinide plus metformin during their 24-week study. The authors noted 1 death was sudden death and 1 was due to cardiac arrest, and neither were thought to be due to nateglinide. No deaths occurred in the group of 152 patients receiving placebo plus metformin.

Gerich et al. (2005) reported 1 death among 208 patients treated with nateglinide plus metformin and 1 death among 198 patients treated with glyburide plus metformin. Further information about the deaths was not reported. Patients were followed for 104 weeks.

Ristic et al. (2006) and Ristic et al. (2007) reported no deaths occurred by the 24-week or 52-week follow-up, respectively, among patients treated with nateglinide plus metformin (n=133) or gliclazide plus metformin (n=129).

Hypoglycaemia (Six studies)

To ensure accuracy and scientific rigor, confirmed hypoglycaemia was the primary hypoglycaemia outcome in this analysis. Four studies defined confirmed hypoglycaemia as blood glucose ≤3.3 mmol/L[45-47 51], 1 defined it as ≤4.0 mmol/L [49 50], and 1 did not provide a definition [48]. Other accounts of hypoglycaemia (e.g. symptoms suggestive of hypoglycaemia) are provided in Appendix Table 6 of Appendix IV, but excluded from the main analysis due to subjectivity and related risk of bias.

In 3 studies comparing nateglinide with placebo or no treatment, confirmed events of hypoglycaemia were rare. One study reported no events, whereas the other study reported slightly increased rates in the nateglinide and nateglinide plus metformin groups compared with no events in the placebo group. Statistical analyses of the differences were not performed. Lack of analyses along with individual study limitations and inconsistency led to a 'very low' strength of the evidence rating for this outcome.

- Horton et al. (2000) reported 1.7% (3/179) of patients treated with nateglinide and 2.9% (5/172) patients treated with nateglinide plus metformin had confirmed hypoglycaemia, and none in the placebo group (n=172) did.
- Mita et al. (2007) reported no hypoglycaemic events in either a nateglinide or no-treatment comparison group in their small study (n=78 total).
- Similarly, Gonzales-Clemente (2008) reported no cases of hypoglycaemia in either nateglinide or placebo groups (n=109 total).

Among studies with active comparators, the frequency of confirmed events of hypoglycaemia varied, but only 1 RCT made each comparison. Therefore, consistency could not be established. Because of imprecision due to the infrequency of confirmed events and individual study limitations, the strength of evidence for this outcome is rated as 'very low.'

- Horton et al. (2000) reported 1.7% (3/179) of patients treated with nateglinide and 2.9% (5/172) patients treated with nateglinide plus metformin had confirmed hypoglycaemia, and 0.5% (1/178) in the metformin-only group had confirmed hypoglycaemia.
- Marre et al. (2002) reported none of 155 patients treated with 60 mg nateglinide plus metformin had confirmed hypoglycaemic events, while 3.1% (5/160) of patients treated with 120 mg nateglinide plus metformin and 0.7% (1/152) patients treated with placebo plus metformin had confirmed hypoglycaemic events.
- Gerich et al. (2005) reported 8.2% of 208 patients treated with nateglinide plus metformin had a confirmed episode of hypoglycaemia, and 17.7% of 198 patients treated with glyburide plus metformin had a confirmed episode.
- Ristic et al. (2006) reported 21.5% (28/133) patients treated with nateglinide plus metformin and 22.2% (28/129) patients treated with gliclazide plus metformin had at least 1 confirmed hypoglycaemia event during 24 weeks follow-up. Ristic et al. (2007) reported between 24 and 52 weeks, 15.2% of patients receiving nateglinide and 14.9% of patients receiving gliclazide had 1 or more confirmed hypoglycaemic event.

Weight Change (Six studies): Nateglinide does not appear to be associated with greater weight change than comparators. Weight changes compared with controls were either statistically nonsignificant [46 51] or unlikely to be clinically important (mean difference in change of <1.5 kg) (3 RCTs) versus comparators. Due to the general consistency, findings from studies with different comparators were considered collectively. The strength of evidence was downgraded due to individual study limitations to 'moderate.'

Horton et al. (2000) reported there were "no significant changes" in weight from baseline to 24 weeks follow-up in any study group. Data were not reported.

Gonzales-Clemente reported that there were no significant differences in changes in weight from baseline between nateglinide versus placebo groups (p=0.737). Changes from baseline were negligible for both groups [51].

Marre et al. (2002) reported a mean (standard error of the mean [SEM]) kg weight change from baseline to 24 weeks follow-up of 0.1±0.2 in the 60 mg nateglinide plus metformin group, 0.4±0.2 in the 120 mg nateglinide plus metformin group, and 1.0±0.2 in the placebo plus metformin group. The mean difference for the 120 mg nateglinide group was statistically significantly higher, but at less than 1 kg difference unlikely to be clinically important (mean difference 0.9 [95% CI 0.0 to 1.4]; p>0.05). The difference between the 60 mg nateglinide plus metformin and placebo plus metformin groups were not statistically significantly different (mean difference 0.3 [95% CI -0.2 to 0.8]).

Gerich et al. (2005) reported a mean (SD) body weight change from baseline to 104 weeks of -0.4±0.4 kg in the nateglinide plus metformin group and +0.8±0.5 kg in the glyburide plus metformin group. While statistically significantly different (p=0.01), the mean difference of 1.2 kg may not be clinically important.

Ristic et al. (2007) reported at 52 weeks follow-up a 0.91 kg mean increase from baseline in the gliclazide plus metformin group (p=0.009), and no significant change from baseline in nateglinide plus metformin group (0.42 kg mean change; p=0.201). The difference between groups of less than half a kilogram is unlikely to be clinically important.

Derosa et al. (2009) reported no significant change in body mass index (BMI) from baseline to 12 months in either the nateglinide plus metformin group or glibenclamide plus metformin group. The mean (SD) BMI in the nateglinide plus metformin was 26.4±1.4 at baseline, 26.6±1.3 at 6 months, and 26.8±1.6 at 12 months follow-up. The mean (SD) BMI in the glibenclamide plus metformin was 26.5±1.5 at baseline, 26.7±1.6 at 6 months, and 26.9±1.7 at 12 months. Outcomes were not directly compared by study authors but appear similar.

Withdrawal Due to Adverse Events (Four studies): Nateglinide does not appear to lead to a higher incidence of treatment discontinuation compared with placebo [46 51] or no treatment [48]. However, the strength of evidence for this finding is downgraded to low due to individual study limitations and lack of precision due to the infrequency of discontinuation. Horton et al. (2002) reported the percentage of patients in each group that discontinued participation in the study due to adverse events was 2.7% (5/179) in the nateglinide group, 9.3% (16/172) in the nateglinide plus metformin group, 6.7% (12/178) in the metformin-only group, and 5.2% (9/172) in the placebo group. Of those, the events prompting discontinuation that were considered by investigators prior to unmasking to be definitely, probably, or possibly related to treatment were 20% (1/5); 38% (6/16), 50% (6/12), and 33% (3/9), respectively. Gonzales-Clemente et al. reported that one patient in the nateglinide group (1.8%) and one in the

placebo group (1.9%) discontinued due to adverse events, which were headache and pruritus [51]. Mita et al. (2007) reported 2.6% (1/38) of patients taking nateglinide and 5% (2/40) of the no-treatment control group discontinued participation in the study due to adverse events.

Whether nateglinide has a different incidence of adverse events than active controls is unclear due to lack of power among the studies, diverse comparisons, and inconsistent findings. The strength of evidence was therefore rated as 'very low.' Nateglinide appears to be associated with a lower incidence of discontinuation due to adverse events than metformin in one study [46] but is unclear in another [47] due to lack of statistical power to detect differences between groups in rare events. Also due to the rarity of discontinuations, it is unclear whether it has a similar rate of discontinuation or a similar rate as gliclazide [49 50]. Findings from Horton et al. (2000) are reported above. Marre et al. (2002) reported discontinuation due to adverse events for 5% (8/160) of patients on 60 mg nateglinide plus metformin, 3.9% (6/160) of patients on 120 mg nateglinide plus metformin, and 3.2% (5/155) of patients on metformin with placebo. Ristic et al. (2007) reported that at 52-week follow-up, 0.8% (1/133) of the nateglinide plus metformin and 1.6% (2/129) of the gliclazide plus metformin patients discontinued due to adverse events.

Findings from Systematic Reviews

Few relevant recent systematic reviews (published within the preceding 3 years) were identified that evaluated the effectiveness and safety of nateglinide for T2DM. Findings from identified systematic reviews and meta-analyses are summarised below.

HbA1c

A 2019 network meta-analysis of RCTs evaluated oral hypoglycaemic drugs as monotherapies in patients with T2DM. Authors report that nateglinide was associated with significantly greater reductions in HbA1c versus placebo (mean difference -0.51% [95% CI -0.90 to -0.12%]; $p<0.0001$). Analyses were not presented for other comparators [2].

An archived report from the Agency for Healthcare Research and Quality (AHRQ) published in 2011 evaluated meglitinides for treatment of T2DM, in addition to a variety of other anti-diabetic medications[3]. With regard to HbA1c, evidence from three RCTs favored nateglinide plus metformin over metformin alone (range of between-group differences -0.5% to -1.08%). Pooled quantitative analyses were not performed. Evidence was conflicting regarding the combination of nateglinide plus metformin versus sulfonylurea plus metformin, with one study favoring the nateglinide combination and one reporting no differences between groups. Pooled quantitative analyses were not performed.

Other Clinical Outcomes

In the 2011 AHRQ review, the majority of analyses for other clinical outcomes did not stratify by meglitinide type. Authors conclude that the evidence for mortality and cardiovascular morbidity outcomes is insufficient to draw conclusions. None of the analyses were specific to nateglinide. Notably, the AHRQ review was updated in 2016, and the authors noted that studies of meglitinides were excluded due to their infrequent use in clinical practice in the U.S. [79].

Several outdated systematic reviews and meta-analyses [80-82] were cited in a 2019 narrative review [83] suggesting that glinides are associated with weight gain. The cited systematic reviews and meta-analyses

contained few glinides studies (two to four studies each), and although limited evidence suggested glinides were associated with weight gains, confidence intervals were large and data were not stratified by glinides type (i.e. findings for nateglinide and repaglinide were lumped). These publications are not summarised further.

Evidence-based Conclusions

The evidence base addressing nateglinide to treat T2DM is composed of a small number of RCTs addressing each outcome, with heterogeneous patient populations, treatment protocols, and comparators. Based on studies without sufficient long-term follow-up, there is no evidence that nateglinide administered with or without metformin is associated with increased incidence of mortality, episodes of confirmed hypoglycaemia, study drop-out because of adverse events, or substantive changes in weight compared with controls considered collectively. However, in addition to individual study limitations (i.e. risk of bias or internal validity), the overall strength of evidence was generally reduced by imprecision (particularly for rare outcomes) and inconsistency that could not be explained due to the large number of variables that differed in each study, the small total number of studies addressing nateglinide in general and addressing each outcome, and limited long-term follow-up, which is likely not sufficient to meaningfully inform outcomes of interest. Due to the small number of studies for each comparison, potential causes of inconsistency cannot be investigated in a meaningful way.

4.4 Key Question 3. What is the comparative effectiveness and safety of pioglitazone, alone or in combination with metformin, sulfonylureas, or insulin?

Evidence Base

The body of included evidence for pioglitazone for treatment of T2DM comprised 13 RCTs (n = 522 to 5238 patients, and follow-up 1 to 10.7 years) [52-64], 2 longer-term follow-up publications [65 66], and 12 publications of post hoc analyses are also included [67-78].

Study Characteristics

The following text presents a summary of study characteristics. For more information about each study, refer to Appendix Table 9 in Appendix IV.

Patient Characteristics: Across studies, patients were diagnosed with T2DM. The majority of studies enrolled patients with mean HbA1c levels >6.5%, though 1 study enrolled patients with well-controlled T2DM and HbA1c levels around 6% at baseline[52]. Males were enrolled at a higher rate than females in all studies and mean ages ranged from 54 to 69 years. Four studies enrolled patients with risk factors for macrovascular events [52 55 60 64].

With regard to patients' treatment history:

- Two studies limited enrollment to patients who had not received prior glucose-lowering medications (i.e. drug naïve patients)[54 61]
- Four studies enrolled patients with inadequate glycaemic control despite ongoing treatment

with metformin[53 57 59 63]

- One study enrolled patients with inadequate glycaemic control despite ongoing treatment with a sulfonylurea[61]
- Six studies enrolled patients regardless of prior and ongoing treatment regimens[52 55 58 60 62 64]

Treatment Characteristics:

Across studies, patients received oral pioglitazone at doses of 15, 30, or 45 mg once per day, with variations depending on a patient's individual maximum tolerated dose.

Intervention groups received the following pioglitazone-based treatments:

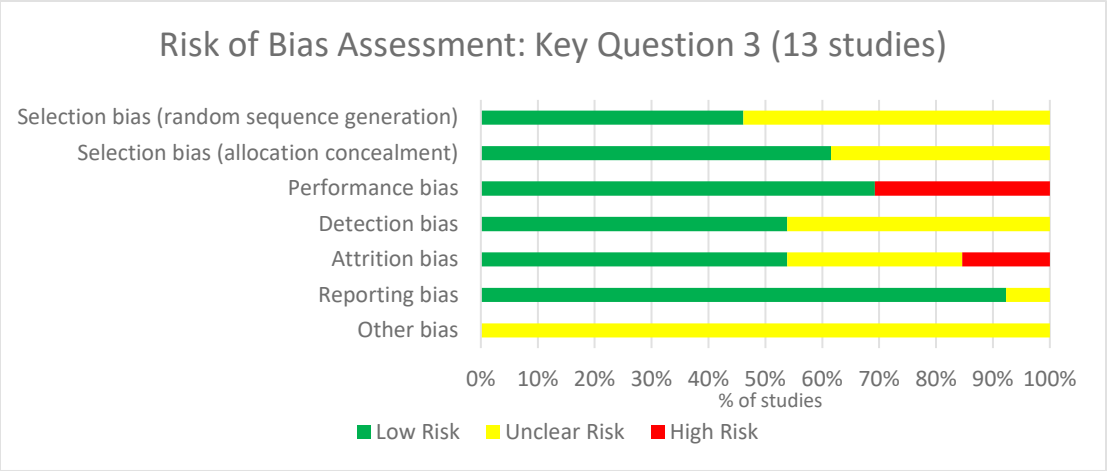
- Pioglitazone alone, without concomitant treatments [54 61]
- Pioglitazone as an add-on to metformin [53 59 63]
- Pioglitazone as an add-on to a sulfonylurea [56]
- Pioglitazone as an add-on to a sulfonylurea and metformin [57]
- Pioglitazone as an add-on to a mix of ongoing medications across the enrolled patient population [52 55 58 60 62 64]

Comparison groups received the following treatments:

- No pioglitazone (a mix of medications other than pioglitazone), with or without placebo [52 55 58 64]
- A sulfonylurea as an add-on to metformin [57 59 63]
- A sulfonylurea as an add-on to a mix of other ongoing medications [60 62]
- Metformin as an add-on to a sulfonylurea [56]
- Metformin alone [61]
- A sulfonylurea alone [54]
- Vildagliptin as an add-on to metformin [53]

Study Quality and Risk of Bias Assessment: Based on an assessment of risk of bias and other quality issues, 12 of the individual studies were of good or fair quality, and 1 was of poor quality [62].Appraisals of key types of common biases across individual studies are depicted in Figure 4. For an itemised account of the risk of bias assessment for each study, refer to Appendix Table 10 of Appendix IV. For summaries of study limitations and quality, refer to Appendix Table 9 of Appendix IV.

Figure 4. Risk of Bias Assessment for Studies Evaluating Pioglitazone



Overview of Studies

Table 8 provides an overview of the included studies, including the patients, interventions, and comparators, and the key outcomes of interest. Adverse event outcomes reported by the studies are presented in Table 9. Unless otherwise specified, data for each outcome in Table 8 and Table 9 are reported as percentage of patients with the outcome in the intervention group and percentage of patients with the outcome in the comparison group. When provided in the publication, confidence intervals and other statistical analyses are also summarised. A narrative synthesis of the findings by outcome follows Table 9.

Table 8. Overview of Key Evidence Evaluating Pioglitazone

Key: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; Gli, gliclazide; Glib, glibenclamide; Glim, glimepiride; Gly, glyburide; HR, hazard ratio; Met, metformin; MI, myocardial infarction; NR, not reported; NS, not statistically significant; PBO, placebo; PCI, percutaneous coronary intervention; Pio, pioglitazone; pt(s), patient(s); RCT, randomised controlled trial; Sulf, sulfonylurea(s); T2DM, type 2 diabetes mellitus; tx, treatment

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Composite Outcomes	All-Cause Mortality	Cardiovascular Events	Stroke
Hanefeld et al. (2004) [56]; Charbonnel et al. (2005)[65] RCT 1 and 2 yrs n = 639 Fair	**P:** Pts w/ T2DM inadequately controlled w/ Sulf **I:** Pio as an add-on to Sulf **C:** Met as an add-on to Sulf	**NR**	**Deaths** 0.003% (1 pt), 0.006% (2 pts); *p* value NR Not tx related	**CV disorders** 1 yr: 3.1%, 4.1%; *p* value NR **Heart failure** 2 yrs: 0.6%, 0.9%; *p* value NR	**NR**
Schernthaner et al. (2004)[61] RCT 1 yr n = 1199 Good	**P:** Pts w/ T2DM and no prior glucose lowering medications **I:** Pio **C:** Met	**NR**	**Deaths** 0.5% (3 pts), 0.3% (2 pts); *p* value NR None tx related	**CV events** 3.7%, 3.9%; *p* value NR	NR
Charbonnel et al. (2005)[54] RCT 1 yr n = 1270 Fair	**P:** Pts w/ T2DM and no prior glycaemic control medications **I:** Pio **C:** Gli (Sulf)	NR	NR	NR	NR
Dormandy et al. (2005)[55†] RCT 2.8 yrs n = 5238 Good	**P:** Pts w/ T2DM and increased risk of macrovascular events **I:** Pio + existing medications **C:** PBO + existing medications	**Primary composite endpoint** *(all-cause mortality; nonfatal MI, including silent MI, stroke, ACS, coronary or endovascular intervention,*	**All-cause death** 6.8%, 7.1% HR 0.96 (95% CI 0.78-1.18) **CV deaths** 4.9%, 5.2%; *p* value NR **Non-CV deaths** 1.9%, 1.9%; *p* value NR	**Nonfatal MI (including silent MI)** 4.6%, 5.5% HR 0.83 (95% CI 0.65-1.06) **ACS** 2.1%, 2.7% HR 0.78 (95% CI 0.55-1.11)	**Stroke** 3.3%, 4.1% HR 0.81 (95% CI 0.61-1.07) **Transient ischemic attack** 1%, 2%; *p*=0.587

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Composite Outcomes	All-Cause Mortality	Cardiovascular Events	Stroke
		amputation above the ankle) HR 0.9 (95% CI 0.80-1.02); *p*=0.095 **Secondary composite endpoint** (*all-cause death; MI, excluding silent MI, or stroke)* HR 0.84 (95% CI 0.72-0.98) *p*=0.027		**Coronary revascularisation** 6.5%, 7.3% HR 0.88 (95% CI 0.72-1.08) **Leg revascularisation** 3.1%, 2.5% HR 1.25 (95% CI 0.90-1.73) **Heart failure** 11%, 8%; *p*<0.0001 favoring PBO **Fatal heart failure** 1%, 1%; *p*=0.634 **Angina pectoris** 3%, 5%; *p*=0.025 favoring Pio **Atrial fibrillation** 2%, 2%; *p*=0.374	
Matthews et al. (2005)[59]; Charbonnel et al. (2005)[65] RCT 1 and 2 yrs n = 630 Fair	**P:** Pts w/ T2DM inadequately controlled by Met **I:** Pio as an add-on to Met **C:** Gli (Sulf) as an add-on to Met	**NR**	**Deaths** 1 yr: 0%, 0.6%; *p* value NR None tx related	**Heart failure** 2 yrs: 1.6%, 0.6%; *p* value NR	**NR**
Nissen et al. (2008)[60] RCT 1.5 yrs n = 547 Fair	**P:** Pts w/ T2DM and coronary artery disease **I:** Pio + existing medications **C:** Glim (Sulf) + existing medications	**Composite 1** *(CV death, nonfatal MI, or nonfatal stroke)* 1.9%, 2.2%; *p*=0.78 **Composite 2** *(CV death, nonfatal MI, nonfatal stroke, hospitalisation for unstable angina,*	**CV death** 1.1%, 0.36%; *p*=0.37 **Non-CV death** 0.0%, 0.36%; *p*>0.99	**Nonfatal MI** 0.7%, 1.5%; *p*=0.69 **Hospitalisation for unstable angina** 1.5%, 0.7%; *p*=0.45 **Coronary revascularisation** 10.7%, 11.0%, *p*=0.93	**Nonfatal stroke** 0.0%, 0.36%; *p*>0.99

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Composite Outcomes	All-Cause Mortality	Cardiovascular Events	Stroke
		or congestive heart failure) 4.1%, 4.8%; *p*=0.70 **Composite 3** *(CV death, nonfatal MI, nonfatal stroke, coronary or carotid revascularisation, hospitalisation for unstable angina, or congestive heart failure)* 14.8%, 15.0%; *p*=0.95		**Hospitalisation for congestive heart failure** 1.5%, 1.8%; *p*=0.99 **Angina pectoris** 7.0%, 12.1%; *p*=0.05	
Bolli et al. (2009)[53] RCT 1 yr n = 576 Good	**P:** Pts w/ T2DM and inadequate glycaemic control on a stable dose of Met **I:** Pio as an add-on to Met **C:** Vildagliptin as an add-on to Met	NR	NR	**Any CV event** 2.1%, 0.7%; *p* value NR **ACS** 0.36%, 0.33%; *p* value NR **Arrhythmia** 0.36%, 0%; *p* value NR **Transient ischaemic attack** 0.36%, 0%; *p* value NR	**Stroke** 0.7%, 0.33%; *p* value NR **Transient ischemic attack** 0.36%, 0%; *p* value NR
Kaku et al. (2009)[58] RCT 4 yrs n = 589 Fair	**P:** Pts w/ inadequately controlled T2DM **I:** Pio + other meds **C:** Other meds only	**Primary composite** *(death, nonfatal MI, silent MI, ACS, CABG or PCI, stroke, lower limb amputation, bypass surgery or angioplasty, onset or worsening of angina pectoris, arteriosclerosis obliterans)* NS (*p*=0.5512); data reported graphically	**Deaths** 1%, 0.3%; *p* value NR Not tx related	**Any macrovascular event** 3.56%, 4.49%; *p* value NR Occurrence of individual macrovascular events NR.	**Any macrovascular event** 3.56%, 4.49%; *p* value NR Occurrence of individual macrovascular events NR.

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Composite Outcomes	All-Cause Mortality	Cardiovascular Events	Stroke
		Secondary composite *(death, acute MI excluding silent MI, or stroke)* 2.4%, 2.4%			
Tolman et al. (2009)[62] RCT 3 yrs n = 2120 Poor	**P:** Pts w/ T2DM inadequately controlled by glycaemic-lowering medication **I:** Pio ± other medications **C:** Glib (Sulf) ± other medications	NR	**Deaths** 0.1% (1 pt), 0.6% (6 pts); *p* value NR None reported to be tx-related	**MI events** 0.7%, 1.1%; *p* value NR	**Stroke** 1%, 0.9%; *p* value NR
Yoshii et al. (2014)[64] RCT 1.8 yrs n = 522 Fair	**P:** Pts w/ T2DM and high risk of stroke **I:** Pio + other medications **C:** Other medications only	**Primary composite outcome** *(all-cause death, nonfatal stroke and nonfatal MI)* 3.8%, 4.0% Kaplan-Meier analysis: HR 1.053 (05% CI 0.427-2.593; *p*=0.9114 **Secondary composite outcome** *(stroke, transient ischaemic attack, cerebral haemorrhage, MI, angina pectoris, CABG or PCI, or ACS excluding MI):* 1.3%, 1.2% Kaplan-Meier analysis: HR, 0.995 (95% CI 0.445-2.222); *p*=0.9898.	**All-cause death** 0.4% (1 pt), 0.8% (2 pts); *p* value NR	**Nonfatal MI** 2.1%, 1.6%; *p* value NR **Angina pectoris** 1.2%, 0.8%; *p* value NR **PCI or CABG** 0.0%, 0.0%; *p* value NR **ACS (excluding MI)** 0.0%, 0.0%; *p* value NR	**Nonfatal stroke** 1.3%, 1.6%; *p* value NR **Transient ischaemic attack** 0%, 0.4%; *p* value NR

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Composite Outcomes	All-Cause Mortality	Cardiovascular Events	Stroke
Home et al. (2015)[57] RCT 1 yr n = 685 Fair	**P:** Pts w/ T2DM inadequately controlled by Met **I:** Pio + Glim (Sulf) + Met **C:** PBO + Glim (Sulf) + Met	**NR**	**Death** 1.1%, 0.9%; *p* value NR Not tx related	**CV events** 15.5%, 8.7%; *p* value NR	**NR**
Vacarro et al. (2017)[63] RCT 4.8 yrs n = 3028 Fair	**P:** Pts w/ T2DM inadequately controlled by Met **I:** Pio as add-on to Met **C:** Sulf as add-on to Met	**Primary composite** *(all-cause death, nonfatal MI, nonfatal stroke, or urgent coronary revascularisation)* 6.8%, 7.2% HR 0.96 (95% CI 0.74-1.26); *p*=0.79 **Secondary composite** *(sudden death; fatal and nonfatal MI; fatal and nonfatal stroke; leg amputation above the ankle; revascularisation of coronary, leg, or carotid arteries)* 5%, 6% HR 0.88 (95% CI 0.65-1.21); *p*=0.44 **Expanded composite** *(all-cause death, nonfatal MI, nonfatal stroke, heart failure, revascularisation of coronary, leg, or carotid arteries)* 11%, 11%	**All-cause death** 4% (55 pts), 3% (50 pts); *p* value NR HR 1.10 (95% CI 0.75-1.61); *p*=0.63	**Nonfatal MI** 1%, 2% HR 0.87 (95% CI 0·48-1·55); *p*=0.63 **Urgent coronary revascularisation** 2%, 2% HR 0.91 (95% CI 0·56-1·48); *p*=0.70 **Heart failure** 1%, 1% HR 1.57 (95% CI 0.76-3.24); *p*=0.22	**Nonfatal stroke** 1%, 1%; *p* value NR HR 0.79 (95% CI 0·41-1·53); *p*=0.49

Authors Study Design Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Composite Outcomes	All-Cause Mortality	Cardiovascular Events	Stroke
		HR 1·03 (95% CI 0.82-1.28); *p*=0.81			
Asakura et al. (2018)[52] RCT 2 yrs n = 630 Good	**P:** Pts w/ T2DM and prior MI **I:** Pio + other medications **C:** Other medications only	**Primary composite** *(CV death, hospitalisation for nonfatal MI, nonfatal unstable angina, tx w/ PCI or CABG, and cerebral infarction)* 14.1%, 14.2% HR 1.005 (95% CI 0.662-1.526); *p*=0.98	**All-cause death** 1.6% (5 pts), 2.3% (7 pts) HR 0.722 (95% CI 0.229-2.274); *p*=0.58 **CV death** 0%, 0.2% (1 pt) HR 0.334 (95% CI 0.004 -30.794); *p*=0.64	**MI** 2.2%, 0.3% HR 5.049 (95% CI 0.786-32.415); *p*=0.09 **Unstable angina** 1.9%, 1.0% HR 1.876 (95% CI 0.477-7.380); *p*=0.37 **Coronary revascularisation** 13.7%, 12.9% HR, 1.083 (95% CI, 0.704-1.666); *p*=0.72 **ACS (MI + unstable angina)** 4.2%, 1.3% HR 3.058 (95% CI 1.020-9.165); *p*=0.05 **Cardiac disorders** 16.3%, 13.2%; *p* value NR **Heart failure** 2.2%, 0.6%; *p* value NR	**Cerebral infarction** 0.3%, 1.0% HR 0.431 (95% CI 0.051-3.662); *p*=0.44

All outcomes are reported as % of pts in intervention group, % of patients in comparator group (unless otherwise specified).

[†]Outcomes from the longer-term follow-up of the PROactive study [66] are not summarised here, as they represent an observational phase of the trial where patients were not assigned to a specific treatment.

Table 9. Overview of Adverse Events Reported for Pioglitazone

Key: ACS, acute coronary syndrome; BL, baseline; btwn, between; CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; grp(s), group(s); HR, hazard ratio; Met, metformin; MI, myocardial infarction; mm Hg, millimetre of mercury; NR, not reported; PBO, placebo; Pio, pioglitazone; pt(s), patient(s); Sulf, sulfonylurea(s); T2DM, type 2 diabetes mellitus; tx, treatment

Authors/ Study Design/ Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Overall Adverse Events	Hypoglycaemia	Oedema	Weight Changes	GI Illness	Other
Hanefeld et al. (2004)[56]; Charbonnel et al. (2005)[65] RCT 1 and 2 yrs n = 639 Fair	**P:** Pts w/ T2DM inadequately controlled w/ sulf **I:** Pio as an add-on to Sulf **C:** Met as an add-on to Sulf	**Any adverse event** 1 yr: 59.9%, 61.9%; *p* value NR **Serious adverse event** 1 yr: 6.6%, 9.7%; *p* value NR **Withdrawal due to adverse events** 2 yrs: 8.8%, 10%; *p* value NR	**Hypoglycaemic episodes** 1 yr: 10.7%, 14.1%; *p* value NR 2 yrs: 11.3%, 15.6%; *p* value NR	**Oedema** 1 yr: 6.9%, 1.6%; *p* value NR 2 yrs: 10.7%, 2.8%; *p* value NR	**Mean weight changes** 1 yr: 2.8 kg gain, 1 kg loss; *p* value NR 2 yrs: 3.7 kg gain, 1.7 kg loss; *p* value NR	**GI disorders** 1 yr: 12.2%, 23.4%; *p* value NR 2 yrs: 6.3%, 19.4%; *p* value NR **Diarrhoea** 1 yr: 2.5%, 12.5%; *p* value NR	**Blood pressure** 1 yr: No clinically significant changes. Details NR.
Schernthaner et al. (2004)[61] RCT 1 yr n = 1199 Good	**P:** Pts w/ T2DM and no prior glucose lowering medications **I:** Pio **C:** Met	**Any adverse event** 53%, 58%; *p* value NR **Severe adverse events** 4.9%, 7.4%; *p* value NR **Discontinuations due to adverse events**	NR	**Oedema, peripheral** 4.5%, 1.7%; *p* value NR **Oedema, not otherwise specified** 2.2%, 0.2%; *p* value NR	**Weight gain** 1.0%, 0%; *p* value NR **Mean weight changes** 1.9kg gain, 2.5 kg loss; *p* value NR	**Diarrhoea** 3.2%, 11.1%; *p* value NR **Nausea** 2.3%, 4.2%; *p* value NR	**Hepatotoxicity** 0.3%, 0.2%; *p* value NR **Bronchitis** 1.8%, 2.3%; *p* value NR **Influenza** 2.4%, 3.7%; *p* value NR **Nasopharyngitis** 4.2%, 3.2%; *p* value NR **Arthralgia**

Authors/ Study Design/ Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Overall Adverse Events	Hypoglycaemia	Oedema	Weight Changes	GI Illness	Other
		7%, 7%; *p* value NR					1.5%, 2.0%; *p* value NR **Back pain** 2.3%, 2.8%; *p* value NR **Headache** 4.4%, 2.3%; *p* value NR **Pharyngitis** 2.5%, 1.5%; *p* value NR **Hypertension** 2.5%, 2.8%; *p* value NR **Abnormal liver function** 0%, 1.5%; *p* value NR **Blood pressure** NS changes from BL in either grp, data NR
Charbonnel et al. (2005)[54] RCT 1 yr n = 1270 Fair	**P:** Pts w/ T2DM and no prior glycaemic control medications **I:** Pio **C:** Gliclazide (Sulf)	**Any adverse event** 75%, 71%; *p* value NR (majority mild or moderate, details NR) **Serious adverse events** NR	**Hypoglycaemia** 3.5%, 10.1%; *p* value NR	**Mild oedema** 8.7%, 4.5%; *p* value NR	**Mean weight changes** 2.8 kg gain, 1.9 kg gain; *p* value NR	NR	NR
Dormandy et al. (2005)[55†]	**P:** Pts w/ T2DM and	**Serious adverse events**	**Hypoglycaemia**	**Oedema (without heart failure)**	**Mean weight changes**	**NR**	**Pneumonia**

Authors/ Study Design/ Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Overall Adverse Events	Hypoglycaemia	Oedema	Weight Changes	GI Illness	Other
RCT 2.8 yrs n = 5238 Good	increased risk of macrovascular events **I:** Pio + existing medications **C:** PBO + existing medications	46%, 48%; *p*=0.110 **Withdrawal for adverse events** 9.0%, 7.7%; *p* value NR	28%, 20%; *p*<0.0001 favoring PBO **Hypoglycaemia resulting in hospital admission** 0.7%, 0.4%; *p*=0.14	21.6%, 13.0%; *p* value NR	3.6 kg gain, 0.4 kg loss; *p*<0.0001 favoring PBO		2%, 1%; *p*=0·047 favoring PBO **Any malignant neoplasm** 4%, 4%; *p* value NR **Bladder cancer** 1%, <1%; *p*=0.069 **Mean blood pressure reduction (systolic)** 3 mm Hg, 0 mm Hg; *p*=0.03 favoring pio
Matthews et al. (2005)[59]; Charbonnel et al. (2005)[65] RCT 1 and 2 yrs n = 630 Fair	**P:** Pts w/ T2DM inadequately controlled by Met **I:** Pio as an add-on to Met **C:** Gliclazide (Sulf) as an add-on to Met	**Any adverse event** 1 yr: 55.5%, 58.1%; *p* value NR **Serious adverse events** 1 yr: 4.7%, 6.4%; *p* value NR **Withdrawal for adverse events** 2 yrs: 6.9%, 6.7%; *p* value NR	**Hypoglycaemia** 1 yr: 1.3%, 11.2%; *p* value NR 2 yrs: 2.2%, 11.5%; *p* value NR	**Oedema** 1 yr: 6.3%, 2.2%; *p* value NR 2 yrs: 7.6%, 3.5%; *p* value NR	**Mean weight changes** 1 yr: 1.5 kg gain, 1.4 kg gain; *p* value NR 2 yrs: 2.5 kg gain, 1.2 kg gain; *p* value NR	**GI disorders** 2 yrs: 3.8%, 5.1%; *p* value NR	**Blood pressure** No clinically relevant changes or btwn grp differences. Data NR.
Nissen et al. (2008)[60] RCT 1.5 yrs	**P:** Pts w/ T2DM and coronary artery disease **I:** Pio +	**Withdrawal for adverse events** 11.1%, 12.5%; *p*=0.63 **Hypertension**	**Hypoglycaemia** 15.2%, 37.0%; *p*<0.001 favoring Pio grp	**Peripheral oedema** 17.8%, 11.0%; *p*=0.02 favoring glimepiride grp	**Weight changes:** Pts in both grps gained weight, gain was 2 kg higher for Pio grp	**NR**	**Bone fracture** 3.0%, 0%; *p*=0.004 favoring glimepiride grp **Blood pressure, median mm Hg change from BL**

Authors/ Study Design/ Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Overall Adverse Events	Hypoglycaemia	Oedema	Weight Changes	GI Illness	Other
n = 547 Fair	existing medications **C:** Glimepiride (Sulf) + existing medications	4.8%, 8.8%; *p*=0.07					Systolic: 0.1, 2.3; *p*=0.03 favoring pio Diastolic: −0.9, 0.9; *p*=0.003 favoring Pio
Bolli et al. (2009)[53] RCT 1 yr n = 576 Good	**P:** Pts w/ T2DM and inadequate glycaemic control on a stable dose of Met **I:** Pio as an add-on to Met **C:** Vildagliptin as an add-on to Met	**Any adverse event** 68.2%, 67.8%; *p* value NR **Serious adverse events** 4.1%, 8.9%; *p* value NR	**Hypoglycaemia** 0.3%, 0.4%; *p* value NR	**Peripheral oedema** 11.1%, 10.8%; *p* value NR	**Mean weight changes** 2.6 kg gain, 0.2 kg gain; *p*<0.0001 favoring vildagliptin + Met grp	**Any GI adverse event** 14.5%, 20%; *p* value NR **Diarrhoea** 5.0%, 4.7%; *p* value NR **Vomiting** 1.4%, 3.4%; *P* value NR **Nausea** 1.8%, 3.4%; *p* value NR **Dyspepsia** 1.1%, 2.7%; *p* value NR	**Headache** 6.1%, 6.4%; *p* value NR **Nasopharyngitis** 7.1%, 5.4%; *p* value NR **Back pain** 5.4%, 5.1%; *p* value NR
Kaku et al. (2009)[58] RCT 4 yrs	**P:** Pts w/ inadequately controlled T2DM **I:** Pio + other meds	**Any adverse event** 97.6%, 96.9%; *p* value NR **Serious adverse events**	**Hypoglycaemia** 15.7%, 12.9%; *p* value NR	**Peripheral lower limb oedema** 16.4%, 4.1%; *p* value NR **Generalised oedema**	**Weight changes** Pio grp gained significantly more weight vs. no Pio grp (*p*<0.01). Data NR.	**NR**	**Bone fractures** 6.1%, 6.1%; *p* value NR **Nephropathy** 8.9%, 12.9%

Authors/ Study Design/ Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Overall Adverse Events	Hypoglycaemia	Oedema	Weight Changes	GI Illness	Other
n = 589 Fair	**C:** Other meds only	20.1%, 21.8%; *P* value NR		15.7%, 1.0%; *P* value NR			
Tolman et al. (2009)[62] RCT 3 yrs n = 2120 Poor	**P:** Pts w/ T2DM inadequately controlled by glycaemic lowering medication **I:** Pio ± other medications **C:** Glibenclamide (Sulf) ± other medications	**Any adverse event** 81.7%, 83.7%; *p* value NR **Serious adverse event** 15.1%, 16.6%; *p* value NR **Withdrawal for adverse events** 13.9%, 11.7%; *p* value NR	**Hypoglycaemia** 3.8%, 11.4%; *p* value NR	**Oedema** 8.0%, 3.4%; *p* value NR	**Mean weight change** 5.2 kg gain, 0.9 kg gain; *p* value NR	**Diarrhoea** 8.8%, 7.6%; *p* value NR **Nausea** 7.3%, 8.0%; *p* value NR	**Bone fracture (men)** 2.3%, 2.4%; *p* value NR **Bone fracture (women)** 3.6%, 2.8%; *p* value NR **Upper respiratory tract infection** 15.2%, 15%; *p* value NR **Sinusitis** 9.3%, 8.6%; *p* value NR **Bronchitis** 7.8%, 7.7%; *p* value NR **Cough** 6.4%, 10.3%; *p* value NR **Arthralgia** 11.3%, 10.9%; *p* value NR **Limb pain** 8.5%, 7.6%; *p* value NR **Back pain** 7.5%, 7.5%; *p* value NR **Headache**

Authors/ Study Design/ Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Overall Adverse Events	Hypoglycaemia	Oedema	Weight Changes	GI Illness	Other
							6.7%, 7.6%; *p* value NR **Hepatobiliary serious adverse event** 0.5%, 1%; *p* value NR
Yoshii et al. (2014)[64] RCT 1.8 yrs n = 522 Fair	**P:** Pts w/ T2DM and high risk of stroke **I:** Pio + other medications **C:** Other medications only	**Any adverse event** 14.1%, 5.3%; *p*=0.0001 favoring other medications only grp	NR	**Peripheral oedema** 5.1%, 0%; *p* value NR	**Weight** No changes. Data NR.	**NR**	**Malignancy** 1.3%, 2.0%; *p* value NR **Blood pressure** Pio grp had significant reduction, no change for no Pio grp. Data NR.
Home et al. (2015)[57] RCT 1 yr n = 685 Fair	**P:** Pts w/ T2DM inadequately controlled by Met **I:** Pio + glimepiride (Sulf) + Met **C:** PBO + glimepiride (Sulf) + Met	**Any adverse event** 76.5%, 69.6%; *p* value NR **Serious adverse events** 9.0%, 6.3%, 6.1%; *p* value NR **Tx-related adverse events** 21.7%, 31.7%, 13.9%; *p* value NR	**Hypoglycaemia** 31.4%, 11.3%; *p* value NR **Severe hypoglycaemia** 1.1%, 0.4%, 0%; *p* value NR	NR	**Mean Weight Change** 4.4 kg gain, 0.4 kg loss; *p*<0.001 favoring PBO	**GI events** 26.0%, 17.4%; *p* value NR **Nausea** 4.3%, 3.5%; *p* value NR **Diarrhoea** 5.4%, 2.6%; *p* value NR **Vomiting** 1.8%, 0.9%; *p* value NR	**Pancreatitis** 0%, 0%; *p* value NR **Thyroid cancer** 0%, 0.9%; *p* value NR

Authors/ Study Design/ Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Overall Adverse Events	Hypoglycaemia	Oedema	Weight Changes	GI Illness	Other
		Adverse events leading to withdrawal 6.9%, 4.4%,5.2%; *p* value NR					
Vacarro et al. (2017)[63] RCT 4.8 yrs n = 3028 Fair	**P:** Pts w/ T2DM inadequately controlled by Met **I:** Pio as add-on to Met **C:** Sulf as add-on to Met	**Serious adverse events** 14%, 13%; *p*=0.73	**Severe hypoglycaemia** <1%, 2%; *p*<0.0001 favoring Pio + Met **Moderate hypoglycaemia** 10%, 32%; *p*<0·0001 favoring Pio + Met	**Oedema** <1%, <1%; *p*=0.34	**Weight changes** Differences NS btwn grps (*p*=0.09)	**NR**	**Malignant neoplasm** 5%, 5%; *p*=0.74 **Bladder cancer** 0.5%, 0.5%; *p*=1.00 **Pathological fractures** <1%, <1%; *p*=0.75 **Respiratory, thoracic, and mediastinal disorders** 1%, <1%; *p*=0.03 favoring Sulf + Met **Blood pressure** Blood pressure was similar btwn grps. Data NR. **Nephropathy** 23%, 23% HR 1.03 (95% CI 0·89-1·19); *p*=0.37
Asakura et al. (2018)[52] RCT 2 yrs	**P:** Pts w/ T2DM and prior MI **I:** Pio + other medications	**Any adverse event** 40.6%, 39.5%; *p* value NR	**Hypoglycaemia** 0%, 0.3%; *p* value NR	**Oedema** 0.6%, 3.2%; *p* value NR	NR	**GI disorders** 2.5%, 2.2%; *p* value NR	**Hepatic disorders** 0.6%, 0.6%; *p* value NR **Respiratory disorders** 0.6%, 1.3%; *p* value NR

Authors/ Study Design/ Follow-up Sample Size Study Quality	Population (P) Intervention (I) Comparator (C)	Overall Adverse Events	Hypoglycaemia	Oedema	Weight Changes	GI Illness	Other
n = 630 Good	**C:** Other medications only						**Any benign or malignant disorder** 1.6%, 3.5%; *p* value NR **Bladder cancer** 0%, 0.3%; *p* value NR **Nervous system disorders** 0.6%, 2.9%; *p* value NR **Infectious disorders** 1.9%, 1.3%; *p* value NR **Blood pressure** Blood pressure was NS btwn grps or changed from BL. **Nephropathy** 0.6%, 1.3%
Outcomes are reported as % of pts in intervention group, % of patients in comparator group (unless otherwise specified). †Outcomes from the longer-term follow-up of the PROactive study [66] are not summarised here, as they represent an observational phase of the trial where patients were not assigned to a specific treatment.							

Findings

Studies included in the body of evidence for pioglitazone reported all-cause mortality, macrovascular events, and adverse events. Six studies reported a composite outcome of mortality and macrovascular events as a primary endpoint, and statistical power calculations were based on the expected occurrence of these events [52 55 58 60 63 64]. The remaining studies were statistically powered to detect changes in surrogate outcomes (most commonly HbA1c levels), and reported direct health outcomes (e.g. microvascular and macrovascular complications) and/or adverse events secondarily. In many cases, no statistical comparisons were performed to evaluate differences between groups in the outcomes of primary interest in this short report.

Findings for each outcome with sufficient evidence for analysis are summarised below. An outcome was considered to have sufficient evidence for analysis if it was reported in three or more studies, or two or more studies if the studies evaluated the same intervention and comparison treatments. With the exception of nephropathy, individual microvascular events were reported in one to two studies each, and evidence was insufficient for analysis. For more detailed Evidence Tables with full reporting of outcomes of interest and Strength of the Evidence (SOE) summary tables, refer to Appendix Table 9 and Appendix Table 11 of Appendix IV. For detailed findings by outcome for each comparison type, refer to Appendix Table 11 of Appendix IV.

Composite Outcomes (Six Studies): Six studies reported composite outcomes related to all-cause mortality and/or the first occurrence of macrovascular events (n = 522, 543, 587, 630, 3028, and 5238) [52 55 58 60 63 64] . Components comprising the composite outcomes varied across studies, though the most common composite outcome included all-cause death, myocardial infarction, and stroke [55 58 60 64]. Studies were fairly consistent in reporting no differences between treatment groups for composite outcomes. Pioglitazone was favored over placebo in one study that enrolled T2DM patients who had evidence of macrovascular disease (PROactive) for a preplanned secondary composite outcome of death, MI, and stroke (HR 0.84; 95% CI 0.72 to 0.98; *p*=0.027) [55], and for several retrospectively defined composites [78]. However, there were no differences between treatment groups in this study for a more comprehensive primary composite outcome [55] . The remaining studies reported no statistically significant differences between pioglitazone versus other medications [52 58 64] or pioglitazone versus sulfonylurea [60 63]. The strength of the evidence was rated as moderate due to imprecision.

All-Cause Mortality (11 Studies): All-cause mortality was reported in 11 studies (n = 522, 543, 587, 630, 630, 639, 685, 1199, 2097, 3028, and 5238), with follow-up ranging from 1 to 4.8 years [52 55-64]. There is no evidence that mortality differs across treatment groups. Across studies, mortality rates for groups receiving pioglitazone ranged from 0.003% to 6.8%, and rates across control groups ranged from 0.9% to 7.1%. Three studies reported no statistically significant differences between pioglitazone versus placebo [55], no pioglitazone [52], or sulfonylurea (as add-ons to metformin) [63]. Eight studies did not include statistical comparisons. The strength of the evidence was rated as moderate due to imprecision and a lack of statistical analyses in the majority of studies.

Myocardial Infarction (Six Studies): The occurrence of myocardial infarction was reported in 6 studies (n = 522, 543, 630, 2097, 3028, 5238) with follow-up ranging from 2 to 4.8 years [52 55 60 62-64]. For groups receiving pioglitazone, 0.7% to 4.6% had a myocardial infarction during follow-up, compared with 0.3% to 5.5% of patients in comparator groups. Four studies reported that there were no statistically significant differences between pioglitazone versus other treatments [52 55] or sulfonylurea [60 63], and two

studies did not report statistical comparisons [62 64]. The evidence was determined to be of moderate strength, downgraded due to imprecision and a lack of statistical analyses in several studies.

Stroke (Seven Studies): The incidence of stroke was reported in seven studies (n = 522, 543, 576, 630, 2097, 3028, 5238) with follow-up ranging from 1 to 4.8 years [52 53 55 60 62-64]. For groups receiving pioglitazone, the rate of stroke ranged from 0% to 3.3% of patients. For comparison groups, the rate of stroke ranged from 0.33% to 4.1%. Four studies reported no statistically significant differences between pioglitazone versus other treatments [52 55] or sulfonylurea [60 63], and 3 studies did not report statistical comparisons [53 62 64]. The strength of the evidence was downgraded to moderate due to imprecision and a lack of statistical comparisons in several studies.

Coronary Revascularisation (Five Studies): Five studies (n = 522, 543, 630, 3028, and 5238) reported coronary revascularisation rates with follow up ranging from 1.5 to 4.8 years. For groups receiving pioglitazone, coronary revascularisation rates ranged from 0% to 13.7%, versus 0% to 12.9% across comparison groups. Four studies reported no statistically significant differences between pioglitazone versus other treatments [52 55] or sulfonylureas [60 63] and 1 study did not report statistical comparisons [64]. The strength of the evidence was determined to be moderate due to imprecision and a lack of statistical comparisons in several studies.

Heart Failure (Six Studies): The rate of heart failure was reported in six studies (n = 543, 630, 630, 639, 3028, and 5238) with follow-up ranging from 1 to 4.8 years. Across pioglitazone groups, heart failure occurred among 0.6% to 11% of patients. For comparator groups, rates ranged from 0.6% to 8%. One study reported significantly higher rates of heart failure for patients receiving pioglitazone versus placebo (11% versus 8%; $p<0.0001$), though rates of fatal heart failure were similar between groups [55]. Two studies reported no statistically significant differences between pioglitazone versus sulfonylurea as add-ons to existing medications [60] or metformin [63]. Three studies did not report statistical comparisons between groups [52 56 59], though 2 reported quantitatively higher rates of heart failure for pioglitazone versus other medications or sulfonylurea [52 59]. The strength of the evidence was moderate due to imprecision and a lack of statistical comparisons in several studies.

Any Adverse Event (10 Studies): Ten studies (n = 522, 587, 576, 630, 630, 639, 1199, 1270, and 2097) reported overall rates of adverse events [52-54 56-59 61 62 64]. Across studies, adverse events were reported for 14.1% to 97.6% of patients receiving pioglitazone versus 5.3% to 96.9% of patients receiving a comparator treatment. The majority of studies (8 of 10) reported adverse events among >50% of patients in all treatment groups. One study reported higher rates of adverse events in patients receiving pioglitazone versus no pioglitazone (14.1% versus 5.3%; $p=0.0001$) [64]. Nine studies did not report statistical comparisons, and overall rates were numerically similar between groups. The strength of the evidence was considered to be moderate due to imprecision and a lack of statistical comparisons in the majority of studies.

Serious Adverse Event (Nine Studies): Nine studies (n = 576, 587, 630, 639, 685, 1199, 2097, 3028, and 5238) reported the overall rates of serious adverse events [53 55-59 61-63]. Serious events were typically considered to be events that were life-threatening or required hospitalisation, or prolonged existing hospital stays. Across pioglitazone groups, serious adverse event rates ranged from 4.1% to 46%. Across comparison groups, rates ranged from 6.1% to 48%. Two studies reported no statistically significant difference between pioglitazone and placebo [55] or sulfonylurea [63]. Seven studies did not report statistical comparisons between treatment groups. The strength of the evidence was considered to be moderate due to imprecision and a lack of statistical comparisons in the majority of studies.

Withdrawal Due to Adverse Events (Seven Studies): Seven studies (n = 543, 630, 639, 685, 1199, 2097, 5238) reported the percentage of patients who discontinued study participation due to adverse events [55-57 59-62]. Across pioglitazone groups rates ranged from 6.9% to 11.1% of patients, versus 4.4% to 12.5% of patients in control groups. One study reported no statistically significant difference between pioglitazone versus sulfonylurea (Nissen et al., 2008), and 6 studies did not report statistical comparisons between treatment groups. The strength of the evidence was downgraded to moderate due to imprecision and a lack of statistical comparisons in 6 of 7 studies.

Gastrointestinal Disorders (Seven Studies): Seven studies (n = 576, 630, 630, 639, 685, 1199, 2097) reported the occurrence of gastrointestinal disorders, including nausea, vomiting, or diarrhoea [52 53 56 57 59 61 62]. For patients receiving pioglitazone, rates ranged from 2.5% to 26%. For control groups, rates ranged from 2.2% to 33.6%. No studies reported statistical comparisons between treatment groups. However, four active-controlled studies reported numerically lower rates of gastrointestinal events for pioglitazone [53 56 59 61]. The strength of evidence for gastrointestinal disorders was downgraded to moderate for imprecision and a lack of statistical comparisons across studies.

Liver Toxicity (Three Studies): Three studies (n = 630, 1199, and 2097) reported outcomes related to liver toxicity [52 61 62]. For pioglitazone groups, rates ranged from 0.3% to 0.6%. For control groups (other medications, metformin, sulfonylurea), rates ranged from 0.2% to 1.0%. No statistical comparisons were reported, and the strength of the evidence was downgraded to moderate for imprecision, lack of statistical analyses, and a small number of studies reporting the outcome

Respiratory Infection or Inflammation (Six Studies): Six studies (n = 576, 630, 1199, 2097, 3028, and 5238) reported rates of respiratory illness [52 53 55 61]; two fair quality [62 63]. For patients receiving pioglitazone, rates ranged from 0.6% to 15.2%. For control groups, rates ranged from <1% to 15%. Two studies reported higher rates of respiratory illness for patients receiving pioglitazone versus placebo (pneumonia: 2% versus 1%; *P*=0.047) [55] or sulfonylurea (upper respiratory infection: 1% versus <1%; *P*=0.03) [63]. Four studies did not report statistical comparisons. The strength of the evidence was considered to be moderate due to imprecision and lack of statistical analyses in several studies.

Pain (Arthralgia, Back Pain, or Limb Pain) (Three Studies): Three studies (n = 576, 1199, and 2097) reported arthralgia, back pain, or limb pain among 1.5% to 11.3% of patients receiving pioglitazone versus 2.0% to 10.9% of patients receiving vildagliptin [53], sulfonylurea [62], or metformin [61]. No statistical comparisons were reported. The strength of the evidence was downgraded to moderate for imprecision, lack of statistical analyses, and a small number of studies reporting the outcome.

Headache (Three Studies): Three studies (n = 576, 1199, and 2097) reported headache among 4.4% to 6.7% of patients receiving pioglitazone and among 2.3% to 7.6% of patients receiving sulfonylurea [62], vildagliptin [53], or metformin [61]. No statistical comparisons were reported. The strength of the evidence was downgraded to moderate for imprecision, lack of statistical analyses, and a small number of studies reporting the outcome.

Hypoglycaemia (11 Studies): Rates of hypoglycaemia were reported in 11 studies (n = 543, 576, 630, 587, 630, 639, 685, 1270, 2097, 3028, and 5238) [52-60 62 63]. Studies typically did not clearly distinguish between confirmed versus suspected hypoglycaemic events, and criteria based on symptoms or blood glucose measurements were not reported, with some exceptions. One study defined hypoglycaemia as blood glucose <3.1 mmol/L [53], one defined it as blood glucose <3.3 mmol/L [63], and one noted that

hypoglycaemic events were evaluated based on American Diabetes Association (ADA) classifications [57]. Across studies, hypoglycaemia occurred among 0% to 28% of patients receiving pioglitazone and 0.3% to 37% of patients receiving a comparator treatment. Variation in occurrence may be related to differences in the definition of hypoglycaemia (which was not clear across studies), as well as to differences in treatment combinations and follow-up durations. With regard to comparative findings, two studies favored pioglitazone over sulfonylurea as add-on treatments (15.2% versus 37%; $p<0.001$) [60] and (10% versus 32%; $p<0.0001$) [63]. One study reported higher rates of hypoglycaemia for pioglitazone versus placebo (28% versus 20%; $p<0.0001$) [55]. The remaining eight studies did not report statistical comparisons between groups, though two studies reported numerically higher rates of hypoglycaemia for pioglitazone versus sulfonylurea [54 62]. The strength of the evidence was downgraded to moderate due to some inconsistencies, imprecision, and a lack of statistical analyses in the majority of studies.

Oedema (12 Studies): Twelve studies (n = 522, 543, 576, 587, 630, 630, 639, 1199, 1270, 2097, 3028, and 5238) reported the occurrence of oedema [52-56 58-64]. Across studies, 0.6% to 21.6% of patients receiving pioglitazone experienced oedema, compared with 0% to 13% of patients receiving a comparator treatment. One study reported statistically significantly higher rates of oedema for pioglitazone versus sulfonylurea (17.8% versus 11.0%; $p=0.02$) [60], and one study reported no statistically significant difference between pioglitazone versus sulfonylurea [63]. The remaining 10 studies did not report statistical comparisons, though seven studies reported numerically higher rates of oedema for pioglitazone versus other medications and sulfonylurea as an add-on to other medications [54-56 58 61 62 64]. The strength of the evidence was determined to be moderate due to imprecision and a lack of statistical comparisons in the majority of studies.

Weight Change (12 Studies): Changes in body weight were reported in 12 studies (n = 522, 543, 576, 587, 630, 639, 685, 1199, 1270, 2097, 3028, and 5238) [53 55-65]. In all studies, patients receiving pioglitazone had mean weight gains that ranged from 2.6 kg to 5.2 kg. Changes across comparator groups ranged from 1.7 kg loss to 1.9 kg gain. Four studies reported that pioglitazone was associated with a significantly higher weight gain versus placebo (3.6 kg gain versus 0.4 kg loss; $p<0.0001$) [55], other medications only ($p<0.01$) [57 58], or vildagliptin (2.6 kg gain versus 0.2 kg gain; $p<0.0001$) [53]. One study reported no statistically significant differences between pioglitazone versus sulfonylurea as add-ons to metformin [63]. Seven studies did not provide statistical analyses, though there was a trend toward higher numerical weight gain for pioglitazone compared with comparator groups. The strength of the evidence was downgraded to moderate due to imprecision and a lack of statistical comparisons in the majority of studies.

Malignancy (Five Studies): Malignancy rates were reported in five studies (n = 522, 630, 685, 3028, and 5238), with mean follow up ranging from 1 to 4.8 years[52 55 57 63 64]. Across studies, the rates of malignancy ranged from 0% to 5% for patients receiving pioglitazone and from 0.9% to 5% of patients receiving a comparator treatment. One study reported no statistically significant differences in malignancy rates for pioglitazone versus sulfonylurea [63], and four studies did not report statistical comparisons. Three studies with follow-up ranging from 2 to 4.8 years reported the incidence of bladder cancer, ranging from 0% to 1% of patients receiving pioglitazone versus 0.3% to 0.5% of those receiving a comparator treatment. Differences were not statistically significant in two studies, and statistical analyses were not presented in one study [52 55 63]. The strength of the evidence was determined to be moderate due to imprecision.

Blood Pressure (Eight Studies): Changes in blood pressure were reported in eight studies (n = 522, 543, 630, 630, 639, 1199, 3028, and 5238) [52 55 56 59-61 63 64]. In three studies, pioglitazone was associated with more favorable changes than other medications ± placebo [55 64] or sulfonylurea [60]. The remaining five

studies reported that there were no clinically significant changes in blood pressure from baseline or between treatment groups. The strength of evidence was moderate due to imprecision.

Fracture (Four Studies): Four studies (n = 543, 587, 2097, and 3028) reported fracture rates ranging from <1% to 6.1% of patients receiving pioglitazone versus 0% to 6.1% of patients receiving a comparator treatment [58 60 62 63]. One study reported higher fracture rates for pioglitazone versus sulfonylurea as add-ons to existing medication (3% versus 0%; *p*=0.004) [60], and one study reported no differences between pioglitazone versus sulfonylurea as add-ons to metformin [63]. Two studies did not report statistical comparisons. The strength of evidence was downgraded to low due to imprecision and lack of statistical analyses, inconsistency across studies comparing pioglitazone with sulfonylureas, and individual study quality (all studies were considered to be fair quality).

Nephropathy (Three Studies): Three studies (n = 587, 630, and 3028) reported rates of nephropathy for patients receiving pioglitazone as an add-on to existing medications [52 58] or metformin [63], with mean follow-up ranging from 2 to 4.8 years. Similar rates were observed between treatment groups in all studies. Across studies, 0.6% to 23% of patients receiving pioglitazone had nephropathy, compared with 1.3% to 23% among control groups. Variations may be attributable to different follow-up durations and treatment protocols across studies. One study reported that there were no statistically significant differences in the rate of nephropathy between pioglitazone versus sulfonylureas as add-ons to metformin (23% in both groups, HR 1.03; 95% CI 0.89 to 1.19; *p*=0.37) [63]. Statistical comparisons were not provided in two studies [52 58]. The strength of the evidence was downgraded to moderate for imprecision, lack of statistical analyses, and a small number of studies reporting the outcome.

Findings from Systematic Reviews

Findings from systematic reviews and meta-analyses evaluating outcomes of interest for pioglitazone are summarised below. Detailed summaries of the scope and conclusions of relevant publications are available in Appendix V.

HbA1c

Although outside the scope of this report, findings regarding HbA1c from relevant systematic reviews and meta-analyses are summarised for discussion purposes and to provide additional context and supplementary information. Overall, systematic reviews and meta-analyses suggest that there are few substantial differences in HbA1c reductions for pioglitazone versus comparator treatments. Specific findings are summarised below.

In a 2016 AHRQ comparative effectiveness review, authors conclude that for monotherapy comparisons, most oral diabetes medications have similar efficacy in achieving reductions in HbA1c. For metformin-based combination therapies, authors conclude that there were no significant or no clinically meaningful between-group differences in HbA1c between treatment arms. The majority of analyses for glitazones did not distinguish between pioglitazone versus rosiglitazone. Evidence suggested that metformin was similar to thiazolidinedione monotherapy (pooled between-group difference -0.04%; 95% CI -0.11% to 0.03%), and similar to sulfonylurea monotherapy (pooled between-group difference of -0.04%; 95% CI -0.13% to 0.06%). With regard to combination therapies, metformin plus thiazolidinedione was favored over metformin monotherapy, and there were no statistically or clinically significant differences between metformin plus thiazolidinedione versus metformin plus sulfonylurea (pooled between-group

difference of -0.06%; 95% CI -0.19% to 0.06%; *p*=0.121). Evidence for other comparisons was either not available or of insufficient strength [5].

In a 2018 systematic review and meta-analysis comparing pioglitazone with sodium glucose cotransporter 2 inhibitors as add-ons to insulin in patients with T2DM, the authors report similar HbA1c reductions between groups (weighted mean difference -0.01%; 95% CI -0.25 to 0.22%; *p*=0.896) [18].

In a 2019 systematic review and meta-analysis comparing pioglitazone monotherapy versus monotherapy with a variety of alternative oral antidiabetic drugs in patients with T2DM, pioglitazone had similar reductions in HbA1c versus comparators (mean difference 0.05%; 95% CI −0.21% to 0.11%; *p*=0.56)[4].

All-Cause Mortality, Macrovascular Morbidity, and Microvascular Morbidity

In a 2016 update of an AHRQ review of medications for T2DM [5], 30 active controlled RCTs and observational studies were included in the body of evidence for pioglitazone compared with a variety of other anti-diabetic drugs. Inclusion criteria were less stringent than those employed in the current report, and studies with smaller sample sizes and shorter follow-up periods were included. Relevant conclusions and strength of evidence are summarised below:

- Mortality
    - Low-strength evidence suggested that neither pioglitazone nor metformin are favored for short-term mortality or short-term cardiovascular mortality.
    - Low-strength evidence suggested that neither pioglitazone nor sitagliptin were favored for short-term mortality.
- Macrovascular Morbidity
    - Moderate-strength evidence suggested that neither pioglitazone nor metformin are favored for short-term cardiovascular morbidity.
    - Low-strength evidence favored pioglitazone over sulfonylureas for short-term cardiovascular disease.
    - Low-strength evidence favored a combination of exenatide plus metformin over pioglitazone plus metformin for macrovascular events.
    - Low-strength evidence suggests neither pioglitazone nor dipeptidyl peptidase-4 (DPP-4) inhibitors are favored for heart failure.
- Microvascular Morbidity
    - Low-strength evidence suggests neither pioglitazone plus metformin nor DPP-4 inhibitors plus metformin are favored for outcomes related to nephropathy.
    - Low-strength evidence suggests that glucagon-like peptide 1 (GLP-1) receptor agonist plus metformin is favored over pioglitazone plus metformin for nephropathy.

Evidence for other outcomes and comparisons was insufficient to draw conclusions, and in many cases, outcomes were not stratified by pioglitazone versus rosiglitazone.

Two 2017 systematic reviews and meta-analyses assessed the association between pioglitazone use and cardiovascular disease in active- or placebo- controlled trials in individuals with T2DM, prediabetes, or impaired glucose tolerance [85] [86]. Both reviews conclude that pioglitazone is associated with a decreased risk of major adverse cardiac events, stroke, and myocardial infarction, and an increased risk of heart

failure. These findings may differ from those of the current report due to the inclusion of studies evaluating patients with diagnoses other than T2DM in the analyses. One review performed a separate analysis of studies of patients with T2DM and found a decreased risk for major adverse cardiac events and no statistically significant association for individual events of myocardial infarction or stroke [85]. These findings are not in conflict with those of the current report; where we present limited, inconsistent evidence suggesting decreased risk for a composite of all cause death, stroke, and myocardial infarction, without any significant associations for individual events. Finally, and also in line with findings in the present report, a 2019 systematic review and meta-analysis reported no association between pioglitazone monotherapy and risk of cardiovascular or vascular disorders [4].

Fracture

A 2018 systematic review and meta-analysis of 6 RCTs reported that there was no apparent increased risk for fracture associated with pioglitazone [87]. In contrast, a 2019 meta-analysis of observational studies concluded that pioglitazone was associated with an increased risk of fracture [88]. In the present report, one study reported an increased risk of fracture associated with pioglitazone versus sulfonylureas [60], and two finding no difference between pioglitazone and sulfonylurea [62 63] or no treatment groups [58].

Bladder Cancer

Three systematic reviews and meta-analyses evaluated the risk of bladder cancer associated with pioglitazone using evidence from both RCTs and observational studies [19-21]. All 3 reviews conclude that pioglitazone is associated with a slight, but significant, increased risk of bladder cancer compared with never-use of pioglitazone. Odds ratios and 95% confidence intervals were consistent across reviews (OR 1.13 [95% CI 1.03 to 1.25] [21]; OR 1.16 [95% CI 1.04 to 1.28] [20]; HR 1.16 [95% CI 1.06 to 1.25] [19]). The majority of studies evaluated in these meta-analyses were observational in nature, and it is not possible to rule out confounding factors that might underlie the overall conclusions. Each publication employed systematic methods for evidence identification, and the included studies were evaluated for risk of bias. Further, statistical methods included random effects models and sensitivity analyses.

Based on evidence in the current short report, findings from three RCTs suggest similar rates of bladder cancer for pioglitazone versus comparators [52 55 63]. However, it is unlikely that these studies were sufficiently powered to detect differences in this rare outcome. Large, nationwide observational studies, like those included in these systematic reviews and meta-analyses, are better equipped to address this outcome.

Other Adverse Events

A 2018 systematic review and meta-analysis compared pioglitazone with sodium glucose cotransporter 2 inhibitors as add-ons to insulin in patients with T2DM. The authors report that pioglitazone was associated with significantly less weight loss and a trend towards higher rates of hypoglycaemia [18]. None of the studies included in the current report evaluated this treatment comparison.

A 2019 systematic review and meta-analysis compared the safety and efficacy of pioglitazone monotherapy versus monotherapy with alternative oral anti-diabetic drugs in patients with T2DM. Meta-analyses showed that pioglitazone was associated with significantly greater improvements in blood pressure and lower rates of hypoglycaemia compared with alternative monotherapies.

Pioglitazone was also associated with an increased risk of oedema and weight gain. There were no differences between groups for cardiovascular disorders, vascular disorders, non-cardiac chest pain, upper respiratory tract infections, nervous system disorders, gastrointestinal illness, musculoskeletal disorders, liver function, breast and colon cancer [4]. These findings are consistent with the current report, though only two studies included in the current body of evidence evaluated pioglitazone as a monotherapy.

In the 2016 update of an AHRQ review of medications for T2DM presented several analyses of adverse event outcomes related to pioglitazone. Analyses considered to have sufficient evidence that stratified by pioglitazone versus rosiglitazone are summarised below.

- Weight gain
    - Moderate strength evidence suggested that GLP-1 receptor agonists and DPP-4 inhibitors are associated with less weight gain compared with pioglitazone.
- Hypoglycaemia
    - Low-strength evidence suggested that neither pioglitazone nor DPP-4 inhibitors are favored for severe hypoglycaemia.
    - Low-strength evidence favored pioglitazone over GLP-1 receptor agonists for mild, moderate, or total hypoglycaemia.
    - Low-strength evidence suggested that neither pioglitazone nor GLP-1 receptor agonists were favored for severe hypoglycaemia.
- Gastrointestinal events
    - Low-strength evidence suggests that neither pioglitazone nor sitagliptin are favored.
    - Low-strength evidence favors pioglitazone over exenatide.
    - Moderate-strength evidence favored pioglitazone plus metformin over GLP-1 plus metformin.
- Other events
    - Low-strength evidence suggests pioglitazone was favored over a GLP-1 agonist for pancreatitis.
    - Low-strength evidence favored a DPP-4 inhibitor plus metformin combination over pioglitazone plus metformin for short-term risk of pancreatitis.
    - Low-strength evidence favored a GLP-1 receptor agonist plus metformin combination over pioglitazone plus metformin for short-term risk of pancreatitis.
    - Low-strength evidence suggested neither pioglitazone nor exenatide are favored for systemic hypersensitivity reactions.

Evidence-based Conclusions

The evidence base addressing the use of pioglitazone alone or in combination with sulfonylureas, metformin, and/or insulin for treatment of T2DM is composed of a moderate number of RCTs with large sample sizes and follow-up greater than one year. Limited evidence from one large RCT favored pioglitazone over placebo (in addition to ongoing medications) for MACE; however, this finding was not replicated in three other placebo or no-treatment controlled studies, and two other active controlled studies; all of which reported no differences between groups for MACE and similar composite outcomes. Limited evidence suggests that pioglitazone may be associated with an increased risk of certain adverse events, including heart failure, oedema, and weight gain compared with groups receiving no

pioglitazone, sulfonylurea, and/or metformin. Pioglitazone may be associated with fewer episodes of hypoglycaemia compared with sulfonylurea regimens and may be associated with improvements in blood pressure relative to no pioglitazone.

The overall body of evidence was limited most commonly by imprecision. Confidence intervals were relatively large for many outcomes, and statistical analyses were frequently not performed. Reasons for heterogeneity across studies may be attributable to differences in patient populations (some studies enrolled patients with risk factors for macrovascular events, while others excluded at-risk patients) and treatment combinations. Although studies with smaller sample sizes and/or shorter follow up duration are available, it is unlikely that they have sufficient statistical power and length of follow-up to contribute meaningful information for outcomes of interest in this report.

5 ADDITIONAL INFORMATION AND CONSIDERATIONS

5.1 FOOD AND DRUG ADMINISTRATION (FDA) INDUSTRY GUIDANCE

In December 2008, the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) issued new recommendations for assessing the clinical benefits and safety of therapies to treat T2DM [89]. Specifically, the CDER recommended that T2DM drugs be evaluated in cardiovascular outcome trials (CVOT), or clinical studies designed to evaluate endpoints related to cardiovascular risk. Updated industry guidance states that trial sponsors should establish independent cardiovascular endpoints committees to prospectively adjudicate cardiovascular events including cardiovascular mortality, myocardial infarction, stroke, hospitalisation for acute coronary syndrome, urgent revascularisation procedures, and possibly other endpoints.

Given that the majority of studies evaluating glinides were published before the 2008 CDER guidance, it is not surprising that few evaluate outcomes related to cardiovascular risk. Based on the current body of evidence for glinides, an association between glinides and either benefits or harms related to these outcomes cannot be ruled out. Large long-term studies are needed to evaluate this possibility; though given the trend of waning use of these drugs [5], this appears unlikely.

5.2 SUBPOPULATIONS AND PATIENT SELECTION CRITERIA

Based on the evidence evaluated in this short report, it cannot be ruled out that some populations (or subpopulations of patients with T2DM) may derive benefit from repaglinide, nateglinide, and/or pioglitazone.

For some patients, case-by-case consideration of the benefits versus harms of any medication may be appropriate.

Four post hoc analyses of the PROactive study evaluated pioglitazone in subpopulations of patients with T2DM and high cardiovascular risk [69 71 76 77]. In the PROactive study [55], 5238 patients received pioglitazone or placebo in addition to existing medications. In the overall patient population, there were few clear benefits for pioglitazone over placebo; though the secondary composite outcome of cardiovascular death, myocardial infarction, or stroke occurred less frequently for patients receiving pioglitazone [55]. Findings for specific patient subgroups are summarised below:

- Chronic kidney disease: For patients with chronic kidney disease, pioglitazone was associated with a reduced occurrence of the secondary composite outcome (cardiovascular death, myocardial infarction, or stroke) versus placebo (HR 0.66; 95% CI 0.45 to 0.98) [76].
- Prior myocardial infarction: For patients with prior myocardial infarction, pioglitazone was associated with a statistically reduced risk of fatal or nonfatal myocardial infarction (*p*=0.045) and acute coronary syndrome (ACS) (*P*=0.0336) [71].
- Prior stroke: For patients with prior stroke, pioglitazone was associated with a statistically significantly lower risk of recurrent stroke (HR 0.53, 95% CI 0.53 to 0.85; *p*=0.009) and a composite of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction (HR 0.72, 95% CI 0.53 to 1.00; *p*=0.047) [77].
- Peripheral arterial disease: For patients with peripheral arterial disease at baseline, benefits of reduced rates macrovascular events were not observed. In contrast, patients without peripheral arterial disease at baseline receiving pioglitazone had lower rates of macrovascular events compared with those receiving placebo (*p*<0.05) [69].

Current clinical practice may involve case-by-case consideration of glinides or pioglitazone for patients with other clinical presentations or comorbidities. However, the studies reviewed for this short report did not present findings for any other T2DM patient subgroups.

5.3 Financial Considerations for Glinides:

Three studies published from 2002 to 2004 reported that the addition of nateglinide to metformin monotherapy was associated with reduced overall costs. Although the costs of treatment were increased with the addition of nateglinide, they were offset by the reduction of costs associated with lower complication rates [90-92]. Another study published in 2003 reported that repaglinide as a first-line therapy was associated with the highest overall 3-year treatment costs when compared with first-line sulfonylurea, metformin, or rosiglitazone [93]. A 2016 study suggested that dual therapy with glinides plus metformin had the lowest cost compared with other dual therapies (metformin plus sulfonylurea, acarbose, or thiazolidinediones) [94].

Studies evaluating cost and cost-effectiveness of glinides are summarised in Table 10.

Table 10. Summary Findings: Cost and Economic Evaluation Studies of Glinides

Key: Met, metformin; QALY, quality-adjusted life-year; Sulf, sulfonylurea; T2DM, type 2 diabetes mellitus; USD, US Dollars

Reference	*Title* Stated Objective(s)	Summary of Main Findings	Author's Conclusions
Salas (2002)[90]	*Health and economic effects of adding nateglinide to Met to achieve dual control of glycosylated haemoglobin and postprandial glucose levels in a model of T2DM* Estimate the lifetime costs of complications related to diabetes in a theoretical patient population receiving	The cost-effectiveness ratio of adding nateglinide to Met monotherapy was estimated at $27'131 per undiscounted life-year gained (95% CI $23'710-$28'577), and $43'024 (95% CI $37'285-$45'193) per additional discounted life-year gained. Costs are presented as year 2000 USD.	The addition of nateglinide to Met monotherapy (vs. Met alone) was predicted to reduce complication rates and treatment costs in this theoretical model. Increased drug treatment costs associated with nateglinide add-on therapy were estimated to be offset by the long-term savings associated with reduced complication rates.

Reference	*Title* Stated Objective(s)	Summary of Main Findings	Author's Conclusions
	Met monotherapy and predict the health and economic impact of combining met with nateglinide.	The addition of nateglinide was estimated to be associated with higher management costs, lower complication-related costs, and greater mean survival compared with Met monotherapy.	
Caro (2003)[91]	*Combination therapy for T2DM: What are the potential health and cost implications in Canada?* Estimate the lifetime costs of T2DM complications and management for patients receiving Met monotherapy, and predict the health and economic impacts of adding nateglinide to Met therapy.	The cost-effectiveness ratio of adding nateglinide to met monotherapy was estimated to be $10'504 (95% CI $9143 to $11'690) per undiscounted life-year gained, and $16'657 (95% CI $14'447 to $18'366) per discounted life-year gained. Costs are reported as year 2000 Canadian dollars. The addition of nateglinide was estimated to be associated with higher treatment costs, but lower costs related to complications.	Nateglinide as an add-on to Met may improve glycaemic control and reduce complication rates, with a reasonable associated increase in costs. Authors note that the results should be interpreted with caution, given the lack of clear long-term effects of this combination.
Ramsdell (2003)[93]	*Economic model of first-line drug strategies to achieve recommended glycaemic control in newly diagnosed T2DM* Estimate short-term direct medical costs and effectiveness associated with glycaemic control for commonly prescribed first-line oral antihyperglycaemic medications in T2DM using a literature-based decision tree model.	*3 year overall costs of treatment (cumulative discounted overall cost of treatment):* Glipizide (Sulf) gastrointestinal therapeutic system: 6106 USD Met immediate release: 6727 USD Met extended release: 6826 USD Glibenclamide (glyburide; Sulf)/Met: 7141 USD Rosiglitazone: 7759 USD Repaglinide: 9298 USD Drug acquisition cost was the main factor determining overall cost, and was highest for repaglinide Costs are reported as year 2000/2001 USD.	There are substantial short-term costs associated with comprehensive diabetes care. Repaglinide was associated with the highest costs of the drugs analysed. The authors suggest that a sulphonylurea-based strategy may be associated with similar effectiveness and cost savings over other agents, and deserves consideration as an initial drug therapy in newly diagnosed patients with T2DM.
Ward (2004)[92]	*Health and economic impact of combining met with nateglinide to achieve glycaemic control: Comparison of the lifetime costs of complications in the UK* Model the long-term economic and health impact of combination nateglinide + Met therapy vs. Met monotherapy to control T2DM.	Cumulative costs for complications were lower for combination therapy, and total costs were higher for combination therapy. Combination therapy was associated with longer survival (mean 0.39 life-years, 0.32 discounted; 0.46 QALY, 0.37 discounted) The cost per QALY was £4500 (£5'609 discounted QALY). Costs are reported as year 1999 Great Britain Pounds.	Combination therapy was associated with increased treatment costs, but these are predicted to be offset by a reduction in costs associated with treating long-term diabetes complications.

Reference	*Title* Stated Objective(s)	Summary of Main Findings	Author's Conclusions
Ou (2016)[94]	*Comparative cost-effectiveness of Met-based dual therapies associated with risk of cardiovascular diseases among Chinese patients with type 2 diabetes: Evidence from a population-based national cohort in Taiwan* Evaluate the cost-effectiveness of Met-based dual therapies associated with cardiovascular disease risk in patients with T2DM using Taiwan's National Health Insurance Research Database.	In a comparison of direct medical costs associated with Met + Sulf, Met + acarbose, Met + thiazolidinediones, and Met + glinides, the most cost-effective in the base-case analysis was Met + glinides ($194 USD savings per percentage point reduction in cardiovascular disease risk vs. Met + Sulf). It was not clear whether the glinides were repaglinide or nateglinide. Costs were converted to 2011 New Taiwan dollars, then expressed in USD.	Authors report that Met + glinides was the least expensive and most effective in avoiding cardiovascular events.

5.4 FINANCIAL CONSIDERATIONS FOR PIOGLITAZONE:

Four post hoc analyses of the PROactive study reported that pioglitazone in addition to existing medications was associated with improved life expectancy, an increase of quality-adjusted life expectancy, and higher overall costs compared with placebo in the UK, Switzerland, Germany, and the United States [95-98]. Authors report that pioglitazone in addition to existing medications would be considered to be of good value in each setting based on accepted standards.

Studies evaluating the cost and cost effectiveness of pioglitazone are summarised in Table 11.

Table 11. Summary Findings: Cost and Economic Evaluation Studies of Pioglitazone

Key: CHF, Swiss franc; ICER, incremental cost-effectiveness ratio; Pio, pioglitazone; QALY(s), quality-adjusted life-year(s); T2DM, type 2 diabetes mellitus

Reference	*Title* Objective	Summary of Main Findings	Author's Conclusions
Valentine (2007)[96]	*PROactive 06: cost-effectiveness of Pio in T2DM in the UK* Evaluate the cost-effectiveness of adding Pio to existing treatment regimens in patients with T2DM and macrovascular disease risk in the PROactive study in the UK.	*Within trial cost-effectiveness analysis:* Pio was associated with improved life expectancy (undiscounted 0.0109 years), an increase of 0.0190 quality-adjusted life-years, and higher costs (£102 per patient). After 3 years, the ICER of Pio vs. placebo was £5396 per QALY gained. *Lifetime modeling analysis:* In a 35-year model, Pio was associated with improved life expectancy (undiscounted 0.406 years), an increase of 0.152 QALY, and higher costs of care (£619 per patient) vs. patients receiving no Pio. A base-case analysis estimated an ICER of £4060 per QALY gained	Pio added to existing therapy was determined to be cost effective and represents good value for money based on currently accepted standards in the UK.

Reference	*Title* Objective	Summary of Main Findings	Author's Conclusions
		for Pio vs. no Pio. Costs are reported as year 2005 UK-specific unit costs.	
Brandle (2009)[95]	*A post hoc analysis of the PROactive study, designed to evaluate the cost-effectiveness of Pio vs. placebo, given in addition to existing treatment regimens, in patients with T2DM and evidence of macrovascular disease in Switzerland.* Evaluate the cost effectiveness of Pio vs. placebo in patients in the PROactive study with T2DM and macrovascular risk in Switzerland.	Pio was associated with improved quality adjusted life expectancy vs. placebo (0.180 QALY) Pio was associated with an increase in direct costs (CHF 10,914 per patient over a lifetime horizon). ICER for Pio vs. placebo: CHF 42'274 per life-year gained and CHF 60'596 per QALY gained Costs are reported as 2005 Swiss-specific unit costs.	The addition of Pio to existing therapy was projected to be associated with reduced complication rates and improved quality-adjusted life expectancy. Authors conclude Pio is likely to be a cost-effective treatment option in the Swiss setting.
Valentine (2009)[97]	*Long-term cost-effectiveness of Pio vs. placebo in addition to existing diabetes treatment: a US analysis based on PROactive* Evaluate the cost effectiveness of Pio vs. placebo in patients in the PROactive study with T2DM and macrovascular risk in the US.	Pio added to existing treatment was associated with increased life expectancy (0.237 life-years), improved quality-adjusted life expectancy (0.166 QALYs) vs. placebo, and fewer complications. Lifetime total direct costs were higher for Pio vs. placebo ($272,694 vs. $265,390, difference $7'305). ICER for pio versus placebo was $44'105 per QALY gained. Costs are reported as 2005 USD.	Pio in addition to existing therapy in patients with T2DM and high macrovascular risk was associated with improved life expectancy, quality-adjusted life expectancy, and lower complication rates compared with placebo, and was in a cost-effectiveness range considered to be generally acceptable.
Scherbaum (2009)[98]	*Cost-effectiveness of Pio in T2DM patients with a history of macrovascular disease: a German perspective* Evaluate the cost effectiveness of Pio vs. placebo in patients in the PROactive study with T2DM and macrovascular risk in Germany.	Pio added to existing treatment was associated with improved quality-adjusted life expectancy (0.120 QALYs) and higher direct medical costs. ICER ratio was estimated at €13,294 per QALY gained. Costs are expressed as year 2005 Euro using Germany specific sources when possible.	Authors conclude that Pio added to existing therapy is associated with reduced long-term diabetes complications and associated costs, and would be considered to represent good value for money in the German setting.

6 DISCUSSION

The current short report evaluates the best available evidence from randomised controlled trials (RCTs) for patient-centered, clinically relevant outcomes related to repaglinide, nateglinide, and pioglitazone. A discussion of each key question is presented below, followed by a discussion of overall strengths and limitations of this short report.

Key Question 1 (repaglinide)

The evidence base addressing repaglinide for treatment of T2DM is composed of a small number of RCTs addressing each outcome, with moderate sample sizes and limited follow-up of 1 year. Evidence evaluated in this short report suggests that there are no-treatment-related differences in hypoglycaemia, blood pressure, weight changes, cardiovascular morbidity, or adverse events related to repaglinide monotherapy versus comparators. Evidence for outcomes related to mortality was insufficient to draw conclusions. None of the studies included in the evidence were explicitly designed or powered to detect differences between groups in adverse events, and it is unlikely that the maximum available follow-up of one year is sufficient to meaningfully inform these outcomes.

The findings in the current report are consistent with those of published systematic reviews [14], the Agency for Healthcare Research and Quality (AHRQ) [99], and the Institute for Quality and Efficiency in Health Care [6]; which largely concluded that evidence for outcomes related to mortality, macrovascular events, and other adverse events is lacking for glinides and insufficient to draw conclusions. In the evaluated systematic reviews and meta-analyses, evidence was insufficient to evaluate for the majority of outcomes, or evidence was not stratified by glinide type; with two exceptions. In the AHRQ review, one analysis noted that changes in body weight were negligible and similar between repaglinide and sulfonylurea groups [99]. Another analysis reported no differences between repaglinide versus sulfonylurea for the risk of adverse events or hypoglycaemia [14]. These findings are in line with our conclusions that there is no evidence of treatment-based differences between repaglinide and sulfonylureas for body weight, hypoglycaemia, or adverse events; and that evidence for most outcomes is insufficient to evaluate or draw conclusions.

Glycaemic control outcomes are outside the scope of this report, though evidence from systematic reviews and meta-analyses suggests that repaglinide is associated with reductions in HbA1c. These reductions are greater than those associated with placebo, and in some analyses metformin. Evidence also suggests that HbA1c reductions are similar between repaglinide and sulfonylureas [2 14 99].

Given that the majority of studies related to glinides were published before the CDER issued recommendations for evaluation of cardiovascular risk endpoints [89], it is not surprising that studies addressing these outcomes are not available. Larger, longer term trials are needed to more fully address the outcomes of interest of this report; which, given the waning use of glinide drugs[5], are not likely to be forthcoming.

Key Question 2 (nateglinide)

The evidence base for nateglinide to treat T2DM is composed of a small number of RCTs addressing each outcome with limited follow-up and heterogeneous patient populations, treatment protocols, and comparators. Although there is no evidence that nateglinide administered with or without metformin increases the incidence of mortality, episodes of confirmed hypoglycaemia, study drop-out, or causes substantive changes in weight compared with controls the body of evidence is limited by a small quantity of studies, imprecision, and inconsistency. Due to the small number of studies, potential causes of inconsistency cannot be investigated in a meaningful way. None of the studies included in the evidence were explicitly designed or powered to detect differences between groups in adverse events, and it is unlikely that the follow-up durations are sufficient to meaningfully inform outcomes of interest.

The findings in the current report are consistent with those of the Institute for Quality and Efficiency in Health Care [6] and the AHRQ [3], which largely concluded that evidence for outcomes related to mortality, macrovascular events, and other adverse events is lacking for glinides, and insufficient to draw conclusions. No stratified analyses of nateglinide were available in the 2011 AHRQ review, due to the lack of sufficient evidence.

Glycaemic control outcomes are outside the scope of this report, though evidence from systematic reviews and meta-analyses suggests that nateglinide is associated with reductions in HbA1c. In a network meta-analysis, nateglinide was associated with significantly greater reductions in HbA1c versus placebo [2]. In the 2011 AHRQ report, nateglinide plus metformin was favored over metformin alone for HbA1c, and conflicting evidence suggested that nateglinide plus metformin was associated with similar or superior reductions in HbA1c compared with sulfonylurea plus metformin [3].

The majority of included studies evaluating nateglinide were published before the CDER issued recommendations for cardiovascular risk study endpoints [89], which likely underlies the lack of studies addressing these outcomes. Larger, longer-term trials are needed to more fully address the outcomes of interest of this report, which given the waning use of glinide drugs [5], are not likely to be forthcoming.

Key Question 3 (pioglitazone)

The evidence base addressing the use of pioglitazone is composed of a moderate number of RCTs with large sample sizes and follow-up greater than one year. Based on findings in the current report, there is no evidence for differences between pioglitazone versus active comparator groups for the occurrence of all-cause mortality or individual macrovascular events. One large trial favored pioglitazone over placebo for a composite secondary outcome of all-cause mortality, myocardial infarction, or stroke in patients with elevated cardiovascular risk[55]; although this finding was not replicated in other studies of patients with elevated cardiovascular risk [52 58 64]. For other adverse events, evidence from several included trials suggests that pioglitazone may be associated with an increased risk of heart failure, oedema, and weight gain compared with groups receiving no pioglitazone, sulfonylurea, and/or metformin. Favorable effects of pioglitazone may include fewer episodes of hypoglycaemia compared with sulfonylurea regimens, and greater improvements in blood pressure compared with no pioglitazone. The strength of evidence was limited by imprecision and a lack of statistical analyses for many outcomes. Heterogeneity in populations, interventions, and comparators precluded quantitative analysis of the findings.

A substantial number of relevant systematic reviews and meta-analyses evaluating the benefits and harms of pioglitazone have been published. These publications provide additional context and perspective on the use of pioglitazone. None exactly matched the scope of the current report; and although our findings are largely consistent with published reports, differences can be attributed to variations in PICO statements or inclusion criteria. A discussion of our findings by outcome relative to other published reports follows:

Mortality and Macrovascular Events: Our findings regarding mortality and macrovascular risk associated with pioglitazone are largely in line with those of published systematic reviews and meta-analyses, and differences can be attributed to variations in scope across reports [4 5 85 86]. In line with our findings, a 2016 AHRQ review found low-strength evidence suggesting no differences between pioglitazone versus metformin in mortality or cardiovascular risk outcomes [5]. One analysis in the AHRQ review favored pioglitazone over sulfonylurea for short-term cardiovascular disease [5]. This was based on low-strength evidence from one study that did not meet our inclusion criteria. Four studies included in the current body of evidence for this report compared pioglitazone with sulfonylurea (alone or in combination), and none reported differences in macrovascular risk, though short-term cardiovascular disease, specifically, was not reported as an outcome [59 60 62 63].

Evidence from two 2017 systematic reviews and meta-analyses concluded that pioglitazone is associated with a decreased risk of major adverse cardiac events, stroke, and myocardial infarction, and an increased risk of heart failure [85 86]. These systematic reviews and meta-analyses enrolled non-T2DM populations, which may underlie the slight difference with conclusions in the current report. Specifically, these meta-analyses included findings from the IRIS study [100] and the ACT NOW study [101], which report cardiovascular benefit for pioglitazone in patients with prediabetes or impaired glucose tolerance. These studies were considered outside the scope of the current report, given that pioglitazone is not reimbursed for non-T2DM populations in Switzerland. In a 2019 systematic review and meta-analysis, pioglitazone monotherapy had no association with risk of cardiovascular or vascular disorders [4]; this finding is in line with our conclusions.

Hypoglycaemia: We report limited evidence that pioglitazone is associated with fewer hypoglycaemic events compared with sulfonylureas, and a greater number of events compared with placebo or no treatment controls. Several studies did not employ statistical methods for these analyses, and heterogeneity across studies precluded clear quantitative interpretation of the findings. A 2019 systematic review and meta-analysis found lower rates of hypoglycaemia associated with pioglitazone monotherapy versus a pooled analysis of other therapies [4]. In the 2016 AHRQ review, evidence was not stratified by glitazone type, though fewer hypoglycaemic events were observed for glitazones compared with sulfonylureas [5].

Blood Pressure: We report limited evidence that pioglitazone is associated with favorable changes in blood pressure compared with placebo, and conflicting evidence regarding its comparative impact with other therapies. In a 2019 systematic review and meta-analysis of pioglitazone monotherapy, meta-analyses showed that pioglitazone was associated with significantly greater improvements in blood pressure compared with a pooled analysis of alternative therapies [4].

Body Weight: Evidence in the current report suggests a trend toward less favorable body weight outcomes associated with pioglitazone versus comparators, though few studies provided statistical analyses for this outcome, and heterogeneity across studies for populations, interventions, and

comparators precludes clear interpretations of these findings. In a 2019 systematic review and meta-analysis, weight outcomes were less favorable for pioglitazone monotherapy versus a pooled evaluation of alternative monotherapies [4]. Similarly, in the 2016 AHRQ review, glitazones had less favorable weight outcomes compared with metformin and sulfonylureas; however, these analyses did not stratify by pioglitazone or rosiglitazone, and conclusions regarding pioglitazone cannot be clearly drawn [5].

Oedema: Evidence in the current report suggests a trend towards increased rates of oedema associated with pioglitazone versus comparators; however, few studies provided statistical analyses for this outcome, and heterogeneity across studies precluded clear quantitative interpretations of these findings. In a 2019 systematic review and meta-analysis, pioglitazone monotherapy was associated with an increased risk of oedema compared with a pooled analysis of other oral antidiabetic monotherapies in patients with T2DM [4].

Bladder Cancer: Bladder cancer is a rare event, and in order to estimate effectively, it requires studies with large sample sizes and follow-up periods. Based on evidence from RCTs in patients with T2DM, there does not appear to be an increased risk of bladder cancer for pioglitazone [52 55 63]. However, it is likely that these studies lack statistical power and follow-up durations to provide accurate data. Three systematic reviews and meta-analyses were identified that evaluated the risk of bladder cancer associated with pioglitazone using evidence from both RCTs and observational studies, some with heterogeneous or non-T2DM populations [19-21]. All three reviews conclude that pioglitazone is associated with a small statistically significant increased risk of bladder cancer compared with never-use of pioglitazone; though it is not possible to rule out confounding factors that might underlie these conclusions.

Fracture: There is conflicting evidence regarding the risk of fracture associated with pioglitazone, reflected both in the current short report and in published systematic reviews and meta-analyses [87 88]. Some evidence suggests an increased risk for pioglitazone versus sulfonylureas [60 88], and some evidence suggests no treatment-related differences [62 63 87]. Differences in findings may be due to heterogeneity in patient populations, risk factors, and comorbidities across evaluated studies.

HbA1c: Glycaemic control outcomes were outside the scope of this report, though findings from systematic reviews and meta-analyses suggest that pioglitazone is associated with decreased HbA1c, with few differences compared with alternative antidiabetic treatments [4 5 18].

Strengths and Limitations of this Short Report

The following describes the strengths and limitations of this short report.

Strengths:

- Included studies represent the upper tier of evidence for the outcomes of interest in terms of being the largest and longest-term trials available for each drug. The outcomes of interest for this short report are likely to be rare and require long-term follow-up (e.g. mortality and occurrence of macrovascular events). This body of evidence represents studies with the highest likelihood of providing clinically meaningful data for these outcomes of interest.

- Evidence for this report was identified using carefully crafted systematic searches of bibliographic databases, and verified with extensive cross checking of systematic reviews, meta-analyses, and published guidelines.
- The studies included in the body of evidence are RCTs of generally acceptable quality, and a generally low risk of bias, reflecting satisfactory internal validity of the individual studies.
- The findings of this report are largely consistent with those of published systematic reviews and meta-analyses, with any differences largely attributable to scope variations. A detailed discussion of findings from systematic reviews and meta-analysis is included to provide supplementary context to the body of evidence evaluated in this short report.

Limitations:

- This short report excluded studies with small sample sizes and short follow-up duration from the body of evidence. Although excluded studies might provide additional details on comparisons of interest, smaller studies are unlikely to have sufficient statistical power to accurately evaluate rare events, and shorter follow-up durations are unlikely to be sufficient for detecting outcomes such as mortality and cardiovascular risk. We suggest that it is unlikely that broader inclusion criteria would substantively impact conclusions drawn in the report.
- This short report employs a tightly focused PICO statement and strict study selection criteria. Non-diabetic populations, interventions, and comparators not reimbursed in Switzerland, and intermediate outcomes (e.g. HbA1c) were outside the scope. As mentioned above, a discussion of findings from systematic reviews and meta-analyses is included to provide supplementary information further context.
- This short report does not employ quantitative data analysis. Although this was considered during the protocol development, meta-analysis was ultimately deemed inappropriate due to the heterogeneity of interventions, comparators, outcome definitions, and follow-up durations. A narrative synthesis was employed, which involves logical presentation of findings by outcome with discussion of relationships across studies, precision and effect size, clinical importance, and potential sources of heterogeneity.
- This short report was not scoped to evaluate the use of these drugs in subpopulations of patients with T2DM, or in patients with specific comorbidities. It cannot be ruled out that repaglinide, nateglinide, or pioglitazone warrant a separate evaluation of benefits versus harms for specific patient subgroups, as discussed in the “Subpopulations and Patient Selection Criteria” section.

7 CONCLUSIONS

Key Question 1: Findings from RCTs with 1-year follow-up suggest that repaglinide monotherapy does not appear to be associated with differences in hypoglycaemia, blood pressure, weight changes, cardiovascular morbidity, or adverse events relative to comparators (sulfonylurea or metformin). Evidence for outcomes related to mortality was reported in a single study and was insufficient to draw conclusions. Interpretation of the findings is limited by clinical heterogeneity across studies (which precluded quantitative analyses of the findings), and a lack of statistical analyses within studies for many

outcomes. The evidence is limited most notably by the lack of follow-up beyond 12 months, which is unlikely to inform outcomes of interest for this short report.

Key Question 2: The evidence base addressing nateglinide to treat T2DM is composed of a small number of RCTs addressing each outcome, with heterogeneous patient populations, treatment protocols, and comparators. Based on studies without sufficient long-term follow-up, there is no evidence that nateglinide administered with or without metformin is with associated differences in mortality, episodes of confirmed hypoglycaemia, study drop-out, or substantive changes in weight compared with controls. Evidence was not available for the incidence of macrovascular or microvascular events. Interpretation of the findings is limited by clinical heterogeneity across studies (which precluded quantitative analyses of the findings), and a lack of statistical analyses within studies for many outcomes The evidence is limited most notably by small study sizes with limited follow-up that are unlikely to be sufficient to meaningfully inform the outcomes of interest.

Key Question 3: When compared with other antidiabetic drugs, pioglitazone was not associated with differences in the risk for all-cause mortality or individual macrovascular events. Limited, conflicting evidence suggests that major adverse cardiovascular events (MACE) may occur at a lower rate in patients receiving pioglitazone versus placebo, although this finding was not replicated in other placebo or active controlled studies. Evidence suggests that pioglitazone may be associated with an increased risk of certain adverse events including heart failure, oedema, and weight gain compared with groups receiving no pioglitazone, sulfonylurea, and/or metformin. Pioglitazone may also be associated with fewer episodes of hypoglycaemia compared with sulfonylurea regimens and may be associated with improvements in blood pressure relative to no pioglitazone. Clinical heterogeneity across studies precluded quantitative analyses of the findings and many individual studies did not report statistical analyses. The lack of consistently established benefit with respect to direct health outcomes and apparent risks associated with pioglitazone should be considered in treatment and coverage decisions.

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261. Ramachandran A, Snehalatha C, Salini J, et al. Use of glimepiride and insulin sensitizers in the treatment of type 2 diabetes--a study in Indians. The Journal of the Association of Physicians of India 2004;52:459-63 [published Online First: 2005/01/14]

262. Goke B. Improved glycemic control and lipid profile in a randomized study of pioglitazone compared with acarbose in patients with type 2 diabetes mellitus. Treatments in endocrinology 2002;1(5):329-36 [published Online First: 2005/04/19]

9 APPENDIXES

9.1 APPENDIX I. LITERATURE SEARCH STRATEGIES

Appendix Table 1. PubMed Search Details

Term	PubMed Translations
pioglitazone	"pioglitazone"[MeSH Terms] OR "pioglitazone"[All Fields]
Actos	"pioglitazone"[MeSH Terms] OR "pioglitazone"[All Fields] OR "actos"[All Fields]
thiazolidinedione	"2,4-thiazolidinedione"[Supplementary Concept] OR "2,4-thiazolidinedione"[All Fields] OR "thiazolidinedione"[All Fields] OR "thiazolidinediones"[MeSH Terms] OR "thiazolidinediones"[All Fields]
thiazolidinediones	"thiazolidinediones"[MeSH Terms] OR "thiazolidinediones"[All Fields]
glitazone	"thiazolidinediones"[MeSH Terms] OR "thiazolidinediones"[All Fields] OR "glitazone"[All Fields]
glitazones	"thiazolidinediones"[MeSH Terms] OR "thiazolidinediones"[All Fields] OR "glitazones"[All Fields]
diabetes mellitus	"diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]
type 2 diabetes	"diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "type 2 diabetes"[All Fields]
type ii diabetes	"diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR ("type"[All Fields] AND "ii"[All Fields] AND "diabetes"[All Fields]) OR "type ii diabetes"[All Fields]
mortality	"mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]
morbidity	"epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms]
cardiac	"heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]
heart	"heart"[MeSH Terms] OR "heart"[All Fields]
cardiovascular	"cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]
fracture	"fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]
malignancy	"neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "malignancy"[All Fields]
cancer	"neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]
stroke	"stroke"[MeSH Terms] OR "stroke"[All Fields]
kidney	"kidney"[MeSH Terms] OR "kidney"[All Fields]
retinopathy	"retinal diseases"[MeSH Terms] OR ("retinal"[All Fields] AND "diseases"[All Fields]) OR "retinal diseases"[All Fields] OR "retinopathy"[All Fields]
nephropathy	"kidney diseases"[MeSH Terms] OR ("kidney"[All Fields] AND "diseases"[All Fields]) OR "kidney diseases"[All Fields] OR "nephropathy"[All Fields]

Term	PubMed Translations
myocardial infarction	"myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]
safety	"safety"[MeSH Terms] OR "safety"[All Fields]
death	"death"[MeSH Terms] OR "death"[All Fields]
blood pressure	"blood pressure"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "blood pressure determination"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields] AND "determination"[All Fields]) OR "blood pressure determination"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "arterial pressure"[MeSH Terms] OR ("arterial"[All Fields] AND "pressure"[All Fields]) OR "arterial pressure"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields])
hypoglycemia	"hypoglycaemia"[All Fields] OR "hypoglycemia"[MeSH Terms] OR "hypoglycemia"[All Fields]
weight	"weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "weight"[All Fields] OR "body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields]
randomized controlled trial	"randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]
meglitinide	"meglitinide"[Supplementary Concept] OR "meglitinide"[All Fields]
repaglinide	"repaglinide"[Supplementary Concept] OR "repaglinide"[All Fields]
nateglinide	"nateglinide"[MeSH Terms] OR "nateglinide"[All Fields]
prandin	"repaglinide"[Supplementary Concept] OR "repaglinide"[All Fields] OR "prandin"[All Fields]
GlucoNorm	"repaglinide"[Supplementary Concept] OR "repaglinide"[All Fields] OR "gluconorm"[All Fields]
NovoNorm	"repaglinide"[Supplementary Concept] OR "repaglinide"[All Fields] OR "novonorm"[All Fields]
starlix	"nateglinide"[MeSH Terms] OR "nateglinide"[All Fields] OR "starlix"[All Fields]

Publications referenced during the manual search for additional studies not identified through electronic database searches included the 2011 and 2016 Agency for Healthcare Research and Quality (AHRQ) reports on treatment of T2DM [3 5], as well as systematic reviews and meta-analyses [2 4 14 19-21 80-83 85-88 102-106].

9.2 APPENDIX II. EXCLUDED STUDIES

Key excluded studies are summarised in Appendix Table 2. This table lists publications that were excluded following full text review and the reasons for exclusion.

Appendix Table 2. Studies Excluded Following Full Text Review

Reason for Exclusion	Citations
Mixed or unspecified interventions, with no data reported separately for a drug of interest.	107-147
No outcome of interest, or insufficient data reported to evaluate outcome of interest.	148-159
Insufficient sample size.	160-169
Insufficient patient information.	170-174
Observational study with baseline differences between treatment groups.	175-178
Not a comparison of interest.	179-182
Non-comparative study design.	183-185
No novel or non-duplicate data reported.	186-188
Not a population of interest.	189 190
Non-contemporaneously treated groups.	191
Insufficient follow-up (for the randomised phase).	192 193

9.3 APPENDIX III. EVIDENCE QUALITY ASSESSMENT

The quality of the evidence is assessed in two ways:

- By assessing the quality of individual studies, that is, their internal validity or risk of bias, and
- By assessing the quality of the evidence base for each outcome and duration of follow-up, sometimes also known as rating the strength of evidence (SOE) supporting a conclusion.

Individual Study Quality and Risk of Bias

To assess the quality of individual studies, we employed widely accepted instruments developed by international panels of methodology experts and accepted worldwide.

RCTs: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials is used to assess quality in RCTs [32]. This tool addresses potential selection bias specifically targeting randomised studies, performance bias, detection bias, attrition bias, reporting bias, and other biases. This instrument and its directions can be found here: RoB2 Cochrane Risk-of-Bias Tool for Randomized Trials.

Observational Studies: The Newcastle-Ottawa Scale (NOS) is employed to assess the quality of nonrandomised studies [33]. This tool addresses potential selection bias, comparability between groups, and exposure to the intervention of interest in a way that is appropriate for nonrandomised studies. This instrument and its directions can be found here: The Newcastle-Ottawa Scale (NOS).

Individual studies were labeled as good, fair, or poor based on evaluation of their risk of bias using the instruments noted above, and other quality issues (e.g. follow-up limitations, quality of outcome measurement and reporting, other potential confounding factors). Factors contributing to risk of bias and other quality issues are documented for each individual study in the appendix evidence tables (Appendix IV. Evidence Tables). Studies with a low risk of bias and limited additional quality issues were labeled as "good" quality, those with unclear risk of bias and/or additional quality issues were labeled as "fair", and those with high risk of bias and/or additional quality issues were labeled as "poor".

Overall Quality of the Evidence

The overall quality of the evidence, or strength of evidence, is assessed based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system [34 35]. The GRADE system is applied to the evidence informing a potential conclusion for each PICO.

Application of the GRADE system to determine a strength of evidence rating entails multiple steps. Study design sets the starting GRADE rating (with RCTs rated as 'high' and observational studies as 'low'), which may be adjusted based upon the quality of the individual studies informing the conclusion, as described in the previous section. In this report, only RCTs were included so the starting SOE was "high" for all outcomes. For overall quality, evidence bases composed of predominantly good quality individual studies had no change, evidence bases composed of predominantly fair quality individual studies had -1 point change, and those composed of primarily poor or very poor quality individual studies had -2 point change.

Factors that may further decrease the SOE rating include:

- Inconsistency: Studies reported inconsistent results;

- Imprecision: Variability in effect size or lack of statistical power to detect statistically significant differences in an outcome of interest cause uncertainty about the effect;
- Indirectness: Lack of pertinence to one or more factors in the PICO statement (indirectness was not a consideration in this report because only RCTs relevant to the PICO were included).

Where the impact on confidence in the conclusion was serious, 2 points were detracted and the rationale is provided in the table. Otherwise, 1 point was detracted per factor.

Factors that can increase the rating include:

- Large magnitude of effect;
- All plausible confounders would have decreased the effect size;
- Evidence of a dose-response association.

Upon consideration of these factors, the GRADE system yields an intuitive SOE rating representing level of confidence in the conclusion [35]:

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
    - We rated outcomes with no detractions as having “high” SOE.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
    - We rated outcomes with 1 or 2 total detractions as having “moderate” SOE.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
    - We rated outcomes with 3 total detractions as having “low” SOE.
- Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
    - We rated outcomes with 4 or more total detractions as having “very low” SOE.
- Insufficient: We also applied a rating of ‘insufficient’ where evidence was of insufficient quantity, quality, and/or consistency to derive any estimate of effect or conclusion about direction of effect.
    - An example scenario is if only one underpowered study reported the outcome and found no significant difference between groups.

9.4 APPENDIX IV. EVIDENCE TABLES

9.4.1 Key Question 1. What is the comparative effectiveness and safety of repaglinide, alone or in combination with metformin, pioglitazone, or insulin?

Appendix Table 3. Key Question 1. Studies Evaluating the Effectiveness and Safety of Repaglinide

Key: BMI, body mass index; f/u, follow-up; Glim, glimepiride; Gly, glyburide; grp(s), group(s); HbA1c, glycated hemoglobin; ITT, intention to treat; Met, metformin; mm Hg, millimetre of mercury; mmol, millimole; mo(s), month(s); NR, not reported; pt(s), patient(s); Repa, repaglinide; Sulf, sulfonylurea; T2DM, type 2 diabetes; tx, treatment; wk(s), week(s); yr(s), year(s)

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Marbury et al. (1999)[41] Orlando Clinical Research Center, Orlando, Florida, USA; NovoNordisk Pharmaceuticals Inc., Princeton, New Jersey, USA; State University of New York Health Science Center at Brooklyn, Brooklyn, New York, USA Multiple centers in the United States Randomised, multicentre, double-blind equivalence study comparing Repa vs. Gly as monotherapy in pts w/ T2DM. *F/u:* 1 yr *Time frame:* NR *Funding source:* NovoNordisk Pharmaceuticals	n=576 pts randomly allocated to: Repa grp: 383 pts Gly grp: 193 pts *Power analysis:* Based on a sample size of 450 pts (300 Repa grp, 150 Gly grp), this study had a 98% power to detect equivalence of Repa to Gly. Definition of equivalence NR. *ITT analysis*: Last observation carried forward. ITT population included all pts randomised to tx. *Pt characteristics (Repa grp, Gly grp):* % female: 33%, 34% Mean age, yrs: 58.3, 58.7 Mean BMI, kg/m^2: 29.4, 29.1 Disease duration, yrs: 7.2, 8.3 Pharmacotherapy-naïve: 13%, 13% % mean HbA1c: 8.7, 8.9	Pts were randomised within each center in 2:1 ratio of Repa to Gly. Methods for randomisation, allocation concealment, and blinding NR. Pts stopped using all other oral antidiabetic medications on the morning of the first study visit following randomisation. Pts received 8-wk forced titration period followed by 52-wk maintenance period. Down titration permitted when clinically indicated. *Intervention:* Up to 4 mg Repa 3× daily before meals. Maximum dose (12 mg Repa) achieved in 55% of pts. *Comparator:* Pts received 2.5 mg, 5 mg, or 10 mg Gly daily before breakfast +	*Data reported as Repa grp, Gly grp* *Study completion:* % pts completing study: 56%; 60% Most frequent reason for non-completion was lack of tx effectiveness for both grps. Other reasons include adverse events, noncompliance, other medical problems, loss to f/u, personal problems, and relocation. No difference between grps in frequency of reasons for non-completion. *Adverse events:* Deaths, # pts (% pts): 3/383 (0.8%), 1/193 (0.5%) No deaths were related to tx. All possibly or probably tx-related adverse events, # pts (% pts): 116/383 (30%), 55/193 (28%)	Results suggest that Repa may be associated w/ higher rates of serious adverse events (10% vs. 6%) and cardiovascular events (5% vs. 2%) than Gly; however, statistical and clinical significance of these findings are not clear. *Limitations:* Despite ITT analysis, high overall pt attrition (43%); details of methods for randomisation, allocation concealment, blinding NR. *Study quality:* Poor *Conflicts of interest:* 2 of 4 authors employed by a pharmaceutical manufacturer.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	Inclusion criteria: Pts aged 37-75 yrs w/ a BMI of 20-40 kg/m^2 and T2DM ≥6 mos. BL HbA1c 6.5-14.6%. Pts received prior tx w/ diet/exercise therapy or oral hypoglycaemic agents other than Repa or Gly. *Exclusion criteria:* Chronic insulin use; severe, uncontrolled hypertension; cardiac disorders; proliferative retinopathy; abnormal kidney or liver function; known contraindications to Gly; previous tx w/ systemic corticosteroids.	placebo before lunch and dinner; pts who required higher dose received 10 mg Gly daily before breakfast, placebo before lunch, and 5 mg Gly before dinner. Maximum dose (15 mg Gly) achieved in 52% of pts. *Assessment(s):* Every 10-14 days during titration period, every 2 mos during maintenance period. *Outcome measure(s):* Adverse events. Hypoglycaemic events were pt reported and defined as symptoms of sweating, hunger, dizziness, tremors, and/or a blood glucose level of <45 mg/dL (<2.6 mmol/L). Note that intermediate outcomes were also reported but are not summarised here.	Withdrawal due to adverse events, # pts (% pts): 39/383 (10%), 19/193 (10%) Serious adverse events, # pts (% pts): 39/383 (10%), 12/193 (6%) Cardiovascular adverse events, # pts (% pts): 19/383 (5%), 4/193 (2%) Hypoglycaemia, # pts (% pts): 59/383 (15%), 37/193 (19%) Headache, # pts (% pts): 14/383 (4%), 5/193 (3%) Tremor, # pts (% pts): 15/383 (4%), 5/193 (3%) Dizziness, # pts (% pts): 11/383 (3%), 6/193 (3%) Increased appetite, # pts (% pts): 11/383 (3%), 0/193 (0) Hyperglycaemia, # pts (% pts): 8/383 (2%), 5/193 (3%) Tremor, # pts (% pts): 15/383 (4%), 5/193 (3%) Blood pressure: No clinically significant changes in mean systolic and diastolic blood pressure in either grp. Data NR. Mean body weight change, kg: -0.22, 0.05. Difference NS.	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Wolffenbuttel et al. (1999)[43] University Hospital Maastricht, Maastricht, the Netherlands; University of Munich, Munich, Germany 44 centers in Germany (32), Austria (2), and the Netherlands (10) Randomised, multicentre, double-blind equivalence study comparing Repa (w/ or without Sulf) vs. Gly (w/ or without Sulf) in pts w/ T2DM. *F/u:* 1 yr *Time frame:* NR *Funding source:* NR	n=425 pts randomly allocated to: Repa grp: 286 pts Gly grp: 139 pts *Power analysis:* Sample of 350 pts required to provide 80% power to detect equivalence of Repa to Gly for HbA1c *ITT analysis:* Last observation carried forward. ITT population included all pts randomised to tx *Pt characteristics: (repa grp, gly grp):* % female: 38%, 32% Mean age, yrs: 61, 61 Mean BMI, kg/m^2: 28.4, 28.0 Mean body weight, kg: 81.5, 81.3 Disease duration, yrs: 6, 6 Pharmacotherapy-naïve: 9%, 7% % mean HbA1c: 7.1, 7.0 *Inclusion criteria:* Pts aged 40-75 yrs w/ a BMI of 21-35 kg/m^2 and T2DM. Baseline HbA1c >6.5% when treated w/ diet alone, and <12% when treated w/ diet and pharmacotherapy. Pts received prior tx w/ diet/exercise therapy or oral hypoglycaemic agents. *Exclusion criteria:* Chronic insulin use; severe, uncontrolled hypertension; cardiac disorders; abnormal kidney or liver function; other diseases that could interfere w/	Pts were randomised into blocks of 6 pts per tx grp in 2:1 ratio of Repa to Gly. Methods for randomisation, allocation concealment, and blinding NR. Pts stopped using all other oral antidiabetic medications except Sulf at the beginning of titration period. Pts received 6-8 wk forced titration period followed by 52-wk maintenance period. *Intervention:* Up to 4 mg Repa 3× daily before meals. *Comparator:* Pts received 1.75 mg, 3.5 mg, or 7.0 mg Gly daily before breakfast + placebo before lunch and dinner; pts who required higher dose received 7.0 mg Gly daily before breakfast, placebo before lunch, and 3.5 mg Gly before dinner. *Assessment(s):* Every 2 wks during titration period, every 2 mos during maintenance period. *Outcome measure(s):* Adverse events. Hypoglycaemic events were pt reported, and were typically accompanied by blood glucose measurements. Blood glucose <4.4 mmol/L were	*Data reported as Repa grp, Gly grp* *Study completion:* % pts completing study: 74%; 78% Most frequent reason for non-completion was adverse events, lack of tx effectiveness, and noncompliance. Differences between grps NR. *Adverse events:* Hypoglycaemic events, # pts (% pts): 26 (9%), 13 (9%), *p*=NR Cardiovascular adverse events: Described by authors as occurring w/ similar frequency in both tx grps (data NR). Blood pressure: Small but statistically significant decrease from BL for both grps but NS between grps. Clinical significance not clear but unlikely. Repa change from 147/86 to 142/84; Gly change from 146/83 to 143/83. Mean body weight change, kg: 0.0, 0.7, *p*=NS.	Results suggest no difference between Repa and Gly in frequency of adverse events. *Limitations:* Details of methods for randomisation, allocation concealment, blinding NR; few safety outcomes reported. *Study quality:* Poor *Conflicts of interest:* Study does not include any information on potential conflicts of interest or source of study funding.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	study participation; known contraindications to sulfonylureas; tx w/ systemic corticosteroids; pts who were pregnant, nursing, or intended to become pregnant.	also reported. Note that intermediate outcomes were also reported but are not summarised here.		
Derosa et al. (2003)[38] University of Pavia, Pavia, Italy Single center in Italy Randomised, single-center, double-blind study comparing Repa vs. Glim as monotherapy in pts w/ T2DM. *F/u:* 1 yr *Time frame:* NR *Funding source:* NR	n=132 pts randomly allocated to: Repa grp: 66 pts Glim grp: 66 pts *Power analysis:* NR *ITT analysis:* NR *Pt characteristics:* *(Repa grp, Glim grp):* % female: 50%, 52% Mean age, yrs: 56, 54 Mean BMI, kg/m^2: 26.1, 26.4 Mean body weight, kg: 76.4, 77.1 *Inclusion criteria:* Pts w/ T2DM ≥6 mos, HbA1c >7.0%; no oral antidiabetic tx. *Exclusion criteria:* Hypertension; renal or cardiovascular disease; smokers.	Pts were randomised into Repa or Glim grps. Randomisation codes placed in envelopes by statistician and drawn upon enrollment. Investigators and pts were blinded, w/ identical medication bottles prepared by hospital pharmacy and dispensed directly to pts. Pts followed specific dietary regimen throughout study period. Diet included 1400-1600 kilocalories/day and consisted of 55% carbohydrates, 2% proteins, 20% lipids, maximum of 105 mg/day cholesterol, and minimum of 36 g/day fiber. Pts also kept food diaries and regular meetings w/ a dietician. Study period began w/ 4-wk placebo washout period. Pts then received forced 8-wk titration period followed by 52-wk maintenance period. *Intervention:* Pts started w/ 1 mg Repa daily. Mean final dose was 2.5 mg daily. *Comparator:* Pts started w/ 1 mg Glim daily. Mean final dose was 3.0 mg daily.	*Data reported as Repa grp, Glim grp* *Study completion:* % pts completing study: 94%; 94% 5 pts (3 Repa grp, 2 Glim grp) withdrew due to ineffectiveness of tx; 1 pt in Repa grp lost to f/u; 2 pts in Glim grp withdrew due to tx-related side effects (dizziness, nausea, headache). *Adverse events:* No specific adverse events or frequency of events reported. Blood pressure: No difference within or between grps. Data NR. Mean body weight change, kg: 0.1-0.5, *p*=NS Mean BMI change, kg/m^2: 0.1, -0.5, *p*=NS.	Results suggest no significant difference in risk of adverse events for Repa and Glim. Note Repa dosage was lower than in other studies (mean final dose 2.5 mg daily). *Limitations:* Power analysis NR. *Study quality:* Fair *Conflicts of interest:* Study does not include any information on potential conflicts of interest or source of study funding.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
		Assessment(s): Every 3 mos during maintenance period. *Outcome measure(s):* Adverse events. Note that intermediate outcomes were also reported but are not summarised here.		
Derosa et al. (2003)[37] University of Pavia, Pavia, Italy Single center in Italy Randomised, single-center, unblinded study comparing Repa vs. Met as monotherapy in pts w/ T2DM. *F/u:* 1 yr *Time frame:* NR *Funding source:* NR	n=112 pts randomly allocated to: Repa grp: 56 pts Met grp: 56 pts *Power analysis:* NR *ITT analysis:* NR *Pt characteristics:* *(Repa grp, Met grp):* % female: 48%, 52% Mean age, yrs: 55, 52 Mean BMI, kg/m^2: 25.2, 24.7 Mean body weight, kg: 70.2, 72.3 % mean HbA1c: 7.6%, 7.4% Mean blood pressure, mm Hg: 124/80, 125/81 *Inclusion criteria:* Pts w/ T2DM for >6 mos duration; >7.0%; low-density lipoprotein cholesterol >2.59 mmol/L; no oral antidiabetic tx. *Exclusion criteria:* Hypertension; renal or cardiovascular disease; smokers.	Pts were randomised into Repa grp or Met grp. Methods for randomisation and allocation concealment NR. Study described as "open label," not blinded. Pts followed specific dietary regimen throughout study period. Diet included 1400-1600 kilocalories/day and consisted of 55% carbohydrates, 2% proteins, 20% lipids, maximum of 105 mg/day cholesterol, and minimum of 36 g/day fiber. Pts also kept food diaries and had regular meetings w/ a dietician. Study period began w/ 4-wk PBO washout period. Pts then received forced 8-wk titration period followed by 52-wk maintenance period. *Intervention:* Pts started w/ 1 mg Repa daily, given as 0.5 mg before lunch and dinner. Dosage titrated to maximum 4 mg daily, divided across 3 meals. Mean final dose was 3.0 mg daily.	*Data reported as Repa grp, Met grp* *Study completion:* % pts completing study: 95%; 88% 7 pts (3 Repa grp, 4 Met grp) withdrew due to ineffectiveness of tx; 1 pt in Met grp lost to f/u; 2 pts in Met grp withdrew due to tx-related side effects (nausea, diarrhoea). *Adverse events:* Authors reported that no serious adverse events were observed in either grp. Hypoglycaemia: Authors reported that no pts experienced mild or severe hypoglycaemia. Blood pressure: 121±7.1 and 81±5.1 mm Hg; 126±5.1 and 80±4.5 mm Hg, *p*=NS from BL or between grps. Mean body weight change, kg: -0.4 (95% CI -0.8 to 0.28), -2.0 (95% CI -6 to 5). Difference NS (*p*=0.14).	Results suggest low risk of adverse events but Repa dosage was low in comparison to other studies (mean final dose 3.0 mg daily). *Limitations:* Power analysis NR; details of methods for randomisation and allocation concealment NR; study not described as blinded. *Study quality:* Poor *Conflicts of interest:* Study does not include any information on potential conflicts of interest or source of study funding, unclear if analyses used ITT population.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
		Comparator: Pts started w/ 1000 mg Met daily, given as 500 mg after lunch and dinner. Dosage titrated to maximum 2500 daily, divided across 3 meals. Mean final dose was 2000 mg daily. *Assessment(s):* Every 3 mos during maintenance period. *Outcome measure(s):* Adverse events. Note that intermediate outcomes were also reported but are not summarised here.	Mean BMI change, kg/m^2: -0.1 (95% CI -0.3 to 0.19), -0.6 (95% CI -1.5 to 1.2). Difference NS (p=0.12).	
Esposito et al. (2004)[39] Second University of Naples, Naples, Italy Single center in Italy Randomised, single-center, single-blind study comparing Repa vs. Gly as monotherapy in pts w/ T2DM who had no previous anti-diabetic pharmacotherapy tx. *F/u:* 1 yr *Time frame:* NR *Funding source:* Second University of Naples, Cardiovascular Research Center, and the Regione Campania.	n=175 pts randomly allocated to: Repa grp: 88 pts Gly grp: 87 pts *Power analysis:* NR *ITT analysis:* For drop-outs, no change from BL for all variables; ITT population included all pts randomised to tx. *Pt characteristics:* *(Repa grp, Gly grp):* % female: 47%, 47% Mean age, yrs: 52, 51 Mean BMI, kg/m^2: 28.5, 28.3 % mean HbA1c: 7.5%, 7.4% Mean blood pressure, mm Hg: 142/87, 143/86 % smokers: 11%, 13% *Inclusion criteria:*	Pts were randomised using a computer-generated random number sequence. Allocation was concealed in sealed study folders in secure location until after pt consent was obtained. Laboratory staff was blinded to pt assignment. Pts and treating physicians were not blinded. Pts received 6-8 wk forced titration period followed by 52-wk maintenance period. *Intervention:* Pts received 0.5 mg, 1 mg, 2 mg, or 4 mg 3× daily before meals. *Comparator:* Pts received 2.5 mg, 5 mg, 7.5 mg, or 10 mg Gly 2× daily before breakfast and dinner.	*Data reported as Repa grp, Gly grp* *Study completion:* % pts completing study: 92%; 92% 7 pts in each grp withdrew from the study; 10 withdrew due to personal reasons, 2 due to severe illness, and 2 were lost to f/u. *Adverse events:* No specific severe adverse events or frequency of events reported. Hypoglycemia, % pts: 9%, 13%; p=NR, authors report the number was similar. Blood pressure change from BL, mean±SD: Systolic: -2±2, -1±2, p=0.17	Results suggest no difference between Repa and Gly in frequency of adverse events. *Limitations:* Power analysis NR; pts not blinded. *Study quality:* Fair *Conflicts of interest:* No potential author conflicts disclosed. Study funding presented no conflict of interest.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	Pts aged 35-70 yrs w/ T2DM for >6 mos and< 3 yrs duration; HbA1c >6.5%; BMI >24 kg/m^2; no history of oral anti-diabetic pharmacotherapy. *Exclusion criteria:* Insulin use; severe uncontrolled hypertension; renal, liver, or cardiovascular disease; women who were or intended to become pregnant; recent acute illness; change in diet, tx, or lifestyle in 3 mos before study.	Maximum daily dosages (12 mg Repa and 20 mg Gly) achieved in 59% of all pts. Separate Repa grp and Gly grp data NR, but authors reported no significant difference between grps. *Assessment(s):* Monthly during maintenance period. *Outcome measure(s):* Adverse events. Hypoglycaemic symptoms were pt reported and accompanied by blood glucose measurements if possible. Note that intermediate outcomes were also reported but are not summarised here	Diastolic: -1±2, 0.5±2, *p*=0.20 BMI change from BL, mean±SD kg/m^2: 0.3±0.4, 0.4±0.4 (*p*=0.22).	
Abbatecola et al. (2006)[36] Second University of Naples, Naples, Italy Randomised, unblinded study comparing Repa vs. Gly as monotherapy in older pts w/ T2DM who had no previous anti-diabetic pharmacotherapy tx. *F/u:* 1 yr *Time frame:* September 2001 – September 2004 *Funding source:* Second University of Naples	n=156 pts randomly allocated to: Repa grp: 77 pts Gly grp: 79 pts *Power analysis:* NR *ITT analysis:* Last observation carried forward. ITT population included all pts randomised to tx. *Pt characteristics:* *(Repa grp, Gly grp):* % female: 51%, 52% Mean age, yrs: 75, 74 Disease duration, y: 1.3, 1.1 Mean BMI, kg/m^2: 27.1, 26.7 % mean HbA1c: 7.3%, 7.2% *Inclusion criteria:*	Pts were randomised into Repa grp or Gly grp. Methods for randomisation and allocation concealment NR. Study "open label," not blinded. Pts received forced 3-wk forced titration period followed by 52-wk maintenance period. *Intervention:* Pts began study receiving 1 mg 2× daily before meals. Titration protocol and maximum dose NR. *Comparator:* Pts began study receiving 2.5 mg 2× daily before meals. Titration protocol and maximum dose NR. *Assessment(s):*	*Data reported as Repa grp, Gly grp* *Study completion:* % pts completing study: 84%; 80% 4 pts in gly grp withdrew due to hypoglycaemic events. All other withdrawals from the study were for reasons unrelated to tx. *Cardiovascular outcomes:* Intima-media thickness, % change mean±SD: 4±3, 12±3, *p*=0.010 *Adverse events:* No specific severe adverse events or frequency of events reported.	Results suggest low risk of adverse events, but data poorly reported. *Limitations:* Power analysis NR; methods for randomisation and allocation concealment NR; study not described as blinded; outcome data poorly reported, >15% attrition. *Study quality:* Poor *Conflicts of interest:* Authors reported no conflicts of interest. Study funding presented no conflict of interest.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	Older pts (age criteria NR but aged 60-78 yrs) w/ T2DM who were pharmacotherapy-naïve and considered to have poorly controlled disease. *Exclusion criteria:* Medium/severe hypertension; cardiovascular disease; heart failure; severe macro- or microangiopathy; cancer; chronic obstructive pulmonary disease; upper limb paresis or paralysis; dementia.	Twice per wk during titration period, every 3 mos during maintenance period. *Outcome measure(s):* Adverse events. Note that intermediate outcomes were also reported but are not summarised here.	Mean BMI: No difference within or between grps. Data NR.	
Jibran et al. (2006)[40] Punjab Institute of Cardiology, Lahore, Pakistan; Women Medical College, Abbottabad, Pakistan Single center in Pakistan Randomised, single-center, unblinded study comparing Repa vs. Gly as monotherapy for pts newly diagnosed w/ T2DM. *F/u:* 1 yr *Time frame:* August 2000 – July 2001 *Funding source:* NR	n=100 pts randomly allocated to: Repa grp: 50 pts Gly grp: 50 pts *Power analysis:* NR *ITT analysis:* NR *Pt characteristics:* *(Repa grp, Gly grp):* % female: 68%, 80% Mean age, yrs: 47, 46 Mean BMI, kg/m^2: 27.1, 30.4 Mean weight, kg: 72.7, 65.8 *Inclusion criteria:* Pts aged 30-70 yrs w/ newly diagnosed T2DM uncontrolled w/ diet and exercise. *Exclusion criteria:* Pts w/ type 1 diabetes; pts using insulin or taking high doses of Sulf; cardiovascular, renal, or gastrointestinal disease.	Pts were randomised into Repa grp or Gly grp. Methods for randomisation and allocation concealment NR. Study open label, not described as blinded. *Intervention:* Pts began study receiving Repa 0.5 mg 3× daily before meals, titrated during f/u visits to maximum dose of 6 mg daily. Mean final dose was 4.3 mg daily. *Comparator:* Pts began study receiving Gly 5.0 mg daily, titrated during f/u visits to maximum dose of 15 mg daily. Mean final dose was 8.8 mg daily. *Assessment(s):* Every 2 wks. *Outcome measure(s):* Adverse events. Hypoglycaemic symptoms were pt reported. Note that intermediate outcomes were	*Data reported as Repa grp, Gly grp* *Study completion:* All pts completed study. *Adverse events:* No specific severe adverse events or frequency of events reported. Hypoglycaemic episodes: None in either grp Body weight change, mean±SD kg: 0.2, -1.0; NS BL: 65.8±9.4, 72.7±17.4 1 yr: 66±8.8, 71.7±15.2	Results suggest low risk of adverse events, but Repa dosage was low in comparison to other studies (mean final dose 4.3 mg daily), and study may not have had sufficient power to detect differences. *Limitations:* Power analysis NR; methods for randomisation and allocation concealment NR; study not described as blinded; outcome data poorly reported. *Study quality:* Poor *Conflicts of interest:* Study does not include any information on potential conflicts of interest or source of study funding.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
		also reported but are not summarised here.		
Shah et al. (2011)[42] King Edward Medical University/Mayo Hospital, Lahore, Pakistan Single center in Pakistan Randomised, single-center, unblinded study comparing Repa vs. Gly as monotherapy for pts newly diagnosed w/ T2DM. *F/u:* 1 yr *Time frame:* September 2005 – September 2006 *Funding source:* NR	n=200 pts randomly allocated to: Repa grp: 100 pts Gly grp: 100 pts *Power analysis:* NR *ITT analysis:* NR *Pt characteristics:* *(Repa grp, Gly grp):* % female: 67%, 80% Mean age, yrs: 46, 45 Mean BMI, kg/m^2: 27.2, 30.2 Mean weight, kg: 71.6, 64.8 *Inclusion criteria:* Pts aged 30-65 yrs w/ newly diagnosed T2DM. *Exclusion criteria:* Pts w/ type 1 diabetes; pts using insulin or taking high doses of Sulf; cardiovascular, renal, or gastrointestinal disease.	Pts were randomised into Repa grp or Gly grp. Methods for randomisation and allocation concealment NR. Study not described as blinded. *Intervention:* Pts began study receiving Repa 0.5 mg 3× daily before meals, titrated during f/u visits to maximum dose of 6 mg daily. Mean final dose was 4.3 mg daily. *Comparator:* Pts began study receiving Gly 5.0 mg daily, titrated during f/u visit to maximum dose of 15 mg daily. Mean final dose was 8.8 mg daily. *Assessment(s):* Every 2 wks. *Outcome measure(s):* Adverse events. Hypoglycaemia symptoms were pt reported. Note that intermediate outcomes were also reported but are not summarised here.	*Data reported as Repa grp, Gly grp* *Study completion:* All pts completed study. *Adverse events:* Authors report that no significant differences were observed between the 2 tx grps w/ respect to adverse events, including hypoglycaemic episodes. No details or data are reported. Mean body weight change, kg: -1.8, 0.2, *p*=NS Mean±SD at BL, 6 mo, 12 mo: Repa: 66.8±9.5, 66±9.5, 65±8.7 Gly: 72.5±17.3, 72.6±16.6, 72.7±15.3	Results suggest low risk of adverse events, but Repa dosage was low in comparison to other studies (mean final dose 4.3 mg daily). *Limitations:* Power analysis NR; methods for randomisation and allocation concealment NR; study not described as blinded; outcome data poorly reported. *Study quality:* Poor *Conflicts of interest:* Study does not include any information on potential conflicts of interest or source of study funding.

Appendix Table 4. Key Question 1. Cochrane Collaboration Tool for Assessing Risk of Bias in RCTs

Key: ITT, intention to treat; LOCF, last observation carried forward; NR, not reported

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
Across 8 studies	2 low risk + 6 unclear risk ? 0 high risk -	2 low risk + 6 unclear ? 0 high risk -	1 low risk + 2 unclear risk ? 5 high risk -	0 low risk + 3 unclear risk ? 5 high risk -	5 low risk + 1 unclear risk ? 2 high risk -	4 low risk + 0 unclear risk ? 4 high risk -	1 low risk + 7 unclear risk ? 0 high risk -	
Marbury et al. (1999)[41]	? (Methods NR)	? (Methods NR)	? (Masking methods NR)	? (Masking methods NR)	- (>15% attrition)	+ (No evidence of selective reporting)	? (Conflict of interest)	Poor
Wolffenbuttel et al. (1999)[43]	? (Methods NR)	? (Methods NR)	? (Masking methods NR)	? (Masking methods NR)	- (>15% attrition)	- (Few safety outcomes reported)	? (Conflict of interest NR)	Poor
Derosa et al. (2003)[38]	+	+	+	?	+	+	?	Fair

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
	(Statistician-generated)	(Envelope method)	(Pharmacy prepared masking to drugs)	(Methods NR)	(<10% attrition)	(No evidence of selective reporting)	(Conflict of interest NR; no power analysis)	
Derosa et al. (2003)[37]	? (Methods NR)	? (Methods NR)	- (Open-label)	- (Open-label)	+ (<10% attrition)	+ (No evidence of selective reporting)	? (Conflict of interest NR, no power analysis)	Poor
Esposito et al. (2004)[39]	+ (Computer-generated randomisation)	+ (Envelope method)	- (Open-label)	- (Open label)	+ (<10% attrition)	+ (No evidence of selective reporting)	? (Conflict of interest NR, no power analysis)	Fair
Abbatecola et al. (2006)[36]	? (Methods NR)	? (Methods NR)	- (Open-label)	- (Open-label)	? (ITT analyses w/ LOCF, >15% attrition)	- (Poor/limited adverse event reporting)	+ (No substantive concerns identified)	Poor
Jibran et al. (2006)[40]	? (Methods NR)	? (Methods NR)	- (Open-label)	- (Open-label)	+ (All patients completed study)	- (Poor/limited adverse event reporting)	? (Conflicts of interest NR, no power analysis)	Poor

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
Shah et al. (2011)[42]	? (Methods NR)	? (Methods NR)	- (Open-label)	- (Open-label)	+ (All patients completed study)	- (Poor/limited adverse event reporting)	? (Conflicts of interest NR, no power analysis)	Poor

Appendix Table 5. Key Question 1. SOE Table

Key: RCT, randomised controlled trial; SOE, strength of evidence

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Mortality	1 RCT reported mortality rates [41]. Similar rates of mortality were reported for repaglinide and glyburide groups and no deaths were treatment related. Evidence from a single underpowered study provides insufficient evidence to support evidence-based conclusions.	High	-2	-1	0	-1	0	0	0	0	Insufficient
Cardiovascular adverse events	2 RCTs reported overall rates of cardiovascular adverse events without reporting details on individual events [41 43]. One reported that 5% of repaglinide recipients and 2% of glyburide recipients had cardiovascular adverse events, though the clinical and statistical significance of this difference was unclear [41]. The second study reported that rates were similar between groups but did not report further details.	High	-2	0	0	-1	0	0	0	0	Low

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Adverse events (any event, serious events, withdrawals)	3 RCTs reported outcomes related to the overall occurrence of adverse events [37 41 42]. Similar rates were observed between repaglinide and comparator groups across studies. One study of repaglinide vs. glyburide reported adverse events in 30% and 28% of patients, serious adverse events among 10% and 6% of patients, and withdrawals due to adverse events among 10% and 10% of patients [41]. One study reported that adverse event rates were similar between repaglinide and glyburide groups and did not provide further detail [42], and 1 study reported that there were no serious adverse events for either group (repaglinide or metformin) [37].	High	-2	0	0	-1	0	0	0	0	Low
Hypoglycaemia	5 RCTs reported rates of hypoglycaemia [37 39 41-43]. Differences in rates were similar between groups across studies.	High	-1	0	0	0	0	0	0	0	Moderate
Blood pressure	5 RCTs reported that there were no significant differences in blood pressure between repaglinide vs. comparator groups [37-39 41 43]. Four studies reported that there were no changes in blood pressure from baseline and 1 reported small but statistically significant improvements for both repaglinide and glyburide groups [43].	High	-1	0	0	0	0	0	0	0	Moderate
Weight change	8 RCTs reported that there were no statistically significant differences between repaglinide and comparator groups in body weight changes [36-43]. For repaglinide groups across studies, mean weight changes ranged from a 1.8 kg loss to a 0.3 kg gain. For comparator groups, mean weight changes ranged from 2 kg loss to a 0.7 kg gain.	High	-1	0	0	0	0	0	0	0	Moderate

9.4.2 Key Question 2. What is the comparative effectiveness and safety of nateglinide, alone or in combination with metformin or pioglitazone?

Appendix Table 6. Key Question 2. Studies Evaluating the Effectiveness and Safety of Nateglinide

Key: BL, baseline; BMI, body mass index, in kg/m^2; btwn, between; CAD, coronary artery disease; CI, confidence interval; FPG, fasting plasma glucose; f/u, follow-up; Glib, glibenclamine; Glic, gliclazide; Gly, glyburide; grp(s), group(s); HbA1c, glycosylated hemoglobin; ITT, intention to treat; LOCF, last observation carried forward; MD, mean difference; Met, metformin; mo(s), month(s); Nat, nateglinide; NR, not reported; PBO, placebo; RCTs, randomised controlled trials; SD, standard deviation; T2DM, type 2 diabetes mellitus; tx, treatment; wks, weeks; yrs, years

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Horton et al. (2000)[46] Joslin Diabetes Center, Boston, Massachusetts; the Idaho Endocrine Specialists, Boise, Idaho; multiple departments, Novartis Pharmaceuticals, East Hanover, New Jersey Randomised, double-blind trial w/ dummy PBO to compare Nat and Met alone and in combination for T2DM pts w/ inadequate control by diet. *F/u:* 24 wks *Time frame:* NR *Funding source:* Novartis	n=701 pts were randomly allocated to: Nat: n=179 Nat + Met: n=172 Met: n=178 PBO: n=172 *Inclusion criteria:* Age ≥30 yrs; T2DM ≥3 mos; BMI 20-35; participation in 4-wk washout and 4-wk PBO run-in *Exclusion criteria:* Type 1 diabetes, secondary form of diabetes, history of significant diabetic complications, renal impairment, nonadherence to run-in *Pt characteristics (Nat; Nat + Met; Met; PBO):* Age, mean±SD yrs: 58.6±10.7; 58.4±10.9; 56.8±10.9; 59.6±10.9 Female: 38.5%,32%, 41%, 34% HbA1c, mean: 8.3±1.0, 8.4±1.1, 8.4±1.2, 8.3±1.1	Pts w/ T2DM inadequately controlled by diet underwent a 4-wk washout and 4-wk PBO run-in then randomly allocated by a computer to a tx grp. The RCT was double-blind and PBO-controlled w/ double-dummy PBO drugs. Method of concealment of allocation NR. Nat: 120 mg 3×/day Met: Titrated per label to 500 mg 3×/day Nat + Met: Both drugs as described above PBO: PBO tablets mimicking appearance and schedule of above	ITT analyses performed. Completers for drug were: Nat 75% (134/179); Nat + Met 78%; (135/172); Met 75% (133/178); PBO 62% (106/172) *Data reported as (Nat; Nat + Met; Met; PBO):* *Mortality, all cause:* 1 death in the Met grp, due to arteriosclerotic and hypertensive heart disease, deemed unlikely to be related to the drug. *Hypoglycaemia, % pts:* *Episodes suggestive of hypoglycaemia:* 12.8%, 26%, 10.1%, NR None of the events were serious, predominantly grade 1 of 4, and 1 grade 2 event occurring in the PBO grp. *Events suggestive of hypoglycaemia leading to study withdrawal, # (%):* 1 (0.5%), 3 (1.7%), 0 (0%), 0 (0%) *Confirmed hypoglycaemic events (glucose ≤3.3 mmol), # (%):*	Results suggest Nat + Met may lead to more hypoglycaemia than either drug alone. Nat alone and Met alone appear to have similar incidence of hypoglycaemia. Other adverse events do not appear substantively different but reporting is incomplete for most. *Limitations:* Attrition >15% and differential across grps, ITT analyses conducted using LOCF. Study not powered to detect adverse events. *Study quality:* Fair *Conflicts of interest:* One author received honoraria from Novartis.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	BMI, mean: 29.6±3.8, 30.0±3.7, 29.6±4.3, 29.2±3.0 Duration of diabetes, mean±SD yrs:4.7±5.5, 4.5±5.3, 4.5±5.5, 4.6±4.7		3 (1.7%), 5 (2.9%), 1 (0.5%), 0 (0%) *Weight*: Authors note "no significant changes" from BL for any grp, data NR *Electrocardiogram abnormalities:* 0 (0%), 1 (0.5%), 0 (0%), 1 (0.5%) Diarrhoea higher w/ Met alone (19.7%) or the combination (14.5%), but data for the other tx grps NR. Other adverse events "similar" among grps, data NR: Upper respiratory tract infection, headache, abdominal pain, nausea, fatigue, sinusitis *Withdrawal due to adverse events:* Total # (%): 5 (2.7%), 16 (9.3%), 12 (6.7%), 9 (5.2%) Of those, definitely/probably/possibly related to tx: 20% (1/5); 38% (6/16), 50% (6/12), 33% (3/9) *Any adverse event, proportion of pts:* 77.7%, 83.1%, 79.2%, 68.6%, *p*=NR	
Marre et al. (2002)[47] Contact author affiliation Department of Diabetology, Hospital Bichat-Claude Bernard, Paris, France Multicentre in Europe, North America, and South Africa Double-blind RCT to evaluate the addition of Nat to Met vs. Met alone in pts w/ T2DM stabilised on high-dose Met.	n=467 pts were randomly allocated to: Nat 120 mg + Met: n=160 Nat 60 mg + Met: n=155 PBO + Met: n=152 *Inclusion criteria:* Met ≥3 mos at ≥1500 mg/day; age ≥30 yrs; HbA1c range 6.8% to 11% *Exclusion criteria:* FPG ≥15 mmol/L; significant diabetic complications; >5% change in	Pts w/ T2DM and inadequate response to Met alone completed a run-in period on optimised Met and randomly allocated. Random allocation was computerised, and allocation was locked until study completion. PBO and dummy tablets used to maintain blinding. RCT was double-blind. *Nat:* 60 mg or 120 mg 3× daily, in addition to 1000 mg Met twice daily	89% (136/152) PBO + Met, 88% (137/155), Nat 60 mg + Met; 91% (145/160). Nat 120 mg + Met pts completed the study. *Data reported as (Nat 60 mg + Met, Nat 120 mg + Met, PBO + Met):* *Mortality, all-cause:* 0.6% (1/155), 0.6% (1/160), 0% Authors note neither death (1 sudden, 1 cardiac arrest) were thought to be due to Nat.	Results suggest hypoglycaemic events might occur more frequently w/ Nat, but whether the difference is statistically significant was NR. Nat 120 mg was associated w/ 0.9 kg greater weight gain that PBO, but the clinical significance is unclear. Mortality occurred in the Nat grps but not the PBO grp, but the deaths were reportedly not considered associated w/ the drug.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
F/u: 24 wks *Time frame:* NR *Funding source:* Novartis	weight during pre-randomisation run-in period; significant or unstable cardiac abnormalities; liver function abnormalities; treated w/ diabetes drug other than Met in previous 3 mos *Pt characteristics (Nat 60 mg, Nat 120 mg, PBO):* Age, mean±SD yrs: 57.9±9.9, 57.3±10.5, 56.4±10.3 Female: 38.7%, 38.8%, 44.7% HbA1c, mean: 7.99, 8.18, 8.20 BMI, mean±SD: 29.4±3.7, 29.3±3.5, 29.6±3.0 Duration of diabetes, mean±SD yrs: 7.2±6.4, 6.8±5.5, 6.5±6.5	*Comparator:* PBO 3× daily, plus 1000 mg Met twice daily *Outcome measure(s):* Mortality, weight change, hypoglycaemia	*Weight change from BL, kg mean (±SEM):* 0.1±0.2, 0.4±0.2, 1.0±0.2 Nat 120 mg vs. PBO MD 0.9 (95% CI 0.0 to 1.4), *p*>0.05. Nat 60 mg vs. PBO MD 0.3 (95% CI -0.2 to 0.8), *p*=NS. *Hypoglycaemic events, suggestive of, # (%):* 13 (8.4%), 25 (15.6%), 6 (3.9%), *p*=NR *Hypoglycaemic events, confirmed (plasma glucose ≤3.3 mmol/L), # (%):* 0 (0%), 5 (3.1%), 1 (0.7%), *p*=NR *Diarrhoea:* 5.6%, 7.9%, 5.8% Other gastrointestinal adverse events reportedly infrequent and occurred in similar proportions across grps. *Upper respiratory tract infection:* 8.1%, 4.6%, 9.7% *Withdrawal due to adverse events # (%):* 8 (5%), 6 (3.9%), 5 (3.2%), *p*=NR *Any adverse event, proportion of pts:* 54.6%, 60.0%, 58.8%, *p*=NR, authors characterised as "similar" *Any adverse event, thought to drug related, proportion of pts:* 11.8%, 16.8%, 19.4%, *p*=NR	*Limitations:* Study not powered to detect adverse events; *p* values not reported for all outcomes. *Study quality:* Good *Conflicts of interest:* Study authors are Novartis employees.
Gerich et al. (2005)[45] General Clinical Research Center, University of Rochester, Rochester, New York; the Department of Internal	n=428 pts were randomly allocated to: Nat + Met: n=208 Gly + Met: n=198	Drug-naïve pts w/ T2DM were randomly allocated. Methods of random allocation and concealment of allocation, if	All randomly allocated pts were included in the safety population; 95% of Nat/Met and 94.7% of control pts were included in the ITT population. Actual completion was lower, w/ 64.4% of Nat + Met pts and	Results suggest Nat w/ Met may be associated w/ less hypoglycaemia and weight gain than Gly w/ Met.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; multiple departments Novartis Pharmaceuticals, East Hanover, New Jersey Multicentre in the United States RCT w/ PBO-control and double masking to compare Nat/Met w/ Gly/Met as initial combination therapy for T2DM. *F/u:* 104 wks *Time frame:* NR *Funding source:* Novartis Pharmaceuticals	*Inclusion criteria:* Drug naïve; age 18-77 yrs; HbA1c 7%-11%; FPG ≤15 mmol; BMI 22-45 *Exclusion criteria:* Diabetes other than T2DM; symptomatic hyperglycaemia w/ 10% weight loss in the previous 8 wks; abnormal renal function or significant diabetes complications; history of lactic acidosis or congestive heart failure requiring pharmacologic tx; liver disease or persistent elevations (twice upper limit of normal) of liver enzymes or other medical conditions that could interfere w/ interpretation of results or pose significant risk to the subject *Pt characteristics (Nat + Met, Gly + Met):* Age, mean±SD yrs: 52.6±11.6, 53.5±11.6 Female: 49%, 52% HbA1c, mean: 8.4%, 8.3% BMI, mean: 33.3±6.0, 33.5±5.6 Duration of diabetes, yrs*:* 1.5±2.9, 2.0±4.3	applicable, NR. Double-blinding methods used. *Nat w/ Met:* 120 mg before meals Nat + 500 mg daily; open-label Met, for 4 wks, then Met titrated for 12 wks. At study end, mean daily dose 357 mg Nat and 1459 mg Met. *Comparator:* 1.25 mg daily Gly + 500 mg daily open-label Met, then both drugs titrated for 12 wks. At study end, mean daily dose 5.1 mg Gly and 1105 mg Met. *Outcome measure(s):* Mortality, all-cause; adverse events	58.4% of Gly + Met pts completing the study. *Data reported as (Nat + Met, Gly + Met):* *Mortality, all-cause:* n=1/grp (0.5% each) *Body weight, change*: -0.4±0.4 kg, +0.8±0.5 kg; *p*=0.01 *Hypertension*: 8.7%, 14.8%, *p*=NR and does not indicate a change from BL *Hypoglycaemia, confirmed episodes (blood glucose ≤3.3 mmol)*: 8.2%, 17.7%, *p*=0.003 *Hypoglycaemia, severe and requiring assistance from outside party*: 0%, 1%, *p*=NR; authors note the episodes were suspected to be related to the study drug *Influenza*: 12.3%, 10.0%, *p*=NR *Headache*: 16.4%, 17.7%, *p*=NR *Arthralgia*: 10.5%, 10.5% *Nausea/vomiting/diarrhoea/abdominal pain:* 6%-20% of grp w/ "similar frequency", no additional data reported by grp, no comparisons made Schwarz et al. (2008) conducted subgroup analysis of older pts (≥65 yrs), 35 were randomised to Nat + Met and 40 to Gly + Met [188]. Note these data are reflected in the data from the main publication and should not be considered unique. n= (Nat + Met, Gly + Met):	*Limitations:* Methods of random allocation and concealment of allocation NR. Study not powered for adverse events; high overall attrition; modified ITT analyses using LOCF. *Study quality:* Fair *Conflicts of interest:* NR, other than funding source.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Hypoglycaemia: 1, 8, *p*<0.023 *Hypoglycaemia, severe and requiring assistance from outside party*: 0, 1, *p*=NR *Withdrawal due to adverse events*: NR *Any adverse event, proportion of pts:* 91.8%, 90.9%	
Ristic et al. (2006)[50]; Ristic et al. (2007)[49] (original and extension studies) Novartis Pharma, Basel, Switzerland Multicentre in 5 countries Double-blind, double-dummy RCT to compare Nat+Met and Glic+Met for tx of T2DM when Met alone is inadequate *F/u:* 52 wks *Time frame:* NR *Funding source:* Novartis Pharma	n=262 pts were randomly allocated to: Nat: n=133 Glic: n=129 *Inclusion criteria:* T2DM ≥6 mos, Met monotherapy ≥3 mos; ≥1000 mg dose metformin/day continuously for ≥2 mos; partake in diet and exercise yet have inadequate glucose control; HbA1c 6.8%-9.0%, BMI 20-35 *Exclusion criteria:* NR *(Nat + Met, Glic + Met):* Age, mean±SD yrs: 62.0±11.0, 61.6±10.1 Female: 45.9%, 49.6% HbA1c, mean: 7.67±0.59, 7.60±0.58 BMI, mean: 28.5±3.5, 29.5±3.6 Duration of diabetes, yrs: 7.16±6.30, 6.70±5.55	Pts w/ T2DM on Met w/ inadequate blood glucose control were randomly allocated using computer-generated sequences and a block size of 4. Double-dummy double-blinding methods used. *Nat + Met:* Nat 60 mg 3×/day; titrated to max 240 mg/day during first 3 mos Glic + Met: Glic 80 mg/day; titrated to maximum 240 mg/day during first 3 mos *Outcome measure(s):* Mortality, all-cause; hypoglycaemia (confirmed events were those accompanied by blood glucose ≤4.0 mmol/L)	Ristic et al. (2006) (24 wks): Hypoglycaemia outcomes were reported for 98% (130/133) Nat pts and 98% (126/129) Glic pts. *Mortality, all-cause:* None *All data reported as (Nat + Met, Glic + Met):* *Hypoglycaemia* # (%): Pts w/ ≥1 event suggestive of hypoglycaemia: 32 (24.6) 32 (25.4) Pts w/ ≥1 confirmed event of hypoglycaemia: 28 (21.5) 28 (22.2) Pts w/ ≥3 events suggestive of hypoglycaemia: 13 (10.0) 17 (13.5) Pts w/ ≥3 events confirmed as hypoglycaemia: 12 (9.2) 16 (12.7) *p*=NR *Clinical symptoms of hypoglycaemia, 100/pts/mo* 15.5; 28.2; *p*=NR *Sweating, 100/pts/mo:* 2.2, 7.7, *p*=NR *Tremour, 100/pts/mo:*	Results suggest incidence of mortality and hypoglycaemia at 24 wks f/u are not substantively different. *Limitations:* Concealment of allocation NR; not powered to detect adverse events; modified ITT analysis for safety outcomes. *Study quality:* Good *Conflicts of interest:* Study authors employed by Novartis.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			3.3, 8.6 *Asthenia, 100/pts/mo:* 1.2, 5.6 The authors noted "no clinically relevant difference for any AE [adverse event] was noted between treatment groups" but full data were NR. *Any adverse event:* NR *Any adverse event, thought to be drug related:* 6.9%, 7.1% Withdrawal due to adverse events: n=2 (1.5%), n=8 (6%), *p*=NR <u>Ristic et al. (2007)</u>: 87% (229/262) pts completed the initial 24-wk phase, and most extended tx 93.3% in Nat + Met and 89.1% in Glic + Met *Mortality, all cause:* None in either grp *Adverse events:* Hypoglycaemic events*:* In overall events per 100 pts/mo (Nat + Met, Glic + Met): Up to 24 wks: 16.4, 31.5, *p*=NR 24 to 52 wks: 8.2, 8.7 24-52 wks hypoglycaemic events (*p*=NR but described in manuscript as "similar"):	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Pts w/ >1 event suggestive of hypoglycaemia, # (%): 19 (17.0%) 16 (15.8%) Pts w/ >1 confirmed event of hypoglycaemia, # (%): 17 (15.2) 15 (14.9) Pts w/ ≥3 events suggestive of hypoglycaemia, # (%): 7 (6.3) 7 (6.9) Pts w/ ≥3 events confirmed as hypoglycaemia, # (%): 7 (6.3) 7 (6.9) *Weight change:* 0.91 kg mean increase from BL in Glic + Met (*P*=0.009), no significant change from BL in Nat + Met grp (0.42 kg mean change, *p*=0.201). *Withdrawal due to adverse events (24-52 wks) # (%)*: 1 (0.8%), 2 (1.6%), *p*=NR *Any adverse event:* NR *Any adverse event, thought to be drug-related:* 0%, 0%	
Mita et al. (2007)[48] Department of Medicine, Metabolism, and Endocrinology, Juntendo University School of Medicine, Tokyo, Japan Single center in Japan Open-label RCT to assess the impact of Nat on carotid intima-	n=78 pts were randomly allocated to: Nat: n=38 No tx: n=40 *Inclusion criteria:* T2DM diagnosed 1-10 yrs ago; aged 40-75 yrs; HbA1c <6.5%; table glycemic control w/ HbA1c	Drug naive pts w/ T2DM were randomly allocated using computer-generated random number sequence. *Nat*: 90 mg 3×/day, total 270 mg/day *No tx control:* No intervention	89% (34/38) of pts in the Nat grp and 90% (36/40) of pts in the control grp completed the study. *Disease-related morbidity:* *Carotid intima-media thickening annual mean±SD change at 1 yr, Nat, no tx:* -0.017±0.054, 0.024±0.066; *p*=0.0064	Results suggest no substantive differences between grps in hypoglycaemic events or other adverse events, but data are limited by the small sample size. *Limitations:* Open-label, methods of random allocation and whether allocation was concealed NR; no masking for pts and treating clinicians,

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
media thickening in drug-naïve pts w/ T2DM *F/u:* 12 mos *Time frame:* January 2005 – August 2005 (enrollment) *Funding source:* NR	variation <0.5% last 6 mos; never taken antidiabetic agents *Exclusion criteria:* Diabetic microangiopathy, severe renal or hepatic disease, overt cardiovascular disease, or malignancy *Pt characteristics (Nat, no tx):* Age, mean±SD yrs: 61.8±6.0, 61.3±8.3 Female: 47%, 47% HbA1c, mean: 6.13±0.37, 6.04±0.37 BMI, mean: 23.6±2.7, 23.6±2.7 Duration of diabetes, yrs: 4.46±3.15, 4.75±2.54	*Outcome measure(s):* Carotid intima-media thickening, adverse events	Significant changes in vascular lumen diameter not observed, data NR. *Hypoglycaemic events:* None in either grp, *p*=NR *Liver dysfunction, mild:* 1 in Nat grp; none in no tx control grp The authors note no changes in metabolic parameters (other than HabA1c and triglyceride, which were not outcomes of interest) were observed. *Withdrawal due to adverse events, # (%)*: 1 (2.6%), 2 (5%), *p*=NR *Any adverse event:* NR	although physicians reading carotid artery imaging were blinded to clinical information. *Study quality:* Fair *Conflicts of interest:* None disclosed.
Gonzalez-Clemente and the Spanish Nateglinide Study Group (2008) [51] **Department of Diabetes, Endocrinology and Nutrition, Hospital de Sabadell, Sabadell, Spain** Multicentre in Spain Double-blind PBO-controlled RCT to compare Nat and PBO in drug-naïve pts w/ T2DM *F/u:* 12 wks *Time frame:* NR *Funding source:* Novartis Pharma and Ministerio de Sanidad y Consumo (Instituto	n=109 drug naïve pts w/ T2DM were randomly allocated to: Nat: n=55 PBO: n=54 *Inclusion criteria:* Drug-naïve; 30-75 yrs-old; T2DM; <5 yrs since diagnosis; BMI 22-35; <13.3 mmol L^{-1}; HbA1c 6·5%-8·5% *Exclusion criteria:* Antihypertensive drugs; T1DM; pregnancy; women of childbearing age not using oral contraceptives; serum creatinine >160 mmol L^{-1}; alanine aminotransferase and/or aspartate aminotransferase >20× upper level of normality; thyroid dysfunction; fasting triglycerides	Random allocation was performed in the pharmacy. Methods of randomisation and concealment of allocation NR. *Nat*: 120 mg before breakfast, lunch, dinner (3×/day) *PBO:* Same schedule as Nat (before meals) *Outcome measure(s):* hypoglycaemia, hyperglycaemia (defined as plasma glucose < 3.3 mmol/L w/ associated signs and symptoms), weight change, blood pressure change	3.6% (2/55) pts on Nat and 5.6% (3/54) pts on PBO did not complete the trial. Outcomes reported at 12 wks. *Hypoglycaemia:* No events in either grp *Hyperglycaemia:* No events in either grp *Weight, mean±SD kg (Nat, PBO):* 77·4±11·3, 76·8±11·2, *p*=0.821 btwn grps *p*=0.737 for change from BL btwn grps *Blood pressure, mean±SD mm Hg (Nat, PBO)* Systolic: 125.3±15.4, 129.3±18.7 *p*=0.015 btwn grps *p*=0.007 for change from BL btwn gps Diastolic: 75.3±10.4, 75.0±9·7 *p*=0.921 btwn grps *p*=0.561 change from BL btwn grps	Results suggest no significant differences in hypoglycaemia or hyperglycemic events or changes in weight or diastolic blood pressure between grps. Systolic blood pressure was statistically significantly more reduced in the Nat grp, but the mean difference was only several mm Hg and for both grps the mean was still slightly about 120 mm Hg. *Limitations:* Methods of randomisation and concealment of allocation NR; f/u only to 12 wks; no power analysis. *Study quality:* Good *Conflicts of interest:* NR (aside from funding source)

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
de Salud Carlos III, Red RGDM 03/212), Spain	>7·0 mmol L^{-1}; total cholesterol >9·1 mmol L^{-1}. *Pt characteristics (Nat, PBO):* Age, mean±SD yrs: 59.9±10.6; 57.2±10.7 Female: 43·6%. 37·0% HbA1c, mean: 7.2±0.6; 7.1±0.7 BMI, mean: 28.9±3.5; 28.7±3.7 Duration of diabetes, yrs: NR		(36% of Nat and 33% of PBO pts had hypertension at BL) Discontinuation due to adverse events (Nat, PBO), # (%): n=1 (1.8%) (headache); n=1 (1.9%) (pruritus), *p*=NR	
Derosa et al. (2009)[44] Department of Internal Medicine and Therapeutics, University of Pavia, Pavia; the 'G. Descovich' Atherosclerosis Study Center, 'D. Campanacci' Clinical Medicine and Applied Biotechnology Department, University of Bologna, Bologna; and the Diabetes Care Unit at S. Carlo Hospital of Milano, Milano, Italy Multicentre in Italy Double-blind RCT to compare Nat + Met and Glib+Met for T2DM *F/u:* 12 mos *Time frame:* NR *Funding source:* NR	n= 248 drug naïve pts w/ T2DM were randomly allocated to: Nat + Met: n=124 Glib + Met: n=124 *Inclusion criteria:* Caucasian; age ≥18 yrs; T2DM ≥6 mos; HbA1c >7.0%; hypertension *Exclusion criteria:* History of ketoacidosis; unstable or rapidly progressing diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function; impaired renal function, severe anaemia, serious cardiovascular disease, or cerebrovascular conditions within 6 mos, women of reproductive age not using contraceptives *Pt characteristics (Nat + Met, Glib + Met):* Age, mean±SD yrs: 55.5±5, 56±4 Female: 51%, 49% HbA1c, mean: 8.1±1.0, 8.2±1.1 BMI, mean: 26.4±1.4, 26.5±1.5	After a 6-mo conservative tx run-in, pts were randomly allocated using codes prepared by a statistician and allocation was concealed until study completion. *Nat + Met*: Starting dose Nat 180 mg/day, mean final dose 300±60 mg/day. After 1-mo run-in, pts also received 1500 mg/day Met, final mean dose 2500±500 mg/day. *Glib + Met:* Starting dose Glib 7.5 mg/day, mean final dose 12.5±2.5 mg/day. After 1-mo run-in, pts also received 1500 mg/day Met, final mean dose 2500±500 mg/day. *Outcome measure(s):* Weight changes, blood pressure changes	At 6-mo f/u, 92% (114/124) Glib + Met and 96% (119/124) Nat + Met pts remained in the study. ITT analyses were performed. *Weight changes:* BMI (BL, 6 mos, 12 mos), mean±SD: Nat + Met: 26.4±1.4, 26.6±1.3, 26.8±1.6 Glib + Met: 26.5±1.5, 26.7±1.6, 26.9±1.7 Neither grp had statistically significant changes from BL. Outcomes were not directly compared by study authors but appear similar. *Blood pressure:* *Blood pressure, systolic (BL, 6 mos, 12 mos), mean±SD:* Nat + Met: 136.8±4.4, 135.3±4.0, 134.5±3.6 Glib + Met: 137.4±4.6, 136.2±4.3, 135.4±3.8 *Blood pressure, diastolic (BL, 6 mos, 12 mo), mean±SD:* Nat + Met: 87.3±3.8, 86.1±3.5, 85.4±3.4 Glib + Met: 88.1±3.5, 88.3±3.6, 86.8±3.5 Neither grp had statistically significant changes from BL. Outcomes were not	Results suggest no substantive changes in blood pressure or BMI for either grp at up to 1 yr. *Limitations:* Attrition after 6 mos unclear; however, ITT analyses performed. *Study quality:* Good *Conflicts of interest:* NR

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	Duration of diabetes, yrs: 5±2, 4±2		directly compared by study authors but appear similar.	

Appendix Table 7. Key Question 2. Cochrane Collaboration Tool for Assessing Risk of Bias in RCTs

Key: ITT, intention to treat; LOCF, last observation carried forward; NR, not reported

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
Across 7 studies	4 low risk + 3 unclear risk ? 0 high risk -	2 low risk + 4 unclear risk ? 1 high risk -	6 low risk + 0 unclear risk ? 1 high risk -	7 low risk + 0 unclear risk ? 0 high risk -	5 low risk + 2 unclear risk ? 0 high risk -	7 low risk + 0 unclear risk ? 0 high risk -	0 low risk + 7 unclear risk ? 0 high risk -	
Horton et al. (2000)[46]	+ (Computerised)	? (Methods NR)	+ (Double-blind)	+ (Double-blind)	? (ITT analyses) with LOCF and high attrition	+ (No evidence of selectivity)	? (Conflict of interest)	Fair
Marre et al. (2002)[47]	+ (Computerised)	+ (Concealed until completion)	+ (Double-blind)	+ (Double-blind)	+	+ (No evidence of selectivity)	? (Conflict of interest)	Good

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
					(<15% attrition, similar among groups)			
Gerich et al. (2005)[45]	? (Method NR)	? (Methods NR)	+ (Double-blind)	+ (Double-blind)	? (ITT analyses) with LOCF and high attrition	+ (No evidence of selectivity)	? (Conflict of interest)	Fair
Ristic et al. (2006)[50] and Ristic et al. (2007)[49]	+ (Computerised)	? (Methods NR)	+ (Double-blind)	+ (Double-blind)	+ (<15% attrition, similar among groups)	+ (No evidence of selectivity)	? (Conflict of interest)	Good
Mita et al. (2007)[48]	? (Method NR)	- (NR and unmasked study)	- (Unmasked study with no-treatment comparison group)	+ For radiological outcomes (reader masked) - For other outcomes (unmasked study with no-treatment	+ (<15% attrition, similar among groups)	+ (No evidence of selectivity)	? (Conflict of interest, funding NR)	Fair

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
				comparison group)				
Gonzalez-Clemente and the Spanish Nateglinide Study Group (2008) [51]	? (Method NR)	? (Method NR)	+ (Double-blind)	+ (Double-blind)	+ (Low attrition, similar between groups)	+ (No evidence of selectivity)	? (Conflict of interest in funding)	Good
Derosa et al. (2009)[44]	+ (Prepared by statistician)	+ (Concealed until completion)	+ (Double-blind)	+ (Double-blind)	+ (ITT analyses)	+ (No evidence of selectivity)	? (Conflict of interest, funding NR)	Good

Appendix Table 8. Key Question 2. SOE Table

Key: PBO, placebo; SOE, strength of evidence

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Mortality, all cause	Nateglinide does not appear to be associated with an increased risk of all-cause mortality compared with placebo [46], metformin alone [47] , glyburide [45], or gliclazide [49 50]. Considered collectively, the incidence of all-cause mortality was low and did not appear to vary by study group assignment; however, consistency cannot be firmly established due to the variation in comparators used among studies.	High	-1	-1	-	-1	-	-	-	-	Low
Hypoglycaemia	Frequency of confirmed events of hypoglycaemia were similar to no treatment in 1 small study (Mita et al. [2007]) and possibly higher than placebo in another [46]); while none occurred in either nateglinide or PBO groups in a third study [51].	High	-1	-1	-	-2*	-	-	-	-	Very Low
	Compared with active controls, relative frequency of confirmed events of hypoglycaemia varied among studies, and no 2 randomized controlled trials made the same comparison [45-47 45 49 50].	High	-1	-1	-	-2*	-	-	-	-	Very Low
Weight change	Nateglinide does not appear to be associated with greater weight change than comparators. Weight changes compared with controls were either nonsignificant [46 51] or unlikely to be large enough to be clinically important (mean change vs. comparators of approximately 1 kg or less) [47 45 49 50].	High	-1	-	-	-	-	-	-	-	Moderate
Withdrawal due to adverse events	Nateglinide does not appear to lead to a higher incidence of treatment discontinuation compared with PBO, based on 2 studies [46 51] or no treatment [48].	High	-1	-	-	-1	-	-	-	-	Low

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
	Nateglinide appears to be associated with a lower incidence of discontinuation due to adverse events than metformin in 1 study [46] but is unclear in another [47] due to lack of statistical power to detect differences between groups in rare events. Also due to the rarity of discontinuations, it is unclear whether it has a similar rate of discontinuation or a similar rate as gliclazide [49 50].	High	-1	-1	-	-2*	-	-	-	-	Very low

*Precision is downgraded twice due to high concern regarding the lack of power in the studies for this outcome, which leads to further uncertainty due to preclusion of assessment of possible reasons for inconsistency.

9.4.3 Key Question 3. What is the comparative effectiveness and safety of pioglitazone, alone or in combination with metformin, sulfonylureas, or insulin?

Appendix Table 9. Key Question 3. Studies Evaluating the Effectiveness and Safety of Pioglitazone

Key: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; BL, baseline; BMI, body mass index; btwn, between; CABG, coronary artery bypass graft; CV, cardiovascular; FDA, Food and Drug Administration; f/u, follow-up; GI, gastrointestinal; Glic, gliclazide; Glim, glimepride; grp(s), group(s); HbA1c, glycated hemoglobin; HR, hazard ratio; hx, history; ITT, intention to treat; LDL, low-density lipoprotein cholesterol; meds, medications; Met, metformin; MI, myocardial infarction; mm Hg, millimeters of mercury; ng, nanogram; NR, not reported; NS, no statistically significant difference; PBO, placebo; PCI, percutaneous coronary intervention; Pio, pioglitazone; PPAR, Pioglitazone Protects DM Patients Against Reinfarction; PROactive, PROspective pioglitazone Clinical Trial In macrovascular Events; PROFIT-J, Primary prevention oF hIgh risk Type 2 diabetes in Japan; pt(s), patient(s); RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; Sulf, sulfonylurea; T1D, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TOSCA.IT, Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial; tx(s), treatment(s); TZD, thiazolidinedione; Vilda, vildagliptin; yr(s), year(s)

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Hanefeld et al. (2004)[56]; Charbonnel et al. (2005)[65]. Technical University Dresden, Dresden, Germany; Universita di Perugia, Perugia, Italy; Rudolfstiftung Hospital, Vienna, Austria; Radcliffe Infirmary, Oxford, UK; Hotel Dieu, Nantes, France Multiple European centers Randomised, multicentre, double-blind comparison of Pio vs. Met as an add-on to Sulf in pts w/ T2DM inadequately controlled w/ Sulf *F/u:* 1 and 2 yrs *Time frame:* NR	n=639 pts Pio + Sulf grp: 319 pts Met + Sulf grp: 320 pts *Power analysis:* NR *ITT analysis:* Last observation carried forward. ITT population was all pts receiving at least 1 dose of study medication. *Pt characteristics (Pio + Sulf grp, Met + Sulf grp):* % female: 46.4%, 45.3% Mean age, yrs: 60, 60 Mean weight, kg: 85.3, 84.9 Mean BMI, kg/m^2: 30.2, 30.0 Mean disease duration, yrs: 7.0, 7.1 Mean % HbA1c: 8.82%, 8.80 %	Pts were randomised to receive Pio or Met as an add-on to sulf. Methods for randomisation, allocation concealment, and blinding NR. Pts received 12 wk forced titration period followed by 40 wk maintenance period. Cessation or down titration was permitted on the basis of tolerability issues. Pts continued on prestudy dose of Sulf. Most common drugs included Glib (42% of pts), Glic (31%), Glim (19%). The distribution of different sulf drugs was not reported separately by grps.	*Data reported as Pio + Sulf grp, Met + Sulf grp* *Study completion:* % of pts completing 1-yr study: 81.5%, 87.2% Reasons for noncompletion included withdrawn consent (higher for Pio grp), adverse events. Mean tx duration was 11 mos for both grps. 75% of pts completed a 104-wk study, w/ data reported in Charbonnel et al. (2005) [65] *Adverse events (1 yr) [56]:* Any adverse event, # pts (% pts): 191/319 (59.9%), 198/320 (61.9%) Majority of events were mild or moderate.	Results suggest that Pio + Sulf was associated w/ numerically lower rates of severe adverse events (6.6% vs. 9.7% of pts) and similar rates of overall adverse events (59.9% and 61.9%) compared w/ Met + Sulf. The statistical and clinical significance of these findings are not clear. *Limitations:* Power analysis NR; no statistical comparisons btwn grps for adverse events; details of methods for randomisation, allocation concealment, and blinding NR; pts received a mix of different Sulf drugs, unclear if distribution was similar btwn Pio + Sulf and Met grps.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Funding source: Takeda Europe and Eli Lilly and Company	*Inclusion criteria:* Male and female pts aged 35-75 yrs w/ T2DM inadequately controlled w/ Sulf alone (at ≥50% of maximum tolerated dose for ≥3 mos), stable or worsening glycemic control for ≥3 mos, HbA1c btwn 7.5%-11%, fasting C-peptide ≥1.5 ng/mL. Female pts were postmenopausal, sterilised, or using satisfactory contraception. *Exclusion criteria:* T1D or ketoacidosis; hx of MI, transient ischemic attacks or stroke in prior 6 mos; symptomatic heart failure; malabsorption or pancreatitis; familial polyposis coli; malignant disease in prior 10 yrs; hx of lactic acidosis or hypoxemia; substance abuse; pregnancy or breastfeeding; prior tx ow/ metformin or TZDs.	Pts could receive thiazides for oedema and antihypertensive tx if indicated (ACE inhibitors, angiotensin II receptor antagonists, or calcium antagonists). *Intervention:* Up to 45 mg once daily of Pio + Met PBO + prestudy Sulf; 62% of pts received maximal dose. *Comparator:* 850 mg Met + Pio PBO up to 3× daily (maximal dose of 2550 mg/day); 55% of pts received maximal dose. *Assessments:* Glycemic control and adverse events measured multiple times over 1-yr tx period. *Outcome measure(s):* Adverse events. The definition of hypoglycaemic episodes was not clear. Note that intermediate outcomes (e.g. HbA1c) were also reported, but are not summarised here.	% pts w/ serious adverse events: 6.6%, 9.7% Deaths, # pts (% pts): 1/319 (0.003%), 2/320 (0.006%) Not related to tx. % pts w/ GI disorders: 12.2%, 23.4% % pts w/ diarrhoea: 2.5%, 12.5% % pts w/ CV disorders: 3.1%, 4.1% % pts w/ hypoglycaemic episodes: 10.7%, 14.1% No cases were considered severe. % w/ mild to moderate oedema: 6.9%, 1.6% Weight changes: Pio + Sulf had a mean weight gain of 2.8 kg Met + Sulf had a mean weight reduction of 1 kg No clinically significant changes in blood pressure. *Adverse events (2 yrs)* [65]*:* No major differences btwn grps w/ respect to # of adverse events. % withdrawal due to adverse events: 8.8%, 10% % w/ hypoglycaemia: 11.3%, 15.6% % w/ GI disorders: 6.3%, 19.4%	*Study quality:* Fair *Conflicts of interest:* Authors report relationships w/ commercial entities.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			% w/ congestive heart failure: 0.6%, 0.9% % w/ oedema: 10.7%, 2.8% Weight: Pio + Sulf grp had a mean increase of 3.7 kg. Met + Sulf grp had a mean decrease of 1.7 kg.	
Schernthaner et al. (2004)[61] Rudolfstiftung Hospital, Vienna, Austria; Radcliffe Infirmary, Oxford, UK; Clinique d'Endocrinologie, Hotel Dieu, Nantes, France; Technical University Dresden, Dresden, Germany; and Universita di Perugia, Italy Quarter Study Group 167 centers in 12 European countries Randomised, double-blind, muliticenter comparison of Pio vs. Met for pts w/ T2DM and no prior use of glucose lowering medication. *F/u:* 1 yr *Time frame:* NR *Funding source:* NR	n=1199 pts randomised (1194 pts treated): Pio grp: 597 pts Met grp: 597 pts *Power analysis:* Sample size of 450 pts/grp required for 90% power to detect non-inferiority of Pio relative to Met. Limit of non-inferiority was 0.2% difference btwn grps in HbA1c changes. *ITT analysis:* Analysis of primary endpoint (HbA1c) performed using last observation carried forward. *Pt characteristics (Pio grp, Met grp):* % female: 47%, 42% Mean age, yrs: 57, 56 Mean disease duration, yrs: 3.4, 3.1 Mean weight, kg: 88.2, 89.7 Mean BMI, kg/m^2: 31.2, 31.4 Mean % HbA1c: 8.7%, 8.7%	Pts randomised centrally using block randomisation and a computer-generated list administered w/ a telephone randomisation and resupply service. Further details of blinding NR. Tx began w/ 12-wk forced titration period (designed to rapidly reach individual maximum tolerated dose), followed by a 40-wk maintenance period. Doses were increased, maintained, or decreased at 4, 8, and 12 wks; 12-wk dose was maintained for remainder of study. *Intervention:* Up to 45 mg Pio + Met PBO (starting w/ 30 mg Pio); 13.4% of pts received 30 mg, 85.9% of pts received 45 mg. *Comparator:* 850 mg Met + Pio PBO up to 3× daily (starting w/ 850 mg); 11.8% of pts received 850 mg, 26.5% received 1700	*Data reported as Pio grp, Met grp (# pts [% pts]) unless otherwise specified* *Study completion:* 1199 pts randomised, 1194 pts treated. Completed study: 499/597 (84%), 501/597 (84%) Reasons for withdrawal (in order from most to least common): Adverse events, lack of efficacy, protocol violations, withdrawal of consent, loss to f/u, or other. *Primary outcome:* Non-inferiority of Pio relative to Met was proven w/ regard to HbA1c. *Mean body weight changes:* Pio grp increased by 1.9kg. Met grp decreased by 2.5 kg. *Mean waist circumference:* Pio grp unchanged. Met grp decreased by 3 cm. *Blood pressure:* NS changes from BL in either grp, though there was a trend towardsa decrease; data NR. *Adverse events:*	Results suggest that Pio was associated w/ numerically lower rates of severe adverse events (4.9% vs. 7.4% of pts) and similar rates of overall adverse event (53% and 58%) compared w/ Met. The statistical and clinical significance of these findings are not clear. Pio was non-inferior to Met w/ regard to glycaemic control. *Limitations:* Study not powered to detect differences in adverse events or other key outcomes of interest, no statistical comparisons of adverse event rates btwn grps. *Study quality:* Good *Conflicts of interest:* NR

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	Inclusion criteria: Pts aged 35-75 yrs w/ T2DM inadequately controlled w/ diet alone. HbA1c of 7.5%-11% and stable or worsening glycemic control for ≥3 mos. Pts taking corticosteroids and beta-blockers were permitted if tx 4 wks prior to screening. *Exclusion criteria:* Prior use of glucose lowering pharmacotherapy, specific contraindications to either drug.	mg, 61.6% of pts received 2550 mg. *Outcome measure(s):* Adverse events. Note that intermediate outcomes were reported (e.g. HbA1c) but are not summarised here.	Any event: 316/597 (53%), 346/597 (58%) Severe adverse events: 4.9%, 7.4% (# pts NR) CV adverse events: 3.7%, 3.9% (# pts and details NR) Deaths: 3/597 (0.5%), 2/597 (0.3%); none tx related Hepatotoxicity: 2/597 (0.3%), 1/597 (0.2%) Withdrawals due to adverse event: 42/597 (7%), 39/597 (7%) *Other adverse events reported in ≥2% of pts:* <u>GI disorders</u>: Diarrhoea: 19/597 (3.2%), 66/597 11.1%) Nausea: 14/597 (2.3%), 25/597 (4.2%) <u>General disorders</u>: Oedema, peripheral: 27/597 (4.5%), 10/597 (1.7%) Oedema, not otherwise specified: 13/597 (2.2%), 1/597 (0.2%) Fatigue: 8/597 (1.3%), 12/597 (2.0%) <u>Infections and infestations</u>: Bronchitis: 11/597 (1.8%), 14/597 (2.3%) Influenza: 14/597 (2.4%), 22/597 (3.7%) Nasopharyngitis: 25/597 (4.2%), 19/597 (3.2%) <u>Musculoskeletal</u>: Arthralgia: 9/597 (1.5%), 12/597 (2.0%) Back pain: 14/597 (2.3%), 17/597 (2.8%)	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Nervous system disorders: Dizziness: 14/597 (2.3%), 11/597 (1.8%) Headache: 26/597 (4.4%), 14/597 (2.3%) Respiratory disorders: Pharyngitis: 15/597 (2.5%), 9/597 (1.5%) Vascular disorders: Hypertension: 15/597 (2.5%), 17/597 (2.8%) AE more common in 1 grp: Liver function tests: 0/597 (0%), 9/597 (1.5%) Weight gain: 6/597 (1.0%), 0/597 (0%)	
Charbonnel et al. (2005)[54] Hotel Dieu, Nantes, France; Radcliffe Infirmary, Oxford, UK; Rudolfstiftung Hospital, Vienna, Austria; Technical University Dresden, Germany; Universita di Perugia, Perugia, Italy 209 centers in 14 European countries, Australia, Canada, South Africa, and Israel Randomised, multicentre, double blind study comparing Pio w/ Glic in pts w/ T2DM and no prior glycemic control medications. *F/u:* 1 yr *Time frame:* NR *Funding source:* Takeda Euro and Eli Lilly	n=1270 pts randomised to: Pio grp (# unclear) Glic grp (# unclear) *Power analysis:* 450 pts required per grp for 90% power to detect non-inferiority of Pio relative to Met in HbA1c reduction. Non-inferiority limit was 0.2% difference from BL in HbA1c btwn grps. *ITT analysis:* ITT approach used for primary outcome (HbA1c). *Pt characteristics (Pio grp, Glic grp):* Mean % HbA1c: 8.7%, 8.7% Demographic data NR. *Inclusion criteria:* Pts aged 35-75 yrs w/ T2DM inadequately controlled w/ diet alone; HbA1c btwn 7.5%-11%; stable or	Pts randomised equally to Pio or Glic tx. Methods for randomisation, allocation concealment, blinding NR. If indicated, antihypertensive tx was provided (ACE inhibitors or calcium antagonists). Pts provided dietary advice at BL. Pts underwent 16-wk forced titration period to maximum dose and 36-wk maintenance period at maximum tolerated dose; 16-wk dose maintained for remainder of study. Cessation or down titration permitted on the basis of tolerability. *Intervention:* Up to maximum daily dose of 45 mg. Maximum	*Data reported as Pio grp, Glic grp.* *Study completion:* >80% of pts took study medication for ≥52 wks. Further details NR. *Weight changes:* Pio grp had mean 2.8 kg increase. Glic grp had mean 1.9 kg gain. *Adverse events:* % pts w/ any adverse event: 75%, 71% The majority were mild or moderate (details NR). % of pts w/ serious adverse events NR. % w/ mild oedema: 8.7%, 4.5% % w/ hypoglycaemia: 3.5%, 10.1% A pt in the Glic grp required hospitalisation for hypoglycaemia.	Results suggest that Pio and Glic were associated w/ similar occurrences of adverse events (75% and 71% of pts), and that the majority were mild or moderate. *Limitations:* Details of randomisation, allocation concealment, blinding NR; no statistical analyses comparing adverse event rates btwn grps; limited data on pt demographics. *Study quality:* Fair *Conflicts of interest:* Authors report relationships w/ commercial entities.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	worsening glycemic control lower prior 3 mos. *Exclusion criteria:* Pts w/ prior glucose lowering pharmacotherapy at any time; pts w/ specific contraindications to study drugs. Long term corticosteroids and beta-blockers not permitted during study or w/in 4 wks prior to screening.	dose achieved in 80.7% of pts. Mean dose 42 mg. *Comparator:* Up to a maximum daily dose of 320 mg. Maximum dose achieved in 27.9% of pts. Mean dose 198 mg. *Outcome measure(s):* Pt-reported adverse events. The definition of hypoglycaemic events was not clear. Intermediate outcomes (e.g. HbA1c) were also reported but are not summarised here.		
Dormandy et al. (2005)[55] **Long term observational f/u:** Erdmann et al., (2016)[66] **Post hoc analyses:** Erdmann et al (2007)[70] Erdemann et al., 2007[71] Wilcox et al., 2007 [77] Schneider et al., 2008 [76] Wilcox et al., 2008 [78] Dormandy et al., 2009 [69] Scheen et al., 2009 [74] Scheen et al., 2009 [75] Charbonnel et al., 2010 [67] Erdmann et al., 2010 [72] Doehner et al., 2012 [68] Pfister et al., 2013[73] **Additional publications not summarised:** Erdmann et al. (2014)[194] (results superseded by 10-yr analysis)	n=5238 pts randomised to: Pio + existing med grp: 2605 pts PBO + existing med grp: 2633 pts *Power analysis:* Calculation based on assumptions of 6% annual primary event rate in PBO grp, recruitment over 18 mos, and 4-yr trial duration. W/ 5000 pts, study had 91% power to detect a 20% reduction in primary outcome; 760 pts must achieve 1 or more endpoint to maintain power. *Pt characteristics:* % female: 33%, 34% Mean age, yrs: 61.9, 61.6 Mean disease duration, yrs: 8, 8 % w/ hx of hypertension: 75%, 76% % current smokers: 13%, 14%	Pts randomised to oral Pio or PBO using a central interactive voice response system, using randomised permuted blocks. Investigators and study personnel were blinded. *Intervention:* Pio (starting at 15 mg for first mo, 30 mg for second mo, 45 mg thereafter) + existing medications. Study drug dose could be adjusted if clinically indicated; 89% of pts reached maximum dose of 45 mg/day. *Comparator:* Matching PBO + existing medications; 91% of pts reached maximum dose. *Assessments:* Monthly for first 2 mos, every 2 mos for first yr, every 3 mos thereafter.	*Data reported as Pio + existing med grp, PBO + existing med grp* *Study completion:* # analysed in ITT population [55]: 2605, 2633 Reached final assessment, # pts (% pts): 2427/2605 (93%), 2446/2633 (93%) Reasons for noncompletion included death (177 Pio pts, 186 PBO pts) or loss to f/u (1 Pio pt, 1 PBO pt). Pts enrolled in long term f/u following completion of PROactive trial, # pts (% pts) [66 194]: 1820/2605 (69.9%), 1779/2633 (67.6%) Withdrawals and loss to f/u were similar btwn Pio and PBO grps. *Primary composite endpoint:* Kaplan-Meier curve (time to any first event) for Pio vs. PBO: HR 0.9 (95% CI 0.80-1.02); *p*=0.095 First events contributing to primary composite, # of events:	Results suggest that Pio added to existing medications may be associated w/ a reduced risk of a secondary composite outcome of death, MI, or stroke compared w/ PBO in pts at high risk for macrovascular events. There were no differences btwn grps in a more expansive primary composite outcome. Individual adverse events occurred at largely similar rates btwn grps; w/ Pio favored for some outcomes (angina pectoris, hospitalisation for diabetes control) and PBO favored for others (heart failure, pneumonia, hypoglycaemia, body weight). A long-term observational study without assigned txs showed no differences btwn Pio and PBO grps w/ 10 yrs f/u, suggesting no legacy effect of the drug.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Spanheimer et al., 2009 [158] (no outcomes or analyses of interest) Ferrannini et al., 2011[151] (no outcomes or analyses of interest) Affiliations in multiple locations in Europe and the US. PROactive trial; 321 centers in 19 European countries. Randomised, double-blind, multicentre, PBO-controlled trial of Pio in pts w/ T2DM and increased risk of macrovascular events. *F/u:* Mean 34.5 mos for primary randomised study Mean 10.7 yrs for long-term observational f/u *Time frame:* May 2001 – April 2002 *Funding source:* Takeda Pharmaceutical Company and Eli Lilly and Company.	% w/ microvascular disease: 43%, 41% Mean % HbA1c: 7.8%, 7.9% Blood glucose–lowering tx: % w/ Met only: 10%, 10% % w/ Sulf only: 20%, 19% % w/ Met + Sulf: 25%, 25% % w/ insulin only: <1%, <1% % w/ insulin + Met: 18%, 18% % w/ insulin + Sulf: 8%, 8% % w/ insulin + Met + Sulf: 4%, 4% % w/ other combo: 12%, 12% % w/ diet only: 4%, 4% Entry criteria (evidence of macrovascular disease): % w/ prior MI: 47%, 46% % w/ prior stroke: 19%, 19% % w/ prior PCI or CABG: 31%, 31% % w/ prior ACS: 14%, 14% % w/ objective evidence of coronary artery disease: 48%, 48% % w/ ≥2 macrovascular disease criteria: 47%, 49% BL CV medications: % w/ beta-blockers: 55%, 54% % w/ angiotensin-converting enzyme inhibitors: 63%, 63% % w/ angiotensin II antagonists: 7%, 7% % w/ calcium channel blockers: 34%, 37% % w/ nitrates: 39%, 40% % w/ thiazide diuretics: 15%, 16%	*Long-term observational f/u study [66 71]:* Following completion of the PROactive study, pts were invited to participate in a 10-yr observational f/u study. During this time pts received medical care according to physician's discretion without specified drug allocation. TZD use during f/u was 20.8% of pts in Pio grp and 16.1% of pts in original PBO grp. *Outcome measure(s):* <u>Primary endpoint</u>: Time to first event of all-cause mortality, nonfatal MI, including silent MI, stroke, ACS, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle. <u>Prespecified secondary endpoints</u>: Time to first event of all-cause death, MI excluding silent MI, or stroke. <u>CV death</u>: Time to individual components of primary composite. All fatal events considered CV related unless there was a clear non-CV cause. <u>Other outcomes</u>: Adverse events; serious adverse events (causing death, life threatening, requiring or prolonging in pt	Any first event: 514, 572 Death: 110, 122 Nonfatal MI (excluding silent MI): 85, 95 Silent MI: 20, 23 Stroke: 76, 96 Major leg amputation: 9, 15 ACS: 42, 63 Coronary revascularisation: 101, 101 Leg revascularisation: 71, 57 *Main pre-specified secondary composite endpoint:* Kaplan-Meier Estimation, time to any first event reported graphically: HR 0.84 (95% CI 0.72-0.98) *p*=0.027 First events contributing to prespecified secondary composite, # events: Any first event: 301, 358 Death: 129, 142 Nonfatal MI (excluding silent MI): 90, 116 Stroke: 82, 100 *Additional composite endpoints:* In a post hoc analysis, Wilcox et al. 2008 reported that Pio was favored over PBO in 5 of 7 additional major adverse cardiac event composite endpoints (HR 0.79-0.83; *p*<0.05). Composite endpoints included 7 different combinations of all-cause mortality, CV mortality, cardiac mortality, nonfatal MI, nonfatal stroke, and/or ACS [78]. *Occurrence of major events comprising primary composite endpoint:* <u>Death</u> # (%) of first events: 177/2605 (6.8%), 186/2633 (7.1%) HR 0.96 (95% CI 0.78-1.18)	*Limitations:* Pts received a mix of existing meds (though drug types were similarly distributed in Pio and PBO grp). *Study quality:* Good *Conflicts of interest:* Authors report relationships w/ commercial entities.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	% w/ loop diuretics: 14%, 14% % w/ antiplatelet medications: 85%, 83% % w/ aspirin: 75%, 72% % w/ statins: 43%, 43% % w/ fibrates: 10%, 11% *Inclusion criteria:* Pts w/ T2DM aged 35-75 yrs; HbA1c ≥6.5% despite existing tx w/ diet alone or oral glucose-lowering agents w/ or without insulin; evidence of extensive macrovascular disease before recruitment (MI, stroke, PCI or CABG in prior 6 mos, ACS in prior 2 mos, or objective evidence of coronary artery disease or obstructive arterial disease in the leg). *Exclusion criteria:* T1D; taking only insulin; planned coronary or peripheral revascularisation; New York Hearet Association class II heart failure or above; ischemic ulcers, gangrene, or resting leg pain; hemodialysis; >2.5× upper limit of normal ALT levels.	admission; resulting in disability; or requiring intervention to prevent the above). Hypoglycaemic episodes were considered based on pt-reported symptoms. Outcomes were assessed by an independent adjudication committee.	# of total events: 177, 186 # (%) CV deaths: 127 (4.9%), 136 (5.2%) # (%) non CV deaths: 50 (1.9%), 50 (1.9%) <u>Nonfatal MI (including silent MI)</u> # (%) of first events: 119/2605 (4.6%), 144/2633 (5.5%) HR 0.83 (95% CI 0.65-1.06) # of total events: 131, 157 <u>Stroke</u> # (%) of first events: 86/2605 (3.3%), 107/2633 (4.1%) HR 0.81 (95% CI 0.61-1.07) # of total events: 92, 119 <u>Major leg amputation</u> # (%) of first events: 26/2605 (1.0%), 26/2633 (1.0%) HR 1.01 (95% CI, 0.58-1.73) # of total events: 28, 28 <u>Acute coronary syndrome</u> # (%) of first events: 56/2605 (2.1%), 72/2633 (2.7%) HR 0.78 (95% CI 0.55-1.11) # of total events: 65, 78 <u>Coronary revascularisation</u> # (%) of first events: 169/2605 (6.5%), 193/2633 (7.3%) HR 0.88 (95% CI 0.72-1.08) # of total events: 195, 240 <u>Leg revascularisation</u> # (%) of first events: 80/2605 (3.1%), 65/2633 (2.5%) HR 1.25 (95% CI 0.90-1.73) # of total events: 115, 92	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Total # of events: 803, 900 *Hazard of BL characteristics for main pre-specified secondary composite endpoint:* Age (yrs): HR 1.05 (95% CI 1.04-1.06); *p*<0·0001 Previous stroke: HR 1.71 (95% CI 1.40-2.08); *p*<0.0001 Current smoker (vs. never smoker): HR 1.70 (95% CI 1.34-2.16); *p*<0.0001 Past smoker (vs. never smoker): HR 1.19 (95% CI 1.00-1.42); *p*=0.0512 Creatinine >130 µmol/L: HR 1.67 (95% CI 1.20-2.31); *p*=0.0022 Previous MI: HR 1.49 (95% CI 1.25-1.78); *p*<0.0001 HBA1c >7.5%: HR 1.48 (95% CI 1.24-1.76); *p*<0.0001 Peripheral obstructive artery disease: HR 1.35 (95% CI 1.10-1.65); *p*=0.0036 Diuretic use: HR 1.33 (95% CI 1.13-1.57); *p*=0.0007 LDL cholesterol >4 mmol/L (vs. <3 mmol/L): HR 1.33 (95% CI 1.05-1.67); *p*=0.0165 LDL cholesterol 3-4 mmol/L (vs. <3 mmol/L): HR 1.22 (95% CI 1.01-1.46); *p*=0.0357 Insulin use: HR 1.32 (95% CI 1.12-1.55); *p*=0.0008	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			PCI or CABG: HR 0.76 (95% CI 0.63-0.93); *p*=0.0083 Statin use: HR 0.83 (95% CI 0.69-1.00); *p*=0.0452 Allocation to Pio: HR 0.84 (95% CI 0·72-0·98); *p*=0.0309 *Serious adverse events, # pts (% pts):* Any serious adverse event: 1204 (46%), 1275 (48%); *p*=0.110 Endpoint events: 389 (15%), 434 (16%); *p*=0.123 Non-endpoint events: 1079 (41%), 1150 (44%); *p*=0.099 Most common events (>1% of pts; excluding endpoints): Angina pectoris: 89 (3%), 122 (5%); *p*=0.025 Hospital admission for diabetes control: 55 (2%), 91 (3%); *p*=0.003 Accident: 51 (2%), 49 (2%); *p*=0.798 Atrial fibrillation: 42 (2%), 51 (2%); *p*=0.374 Pneumonia: 53 (2%), 35 (1%); *p*=0·047 Transient ischemic attack: 34 (1%), 39 (2%); *p*=0.587 Neoplasms: Any neoplasm: 112 (4%), 113 (4%) Malignant neoplasms: 97 (4%), 99 (4%) Colon/rectal: 16 (1%), 15 (1%); *p*=0.834 Lung: 15 (1%), 12 (1%); *p*=0.544 Bladder: 14 (1%), 6 (<1%); *p*=0.069 Haematological: 6 (<1%), 10 (<1%); *p*=0.327 Breast: 3 (<1%), 11 (<1%); *p*=0.034 Other: 47 (2%), 46 (2%); *p*=0.876 *Heart failure:*	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Any heart failure: 281 (11%), 198 (8%); *p*<0.0001 Heart failure not needing hospital admission: 132 (5%), 90 (3%); *p*=0.003 Heart failure needing hospital admission: 149 (6%), 108 (4%); *p*=0.007 Fatal heart failure: 25 (1%); 22 (1%); *p*=0.634 A post hoc analysis of pts w/ serious heart failure showed that there was no subsequent difference btwn Pio vs. no Pio grps for subsequent mortality due to heart failure (0.96%, 0.84%; *p*=0.639) [70]. Oedema without heart failure: 562 (21.6%), 341 (13.0%); *p* value NR Hypoglycaemia: 726 (28%), 528 (20%); *p*<0.0001 Hypoglycaemia resulting in admission to hospital: 19 (0.7%), 11 (0.4%); *p*=0.14 Weight: Mean 3.6 kg increase for Pio grp Mean 0.4 kg decrease in PBO grp; *p*<0.0001 favoring PBO Mean blood pressure reduction (systolic): 3 mm Hg, 0 mm Hg; *p*=0.03 favoring Pio Withdrawal for adverse events: 235/2605 (9.0%), 202/2633 (7.7%) *Long-term observational f/u:* Note that outcomes from the 6-yr observational f/u period are not summarised here [71], as they are	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			superseded by the findings reported in the 10-yr f/u [66]. Outcomes from double blind period + 10-yr f/u period, # pts (% pts): Primary composite endpoint: 1373/1820 (52.7%), 1416/1779 (53.8%) HR 0.94 (95% CI 0.87-1.01); *p*=0.1001 Main secondary composite endpoint: 1092/1820 (41.9%), 1132/1779 (43.0%) HR 0.94 (95% CI 0.87-1.03); *p*=0.1699 All-cause mortality: 795/1820 (30.5%), 834/1779 (31.7%) HR 0.94 (95% CI 0.85-1.04); *p*=0.2143 Nonfatal MI: 306/1820 (11.7%), 310/1779 (11.8%) HR 0.97 (95% CI 0.83-1.14); *p*=0.7078 Stroke: 317/1820 (12.2%), 312/1779 (11.8%) HR 1.00 (95% CI 0.86-1.17); *p*=0.9727 Cardiac intervention: 515/1820 (19.8%), 545/1779 (20.7%) HR 0.92 (95% CI 0.82-1.04); *p*=0.1981 Major leg amputation: 98/1820 (3.8%), 121/1779 (4.6%) HR 0.79 (95% CI 0.61-1.04); *p*=0.0890 Leg revascularisation: 175/1820 (6.7%), 184/1779 (7.0%) HR 0.94 (95% CI 0.76-1.16); *p*=0.5577 CV mortality: 547/1820 (21.0%), 586/1779 (22.3%)	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			HR 0.92 (95% CI 0.82-1.04); *p*=0.1674 Any malignancy: 326/1820 (12.5%), 322/1779 (12.2%) RR 1.02 (95% CI 0.89-1.18) Adrenal: 3/1820 (0.1%), 0/1779 (0%) RR, not applicable Biliary: 5/1820 (0.2%), 3/1779 (0.1%) RR 1.68 (95% CI 0.40-7.04) Brain: 3/1820 (0.1%), 11/1779 (0.4%) RR 0.28 (95% CI 0.08-0.99) Bladder: 27/1820 (1.0%) 26/1779 (1.0%) RR 1.05 (95% CI 0.61-1.79) Breast: 15/1820 (1.7%), 2/1779 (0.8%) RR 0.71 (95% CI 0.37-1.36) Cervix: 1/1820 (0.1%), 2/1779 (0.2%) RR 0.52 (95% CI 0.05-5.73) Colon/rectal: 49/1820 (1.9%), 45/1779 (1.7%) RR 1.10 (95% CI 0.74-1.64) Gastric: 17/1820 (0.7%), 19/17 79 (0.7%) RR 0.90 (95% CI 0.47-1.74) Hematological: 24/1820 (0.9%), 22/1779 (0.8%) RR 1.10 (95% CI 0.62-1.96) Hepatic: 6/1820 (0.2%), 5/1779 (0.2%) RR 1.21 (95% CI 0.37-3.97) Lung: 48/1820 (1.8%), 55/1779 (2.1%) RR 0.88 (95% CI 0.60-1.29)	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Mesothelioma: 2/1820 (0.1%), 1/1779 (<0.1%) RR 2.02 (95% CI 0.18-22.28) Metastases: 12/1820 (0.5%), 11/1779 (0.4%) RR 1.10 (95% CI 0.49-2.49) Esophageal: 2/1820 (0.1%), 2/1779 (0.1%) RR 1.01 (95% CI 0.14-7.17) Oropharyngeal: 5/1820 (0.2%), 8/1779 (0.3%) RR 0.63 (95% CI 0.21-1.93) Ovarian/uterine: 10/1820 (1.1%), 10/1779 (1.1%) RR 1.04 (95% CI 0.44-2.49) Pancreas: 15/1820 (0.6%), 17/1779 (0.6%) RR 0.89 (95% CI 0.45-1.78) Prostate: 58/1820 (3.3%), 35/1779 (2.0%) RR 1.59 (95% CI 1.04-2.41) Renal: 13/1820 (0.5%), 17/1779 (0.6%) RR, 0.77 (95% CI, 0.38-1.59) Skin: 35/1820, (1.3%) 36/1779 (1.4%) RR 0.98 (95% CI 0.62-1.50) Other: 6/1820 (0.2%), 10/1779 (0.4%) RR 0.61 (95% CI 0.22-1.67) *Other post hoc analyses not already summarised:* Erdmann et al. (2007) [71] Purpose:	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Evaluate subpopulation of pts w/ prior MI (n=1230 Pio pts and 1215 PBO pts) Summary of findings: Pio was associated w/ a reduced risk of fatal or nonfatal MI (*P*=0.045) and ACS (*P*=0.0336). There were no differences btwn Pio vs. PBO for other outcomes. Wilcox et al. (2007) [77] Purpose: Evaluate risk of stroke and cv events in pts w/ (n=964) and without (n=4254) prior stroke. Summary of findings: In pts w/ prior stroke, Pio was associated w/ significantly lower risk of recurrent stroke (HR 0.53; 95% CI 0.53-0.85; *p*=0.009) and a composite of CV death, nonfatal stroke, or nonfatal MI (HR 0.72; 95% CI 0.53-1.00; *p*=0.047). There were no differences btwn Pio vs. PBO for pts without prior stroke. Schneider et al., 2008 [76] Purpose: evaluate risk of macrovascular events in pts w/ (n=597) and without chronic kidney disease. Summary of findings: Primary outcome occurred more frequently in pts w/ chronic kidney disease vs. those without (27.5% vs. 19.6%; *p*=0.0001). For pts w/ chronic kidney disease, Pio was associated w/ reduced occurrence of the secondary composite outcome vs. PBO (HR 0.66; 95% CI 0.45-0.98). Dormandy et al., 2009 [69] Purpose:	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Evaluate risk of macrovascular events in pts w/ (n=1274; n=619 Pio, n=655 PBO) and without peripheral arterial disease at BL. Summary of findings: Pts w/ peripheral arterial disease at BL had a higher occurrence of main primary endpoint, secondary endpoint, all-cause mortality, and stroke (p<0.00001). Pts without peripheral arterial disease at BL receiving Pio had lower occurrence of primary endpoint (p=0.016), secondary endpoint (p=0.0453), and ACS (p=0.0287). The same benefit w/ Pio was not observed for pts w/ peripheral artery disease at BL. Scheen et al., 2009 (PROactive 17) [75] Purpose: Evaluate Pio vs. PBO in pts receiving Sulf + Met without insulin at BL (n=1314, n=654 Pio, n=660 PBO) Summary of findings: Safety of Pio + Sulf + Met vs. PBO + Sulf + Met was similar. More pts in Pio grp had hypoglycaemia (27% vs. 20%; p<0.001), oedema (29% vs. 17%; p<0.001), and weight gain (p<0.001). Scheen et al., 2009 (18) [74] Purpose: Evaluate Pio vs. PBO in pts receiving Sulf alone (n=1001; n=508 Pio, n=493 PBO) or met alone (n=514; n=253 Pio, n=261 PBO) without insulin at BL. Summary of findings: For pts receiving Met only at BL, oedema was higher for Pio vs. PBO (27% vs. 15%, p<0.001). All other safety outcomes were similar. For pts receiving Sulf only at BL, pts receiving Pio had significantly higher rates	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			of hypoglycaemia (21% vs. 13%; *p*<0.001), and oedema (22% vs. 11%; *p*<0.001). Body weight gain was significantly higher for Pio vs. PBO in both Sulf and Met grps (*p*<0.001). Charbonnel et al. 2010 (19) [67] Purpose: Evaluate Pio vs. PBO as an add-on in pts receiving insulin at BL (n=1760; n=864 Pio, n=896 PBO). Summary of findings: Ps receiving insulin at BL had more serious adverse events than pts not receiving insulin at BL (*p*<0.0001). Adverse events occurring at a higher rate for Pio vs. PBO in pts receiving insulin at BL included heart failure (13.5% vs. 10.5%; *p*<0.05), hypoglycaemia (42.1% vs. 29.0%; *p*<0.001), and oedema (30.8% vs. 18.2%; *p*<0.001), weight gain (4.2 kg vs. 00.1 kg; *p*<0.0001). Erdmann et al., 2010 (20) [72] Purpose: Evaluate the risk of macrovascular events in Pio vs. PBO in pts using nitrates (n=1018 Pio, n=1045 PBO), renin-angiotensin system blockers (n=1782 Pio, n=1821 PBO), or insulin (n=864 Pio, n=896 PBO) at BL. Summary of findings: Pts receiving vs. not receiving these medications at BL had similar trend for benefit w/ Pio. The main secondary endpoint occurred less often in Pio vs. PBO in pts taking any of the concomitant txs of interest (11.6% vs. 13.6%; *p*=0.0277). Similar findings were reported for a composite of CV mortality, MI, and stroke (9.9% vs. 11.9%; *p*=0.0201).	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			By drug, pts receiving renin-angiotensin system blockers showed a significant benefit for Pio vs. PBO for the secondary endpoint. Pts receiving nitrates showed a significant benefit for Pio vs. PBO for the primary endpoint (*p*=0.0404) and composite of CV mortality, MI, and stroke (*p*=0.0243). The risk of oedema and heart failure was higher for Pio vs. PBO regardless of BL medication grp, and no significant interactions were observed. Doehner et al. 2011 [68] Purpose: Evaluate relationship btwn body weight change and mortality and morbidity outcomes. Summary of findings: The occurrence of all-cause mortality and hospitalisation were higher in pts w/ BMI <25 kg/m^2. Weight loss was associated w/ increased mortality, CV mortality. This was especially true for the PBO grp. The authors suggest the presence of an "obesity paradox" in pts w/ both T2DM and CV risk, where increased weight correlates to better mortality and CV outcomes in this population. Pfister et al., 2013 [73] Purpose: Identify clinical predictors of heart failure (n=233 pts w heart failure) Summary of findings: Significant predictors of heart failure included (*p*=0.03 to *p*<0.0001): Use of Pio vs. placebo (*p*=0.004), age ≥65 yrs, creatinine ≥130 umol/L, diuretic use, HbA1c ≥7.5%, ≥10-yr duration of diabetes,	

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			LDL cholesterol >4, HR >75, left bundle branch block, prior MI, positive microalbuminuria test, right bundle branch block.	
Matthews et al. (2005)[59]; Charbonnel et al. (2005)[65] Churchill Hospital, Oxford, UK; Hotel Dieu, Nantes cedex, France; Technical University, Dresden, Germany; University of Perugia, Via Enrico Dal Pozzo, Perugia, Italy; Rudolfstiftung Hospital, Juchgasse, Vienna, Austria. 75 centers in 9 European countries and Australia. Randomised double-blind double-dummy study comparing Pio w/ Glic as an add-on to Met in pts w T2DM inadequately controlled by Met. *F/u:* 1 yr *Time frame:* NR *Funding source:* Takeda Euro and Eli Lilly and Company	n=630 pts randomised to Pio + Met grp: 317 pts Glic + Met grp: 313 pts *Power analysis:* Sample size based on btwn-grp difference of 0.35% in change in HbA1c from BL. 225 pts/grp required for 95% power. *ITT analysis:* Analysis performed on ITT population (all pts who took ≥1 dose of study drug). *Pt characteristics:* % female: 49.2%, 50.8% Mean age, yrs: 56, 57 Mean weight, kg: 91.8, 92.7 Mean BMI, kg/m^2: 32.6, 32.6 Mean disease duration, yrs: 5.8, 5.5 Mean % HbA1c: 8.71%, 8.53% *Inclusion criteria:* Pts w/ T2DM inadequately managed by Met alone (≥50% of maximum dose for ≥3 mos); aged 35-75 yrs; HbA1c 7.5%-11.0%; fasting C peptide of ≥1.5 ng/mL; stable or worsening glycemic control for ≥3 mos prior to screening. Female pts were postmenopausal, sterilised, or using satisfactory contraception.	Pts randomised equally to Pio + Met or Glic + Met grps. Methods for randomisation, allocation concealment, and blinding NR. Study included 16-wk forced titration phase and 36-wk maintenance phase. Dose achieved at 16 wks maintained for remainder of study. Thiazides were allowed for tx of oedema. If antihypertensive tx was indicated, pts received ACE inhibitors, angiotensin II receptor antagonists, or calcium antagonists. *Intervention:* Pio starting at 15 mg/day titrated to 30 mg or 45 mg (mean 39 mg/day) + pretrial Met dose (mean 1726 mg/day); 70% of pts received maximum Pio dose. *Comparator:* Glic starting 80 mg/day, titrated to 160 mg, 240 mg, or 320 mg (mean 212 mg/day) + pretrial Met dose (mean 1705 mg/day); 33% of pts received maximum Glic dose. *Outcome measure(s):* Adverse events. Note that intermediate outcomes (e.g. HbA1c) are also	*Data reported as Pio + Met grp, Glic + Met grp.* *Study completion:* % of pts completing 1-yr study[59]: 82.3%, 86.6% % of pts discontinued due to adverse events: 4.1%, 4.5% 10/630 pts not eligible for ITT population due to missing HbA1c data. Mean tx duration was 11 mos in both grps. 75% of pts completed a 104 wk study, w/ data reported in Charbonnel et al., (2005) [65] *Adverse events (1 yr) [59]:* Any adverse event: 176/317 pts (55.5%), 182/313 pts (58.1%) Majority were mild or moderate. Serious adverse events: 15/317 pts (4.7%), 20/313 pts (6.4%) Deaths: 0/317 (0%), 2/313 (0.6%) None tx related. Hypoglycaemia: 4/317 pts (1.3%), 35/313 pts (11.2%) No hypoglycaemic events were serious.	Results suggest that Pio + Met was associated w/ a numerically lower occurrence of serious adverse events (4.7% vs. 6.4%) and similar occurrence of adverse events (55.5% and 58.1%) compared w/ Glic + Met. The statistical and clinical significance of these findings is unclear. *Limitations:* Methods for randomisation, allocation concealment, blinding NR; study not powered to detect differences in adverse event rates; no statistical comparisons between grps for adverse events; >15% attrition; modified ITT analysis. *Study quality:* Fair *Conflicts of interest:* NR

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	Exclusion criteria: Type 1 diabetes mellitus; ketoacidosis, MI, transient ischemic attacks, or stroke in prior 6 mos; heart failure; acute malabsorption or pancreatitis; familial polyposis coli; malignant disease in prior 10 yrs; substance abuse; pregnancy or breastfeeding; prior use of insulin, Glic, Pio, other TZDs, or Sulf not permitted.	reported but are not summarised here.	Oedema: 20/317 pts (6.3%), 7/313 pts (2.2%) Oedema led to 1 withdrawal. Other AEs reported more frequently in Pio + Met grp included dizziness, vertigo (details NR). Other AEs reported more frequently in Glic + Met grp included hypertension, arthralgia, diarrhoea, paresthesia, dyspepsia (details NR). Weight: Mean increase of 1.5 kg in Pio + Met grp. Mean increase of 1.4 kg in Glic + Met grp. *Adverse events (2 yrs)* [65]*:* No major differences btwn grps in adverse events (further data NR). % discontinued for adverse events: 6.9%, 6.7% % w/ symptoms of hypoglycaemia: 2.2%, 11.5% % w/ GI disorders: 3.8%, 5.1% % w/ congestive heart failure: 1.6%, 0.6% % w/ oedema: 7.6%, 3.5% Weight: Mean increase of 2.5 kg for Pio + Met Mean increase of 1.2 kg for Glic + Met Blood pressure:	

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			1 yr: No clinically relevant changes or differencess btwn grps. Data NR.	
Nissen et al. (2008)[60] Cleveland Clinic, Cleveland OH, US; Lahey Clinic, Burlington, MA, US; Takeda Global Research and Development, Deerfield, IL, US; Clinica Chutro, Colon, Argentina; Hoˆpital Laval, Quebec City, Quebec, Canada; St. Vincent's Hospital Manhattan, New York NY, US; Atlanta VA Medical Center, Atlanta, GA; Vancouver General Hospital, Vancouver, BC, Canada. PERISCOPE Trial 97 centers in North and South America Randomised, double-blind, multicentre study comparing Pio w/ Glim in pts w/ T2DM and coronary artery disease. *F/u:* 18 mos *Time frame:* August 2003 – March 2006	n=547 pts randomised to: Pio + existing medications grp: 274 pts Glim + existing medications grp: 273 pts *Power analysis:* Based on primary outcome, change in percentage atheroma volume. For 90% power to detect a 1.8% difference btwn grps, 330 pts were required. W/ a 25% drop-out rate, 440 pts were required. Due to a higher drop-out rate during study conduct (35%), the enrollment target was increased to 540 pts. *ITT analysis:* Modified ITT population evaluated, details NR. *Pt characteristics (Pio grp, Glim grp):* % female: 31.1%, 34.1% Mean age, yrs: 60.0, 59.7 Mean weight, kg: 94.2, 92.8 Mean BMI: 32.1, 32.0	Pts were randomised 1:1 to Pio or Glim using an interactive voice response system w/ a block size of 4. Allocation stratified by diabetes tx status. Pts and all study personnel were blinded to assignment. Pts were permitted to continue all diabetic medications during study period except for a TZD, Sulf, or other insulin secretagogues. Independent blinded committee adjudicated adverse CV events. *Intervention:* Pts naïve to glucose-lowering therapy or <2 mg/day Glim (or equivalent dosage of another Sulf) at BL received 15 mg Pio. Pts taking ≥2 mg/day Glim or Met monotherapy received 30 mg/day. *Comparator:* Pts naïve to glucose-lowering therapy or <2 mg/day Glim (or equivalent	*Data reported as Pio grp, Glim grp* *Study completion:* # randomised: 274, 273 # receiving study drug: 270, 273 # (%) non-completion: 92/273 (33.7%), 91/274 (33.2%) Reasons for withdrawal of drug therapy, # pts (% pts): Adverse events: 30 (11.1%), 34 (12.5%); *p*=0.63 Lack of efficacy: 4 (1.5%), 1 (0.4%); *p*=0.21 Lost to f/u: 4 (1.5%), 6 (2.2%); *p*=0.75 Study termination at site: 7 (2.6%), 9 (3.3%); *p*=0.63 Protocol violation: 6 (2.2%), 3 (1.1%); *p*=0.34 Voluntary withdrawal by participant: 40 (14.8%), 34 (12.5%); *p*=0.42 Investigator's discretion: 6 (2.2%), 8 (2.9%); *p*=0.60 Total not completing the trial: 97 (35.9%), 95 (34.8); *p*=0.78 *Composite clinical outcome, # pts (% pts):* CV death, nonfatal MI, or nonfatal stroke: 5 (1.9%), 6 (2.2%); *p*=0.78	Results suggest that Pio or Glim added to existing medications are associated w/ a similar occurrence of major adverse CV events over an 18-mo period. *Limitations:* High percentage of non-completion; study not powered for detection of differences in adverse event rates; pts received a mix of concomitant medications (well-balanced btwn grps). *Study quality:* Fair *Conflicts of interest:* Authors report relationships w/ commercial entities.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Funding source: Takeda Pharmaceuticals North America, Inc.	% current smokers: 11.5%, 19.4%, *p*=0.01 % past smokers: 54.4%, 43.6% Median diabetes disease duration, mos: 70.0, 71.0 Median coronary disease duration, mos: 9.0, 8.0 % w/ hypertension: 83.3%, 91.6%; *p*=0.002 % w/ prior MI: 25.6%, 30.7% Medication use: % w/ aspirin: 89.6%, 91.9% % w/ beta-blocker: 75.9%, 77.3% % w/ ACE inhibitor or angiotensin II receptor blocker: ARB: 80.4%, 83.9% % w/ other lipid-lowering agent: 4.8%, 6.2% % w/ Met: 65.2%, 63.7% % w/ insulin: 18.1%, 23.1% *Inclusion criteria:* Pts aged 35-85 yrs, HbA1c 6%-9% (if taking glucose-lowering drugs) or 6.5%-10% (if not taking glucose-lowering drugs); pts required to undergo coronary angiography for clinical indications demonstrating ≥1 angiographic stenosis w/ ≥20% narrowing. Target vessel for intravascular ultrasound required to have <50% obstruction for ≥40 mm segment. *Exclusion criteria:* T1D; ≥3 current antidiabetic medications; received prior TZD w/ in prior 12 wks; serum	dosage of another Sulf) received 1 mg/day Glim. Pts taking ≥2 mg/day Glim or Met monotherapy received 2 mg/day. *Outcome measure(s):* Major adverse cardiovascular events, CV and non-CV death, nonfatal MI and stroke, hospitalisation for unstable angina or congestive heart failure, coronary revascularisation, other adverse events (hypoglycaemia, angina pectoris, oedema, hypertension, bone fractures). The definition of hypoglycaemia was not clear. Other intermediate outcomes were also reported but are not summarised here (e.g. intravascular ultrasound endpoints).	CV death, nonfatal MI, nonfatal stroke, hospitalisation for unstable angina, or congestive heart failure: 11 (4.1%), 13 (4.8%); *p*=0.70 CV death, nonfatal MI, nonfatal stroke, coronary or carotid revascularisation, hospitalisation for unstable angina, or congestive heart failure: 40 (14.8%), 41 (15.0%); *p*=0.95 *Individual events:* CV death: 3 (1.1%), 1 (0.36%); *p*=0.37 Noncardiovascular death: 0 (0.0%), 1 (0.36%); *p*>0.99 Nonfatal MI: 2 (0.7%), 4 (1.5%); *p*=0.69 Nonfatal stroke: 0 (0.0%), 1 (0.36%); *p*>0.99 Hospitalisation for unstable angina: 4 (1.5%), 2 (0.7%); *p*=0.45 Coronary revascularisation: 29 (10.7%) 30 (11.0%), *p*=0.93 Hospitalisation for congestive heart failure: 4 (1.5%), 5 (1.8%); *p*=0.99 Hypoglycaemia: 41 (15.2%); 101 (37.0%); *p*<0.001 Angina pectoris: 19 (7.0%), 33 (12.1%); *p*=0.05 Peripheral oedema: 48 (17.8%), 30 (11.0%); *p*=0.02 Hypertension: 13 (4.8%), 24 (8.8%); *p*=0.07	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	creatinine >2 mg/dL, triglyceride level >500 mg/dL, uncontrolled hypertension, active liver disease, or left main coronary artery stenosis of >50%.		Bone fracture: 8 (3.0%), 0 (0%); *p*=0.004 Weight: Pts in both grps gained weight, gain was 2 kg higher for Pio grp Median blood pressure change from BL, mm Hg: Systolic: 0.1 (95% CI −1.4 to 1.5), 2.3 (95% CI 0.9-3.7); *p*=0.03 favoring Pio Diastolic: −0.9 (95% CI −1.7 to −0.01), 0.9 (95% CI 0.1-1.7); *p*=0.003 favoring Pio	
Bolli et al. (2009)[53] University of Perugia, Perugia, Italy; University of Siena, Siena, Italy; Novartis Pharma AG, Basel, Switzerland; Novartis Pharmaceutical Corporation, East Hanover, New Jersy, US Randomised, double-blind comparison of Pio vs. Vilda as add-ons to Met in pts w/ T2DM. *F/u:* 1 yr *Time frame:* NR *Funding source:* Novartis Pharmaceuticals Corporation	n=576 pts Pio + Met grp: 281 pts Vilda + Met grp: 295 pts *Power analysis:* NR Designed as a non-inferiority study for vildagliptin w/ respect to Pio, non-inferiority limit of 0.4% btwn-grp difference in HbA1c at 24 wks; 52-wk analysis was secondary. ITT population included all randomised pts w/ ≥1 dose of study drug and ≥1 post BL assessment, # pts NR. Per-protocol population includes pts in ITT grp who discontinued study due to unsatisfactory response in first 24 wks, or completed ≥22 wks tx; # pts NR. *Pt characteristics (Pio + Met grp; Vilda + Met grp):*	Pts randomised 1:1 to Pio + Met or Vilda + Met using an automated central telephone system. Randomisation numbers generated to ensure unbiased assignment and were concealed from pts and investigators. There was no stratification. Study consisted of a double-blind 24 wk phase (pts, investigators, sponsors blinded), followed by a single blind 28 wk phase (sponsors were not blinded but pts and investigators were blinded). 24 wk results published separately. *Intervention:* 30 mg Pio/day as add-on to stable dose of Met >1500 mg (mean 2008 mg). *Comparator:* 50 mg Vilda twice/day (100 mg total) as add-on to stable dose of Met >1500 mg (mean 20132 mg).	*Study completion:* NR *Weight:* Weight increased in Pio + Met grp (mean 2.6 kg gain; *p*<0.0001) and remained stable in Vilda (mean 0.2 kg gain). *CV events:* Any CV or cerebrovascular event: 6 (2.1%), 2 (0.7%) ACS: 1 (0.36%), 1 (0.33%) Stroke: 2 (0.7%), 1 (0.33%) Arrhythmia: 1 (0.36%), 0 (0%) Syncope: 1 (0.36%), 0 (0%) Transient ischemic attack: 1 (0.36%), 0 (0%) *Adverse events:* % pts w/ any event: 68.2%, 67.8% % w/ any serious event: 4.1%, 8.9% Peripheral oedema: 31 (11.1%), 32 (10.8%)	Results suggest that Pio + Met and Vilda + Met are associated w/ numerically similar rates of overall adverse events (68% of pts by 1 yr); although Pio + Met is associated w/ numerically lower rates of severe adverse events (4.1% vs. 8.9%). The statistical and clinical significance of this difference is unclear. *Limitations:* No reporting of power analysis or study completion; study not powered to detect differences in adverse event rates; no statistical analyses of adverse events; attrition data NR; modified ITT analysis for efficacy outcomes. *Study quality:* Good *Conflicts of interest:* Authors report relationships w/ commercial entities.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	% female: 35/9%, 38.3% Mean age, yrs: 57.0, 56.3 Mean weight, kg: 91.2, 91.8 Mean BMI, kg/m^2: 32.1, 32.2 % HbA1c: 8.4%, 8.4% Mean disease duration, yrs: 6.4, 6.4 Mean Met dose, mg: 2008, 2032 *Inclusion criteria:* Men and women aged 18-77 yrs w/ T2DM, receiving a stable dose of Met (≥1500 mg/day), HbA1c of 7.5%-11%, FPG <15 mmol/L, BMI of 22-45 kg/m^2; fertile women were included only if using adequate birth control. *Exclusion criteria:* Acute metabolic complications of diabetes; use of any other oral anti-diabetic medication other than Met in 3 mos prior to study; chronic insulin tx (>4 wks) in prior 6 mos; MI, unstable angina, or CABG within prior 6 mos; congestive heart failure; liver disease; ALT or aspartate aminotransferase >2.5× the upper limit; bilirubin >1.3× the upper limit, >132 mmol/L (men) or >125 mmol/L (women); clinically significant abnormal thyroid-stimulating hormone; fasting triglycerides >7.9 mmol/L.	*Outcome measure(s):* Adverse events. Hypoglycaemic episodes were those confirmed by blood glucose measurements <3.1 mmol/L. Intermediate outcomes were also reported but are not summarised here (e.g. HbA1c). Select clinical events were reviewed by an independent adjudication committee.	Headache: 17 (6.1%), 19 (6.4%) Nasopharyngitis: 20 (7.1%), 16 (5.4%) Back pain: 15 (5.4%), 15 (5.1%) Dizziness 11 (3.9%), 15 (5.1%) Diarrhoea 14 (5.0%), 14 (4.7%) Other reported events, % pts: % w/ any GI adverse event: 14.5%, 20% % w/ vomiting: 1.4%, 3.4% % w/ nausea: 1.8%, 3.4% % w/ dyspepsia: 1.1%, 2.7% % w/ skin-related events: 1.2%, 1.7% % w/ hypoglycaemia: 0.3%, 0.4%; none severe	
Kaku et al. (2009)[58] Kawasaki Medical School, Okayama; Juntendo University School of Medicine, Tokyo;	n=589 pts randomised to Pio + other meds grp: 293 pts Other meds only grp: 294 pts	Pts randomised using a dynamic allocation method, based on presence/absence of CV events, age, sex, and study center.	*Data reported as Pio + existing meds grp; existing meds only grp.* *Study completion:*	Results suggest that the time to macrovascular events was similar for pts receiving Pio + existing meds vs. no Pio in

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Shiga University of Medical Science, Shiga; Tokyo Medical University; Tokyo University of Tokyo, Tokyo Jichi Medical University, Saitama; Iwase Internal Medicine Cardiology Clinic, Tokyo; Osaka University Graduate School of Medicine, Osaka; National Cardiovascular Center, Osaka, Japan 20 centers in Japan Randomised, multicentre, open-label, blinded endpoint study comparing Pio + existing meds vs. existing meds only in pts w/ T2DM and no recent hx of CV events. *F/u:* 2.5-4 yrs *Time frame:* April 2002, June 2006 *Funding source:* Takeda Pharmaceutical, Japan	*Power analysis:* Based on a predicted rate of 35-60 macrovascular events per 1000 pts/yr, 250 pts per grp required for 90% power to detect a 20%-50% difference btwn Pio vs. control grps. W/ 10% attrition rate, 275 pts/grp required. Full analysis set included all pts receiving ≥1 dose of study meds and ≥1 assessment. *Pt characteristics (Pio + other meds grp, other meds only grp):* % female: 37%, 38% Mean age, yrs: 58.1, 57.6 % w/ >5 yrs disease duration: 71.7%, 70.7% % w/ diabetic complications: 98.3%, 100% % w/ hx of CV events: 9.6%, % w/ hx of smoking: 43.7%, 46.6% Mean weight, kg: 69.1, 69.9 Mean BMI, kg/m^2: 26.51, 26.92 Mean % HbA1c: 7.60%, 7.53% Concomitant medications taken at least once during study: % w/ Sulf: 73.0%, 81.6%; p=0.0129 % w/ biguanides: 44.0%, 68.7%; p<0.0001 % w/ α-glucosidase inhibitors: 35.8%, 55.8%; p<0.0001 % w/ rapid-acting insulin secretagogues drugs: 6.5%, 12.9%; p=0.0084 % w/ statins: 44.0%, 45.9%	*Intervention:* 15 or 30 mg/day Pio once daily. Titrated to maximum dose of 45 mg/day. Pio was discontinued if insulin was necessary. Other glucose lowering meds were administered according to approved dosage regimens. Tx adjusted to achieve target HbA1c of <6.5% preferred adjustment was added Pio dose, though addition of an alternative med was permitted. *Comparator:* Other medications only. To achieve target HbA1c, current therapy dosage could be increased, or a concomitant oral glucose lowering drug was added (other than a TZD). *Outcome measure(s):* Primary endpoint: Time to onset of macrovascular events (death, nonfatal MI, silent MI, ACS, CABG or PCI, stroke, lower limb amputation, bypass surgery or angioplasty, onset or worsening of angina pectoris, arteriosclerosis obliterans). Endpoints assessed by blinded independent committee. The definition of hypoglycaemia was not clear. Intermediate outcomes (e.g. HbA1c) were also reported, but are not summarised here.	Missed assessments, # pts (% pts): 54/293 (18%), 36/294 (12%) Reasons: difficulty complying w/ protocol, physician decision, withdrawal of consent. 68/293 pts (23%) discontinued Pio during study. Unclear how many pts discontinued due to adverse events. *Macrovascular events:* Kaplan-Meier curve: Trend toward delayed onset for Pio, but difference NS (p=0.5512). Data reported graphically. % pts w/ macrovascular events: 3.56%, 4.49% Composite of death, acute MI (excluding silent MI), or stroke: 2.4%, 2.4% Occurrence of individual macrovascular events was also similar btwn grps (details NR). *Weight:* Pio grp gained significantly more weight vs. no Pio grp (p<0.01). Data NR. *Adverse events:* % w/ any event: 97.6%, 96.9% Majority of adverse events in Pio grp were not tx related, w/ exception of 12.5% where drug-related cause could not be ruled out. % w/ serious adverse events: 20.1%, 21.8%	addition to other medications. Adverse events occurred in nearly all pts in both grps, and serious adverse events were also common in both grps (20.1% and 21.8% of pts). *Limitations:* Pts and treating physicians not blinded, pts received a mix of ongoing medications that differed significantly btwn grps, and were changeable throughout the study period; 23% of pts discontinued Pio during study period; limited reporting on occurrence of individual macrovascular outcomes. *Study quality:* Fair *Conflicts of interest:* Authors report financial relationships w/ commercial entities.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	% w/ ACE inhibitors: 18.4%, 16.0% % w/ angiotensin II antagonists: 36.9%, 33.3% % w/ calcium channel-blockers: 49.5%, 48.3% % w/ fibrates: 13.0%, 13.3% *Inclusion criteria:* Male and female pts aged 35-74 yrs w/ T2DM (HbA1c ≥6.5%), ≥2 risk factors, including hypertension, hyperlipidemia, obesity, or smoking. *Exclusion criteria:* T1D, heart failure, severe arrhythmias, significant renal/hepatic impairment, BMI <22 kg/m^2 w/ fasting immunoreactive insulin of <5 µU/mL, recent hx (prior 6 mos) of CV disorders (MI, CABG, PCI) or stroke, hospitalised for ACS w/ in prior 3 mos.		4 in Pio grp considered tx related (peripheral oedema, abnormal hepatic function, malaise, gastric cancer). Deaths: 3 pts (1%), 1 (0.3%) Pio grp deaths were not tx related. Causes include cerebral infarction, acute MI, acute cardiac failure. Control grp death due to cardiogenic cause (not further specified). % w/ peripheral lower limb oedema: 16.4%, 4.1% % w/ generalised oedema: 15.7%, 1.0% % w/ hypoglycaemia: 15.7%, 12.9% % w/ diabetic nephropathy: 8.9%, 12.9% Bone fractures: 6.1%, 6.1%	
Tolman et al. (2009)[62] University of Utah, Salt Lake City, UT; University of Connecticut Health Centre, Framingham, CT; Takeca Global Research and Development Center, Deerfield IL, US. 171 centers in the US Randomised double-blind multicentre comparison of Pio vs. Glib for pts w/ T2DM receiving prior Sulf tx. *F/u:* 3 yrs	n=2120 pts randomised to: Pio ± other meds grp: 1063 pts (1051 analysed) Glib ± other meds grp: 1057 pts (1046 analysed) *Power analysis:* Authors report study size was determined by agreement w/ the FDA. *ITT analysis:* Analyses performed on ITT population, which includes all pts receiving ≥1 dose of medication.	Pts randomised 1:1 (stratified by BL Glib use, statin use, and ALT levels). Txs assigned via interactive voice response service vendor. Pts and study personnel were blinded, drugs provided in double-dummy design. Use of antidiabetic agents other than study drug and companion meds, weight loss agents, corticosteroid therapy, or niacin therapy were prohibited during the study.	*Data reported as Pio grp; Glib grp* *Study completion:* Did not complete study, # pts (% pts): 649/1063 (61%); 641/1057 (60.6%) Reasons included withdrawal of consent and loss to f/u. No btwn-grp differences. ITT population: 1051 Pio pts, 1046 Glib pts *Weight increase:* 5.2 kg, 0.9 kg *Adverse events, # pts (% pts):* Any adverse event: 859/1051 (81.7%), 876/1046 (83.7%)	Results suggest that Pio and Glib are associated w/ similar rates of adverse events over 3 yrs. *Limitations:* Very high study attrition (>60% loss); basis of power analysis unclear, study likely not powered to detect differences in adverse event outcomes, no statistical comparisons btwn grps for adverse event outcomes; pts permitted to increase or add other drugs during study period

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Time frame: October 31, 2000 – June 15, 2005 *Funding source:* Takeda Global Research and Development Center	*Pt characteristics of ITT population (Pio grp, Glib grp):* % female: 42.8%, 44.5% Median age, yrs: 54, 55 Mean BMI: 32.5, 32.5 Mean % HbA1c: 9.5%, 9.5% Prior medications (% of pts): % Sulf: 64.8%, 64.7% % Met: 68.7%, 67.7% % statins: 29.4%, 28.3% % fibrates: 4.6%, 5.6% *Inclusion criteria:* Pts aged 18-80 yrs diagnosed w/ T2DM, HbA1c ≥7%, taking maximum daily dose of Glib (20 mg) or other second-generation Sulf, Met monotherapy, or Met + Sulf. Pts who discontinued troglitazone tx for reasons other than adverse events during March or April 2000 were eligible. *Exclusion criteria:* Pts w/ other prior TZD exposure, ongoing use of first-generation Sulf, or taking greater than the maximum Glib dose. Pts w/ T1D, BMI <20 or >48, ALT ≥2.5× upper limit of normal, hx of hepatobiliary disease, pts w/ New York Heart Association class III or IV heart failure, MI, or other cerebrovascular or cardiovascular event in prior 6 mos.	Pts discontinued prior Sulf use at screening. Met tx was continued throughout the study. Study drugs increased to maximum tolerated dose. If maximum tolerated doses of study drugs did not lead to glycaemic control, Met was increased (up to 2000 mg/day) or added to tx regimen. Insulin was also added for pts taking maximum dose of study drug + Met. Downward titration occurred for pts w/ serious hypoglycaemia. *Intervention:* Pio at a maximum tolerated dose of 45 mg/day *Comparator:* Glib at a maximum tolerated dose of 15 mg/day *Assessments:* Every 2 mos for first yr, every 3 mos thereafter *Outcome measure(s):* Adverse events. The definition of hypoglycaemia was not clear. Note that intermediate outcomes related to liver enzyme testing and blood glucose were also reported but are not summarised here.	Withdrawal due to adverse event: 146/1051 (13.9%), 122/1046 (11.7%) Serious adverse event: 159/1051 (15.1%), 174/1046 (16.6%) Deaths: 1/1051 (0.1%), 6/1046 (0.6%) Pio grp death: Acute pulmonary oedema secondary to acute MI Glib grp deaths: Cardiac arrest (n=1), MI (n=4), or respiratory arrest (n=1) *MI events:* 7/1051 (0.7%), 12/1046 (1.1%) *Stroke:* 10/1051 (1%), 9/1046 (0.9%) *Bone fracture:* % men w/ fracture: 2.3%, 2.4% % women w/ fracture: 3.6%, 2.8% *Common adverse events:* % w/ upper respiratory tract infection: 15.2%, 15% % w/ arthralgia: 11.3%, 10.9% % w/ sinusitis: 9.3%, 8.6% % w/ diarrhoea: 8.8%, 7.6% % w/ limb pain: 8.5%, 7.6% % w/ oedema: 8.0%, 3.4% % w/ bronchitis:7.8%, 7.7% % w/ back pain: 7.5%, 7.5% % w/ nausea: 7.3%, 8.0% % w/ headache: 6.7%, 7.6% % w/ cough: 6.4%, 10.3% % w/ hypoglycaemia: 3.8%, 11.4% % w/ hepatobiliary serious adverse events: 0.5%, 1%	if glycaemic control was inadequate. *Study quality:* Poor *Conflicts of interest:* Authors have relationships w/ commercial entities.
Yoshii et al. (2014)[64]	n=522 pts	Pts stratified by age, HbA1c level, BMI, and use of insulin.	*Data reported as Pio + other meds grp; other meds–only grp*	Results suggest there were no differences in the occurrence of

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Juntendo University School of Medicine, Tokyo; University of Tokyo Hospital, Tokyo; Juntendo University Graduate School of Medicine, Tokyo; The University of Tokushima, Tokushima; Hiroshima University Hospital, Hiroshima; Osaka University Graduate School of Medicine, Osaka; National Cerebral and Cardiovascular Center, Suita, Japan PROFIT J study 50 centers worldwide Randomised multicentre open-label study comparing Pio w/ no Pio in pts w/ T2DM and high risk of stroke. *F/u:* Median 672 days *Time frame:* August 2007 – December 2001 *Funding source:* Japan Cardiovascular Research Foundation	Pio + other meds grp: 254 pts Other meds–only grp: 268 pts *Power analysis:* W/ an estimated occurrence of macrovascular events among 10% of pts over 3 yrs in the no Pio grp, and a reduction in macrovascular events of 40% in the Pio grp, an estimated 720 pts/grp was required for 85% power. The authors estimated a sample size of 1000 pts/grp. *ITT analysis:* Authors state that pts were treated under the ITT principle for 3 yrs (details NR). *Pt characteristics (Pio + other meds grp; other meds–only grp):* % female: 37%, 34% Mean age, yrs: 69.0, 68.9 Mean weight, kg: 61.9, 62.4 Mean BMI, kg/m^2: 24.2, 24.3 Mean disease duration, yrs: 11.1, 11.5 Mean % HbA1c: 7.4%, 7.4% Glucose-lowering agents used at study entry, % pts: % Sulf: 45.4%, 47.0% % α-glucosidase inhibitors: 39.4%, 32.0% % biguanide: 32.5%, 29.6% % glinides: 12.6%, 17.4% % insulin: 6.9%, 6.5% % dipeptidyl peptidase-4: 0.0%, 0.4% Other medications:	Pts then randomised to Pio grp or no Pio grp. Details on methods of randomisation and allocation NR. *Intervention:* Pts received Pio at 15 mg/day, increased to 20 mg/day in women and 45 mg/day in men. If HbA1c remained <6.9%, other glucose-lowering drugs could be added. *Comparator:* Pts did not receive Pio. If HbA1c remained <6.9%, other anti-diabetic drugs (excluding Pio) could be added. *Outcome measure(s):* Primary composite outcome: Time to first occurrence of all-cause death, nonfatal cerebral infarction, and nonfatal MI. Secondary outcome: Incidence of cerebral infarction, transient ischemic attack, cerebral hemorrhage, MI, angina pectoris, CABG or PCI, or ACS excluding MI. Adverse events.	*Study completion:* Pre-specified interim analysis: An interim analysis performed in October 2011 showed a lower than expected occurrence of the primary outcome (3.6% after 2 yrs, w/ estimated 3-yr incidence of 5.4%). The data and safety monitoring committee recommended the study be discontinued. Pts included in analysis: 234/254 (92%); 247/268 (92%) Reasons for exclusion: Withdrawal of consent or lack of f/u data. *Primary composite outcome (all-cause death, nonfatal cerebral infarction, and nonfatal MI):* Overall occurrence: 9/234 (3.8%), 10/247 (4.0%) Kaplan-Meier analysis showed no differences in cumulative incidence btwn grps. HR 1.053 (95% CI 0.427-2.593; *p*=0.9114 Individual components of primary composite, # pts (% pts): All-cause death: 1 (0.4%), 2 (0.8%) Nonfatal cerebral infarction: 3 (1.3%), 4 (1.6%) Nonfatal MI: 5 (2.1%), 4 (1.6%) *Secondary composite outcome (cerebral infarction, transient ischemic attack, cerebral hemorrhage, MI, angina pectoris, CABG or PCI, or ACS excluding MI):* Overall occurrence: 3 (1.3%), 3 (1.2%)	macrovascular events between pts receiving Pio vs. other medications, though the study was underpowered and findings should be interpreted w/ caution. Adverse events occurred at a significantly higher rate among pts receiving Pio (14.1% vs. 5.3%). *Limitations:* Study was discontinued early due to a lower than expected occurrence of the primary endpoint, study lacked statistical power needed to detect changes in the primary endpoint; pts received a mix of other txs that were subject to change during study period; no blinding; details of randomisation and allocation NR. *Study quality:* Fair *Conflicts of interest:* Authors report relationships w/ commercial entities.

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	% antihypertensive agents: 56.0%, 65.6%; *p*=0.0321 % lipid-lowering agents: 41.0%, 46.2% *Inclusion criteria:* Pts w/ T2DM aged 55-85 yrs, HbA1c ≤10.5%, fulfilling ≥1 of following criteria: silent cerebral infarction on magnetic resonance imaging, carotid artery atherosclerosis, albuminuria. *Exclusion criteria:* HbA1c >10.5%; hx of cardiac failure, severe hepatic dysfunction, severe renal dysfunction, dementia, cerebral infarction, cerebral hemorrhage, transient ischemic attack, MI, or angina pectoris before study entry. Prior use of TZD in prior 8 wks.		Kaplan-Meier analysis: HR 0.995 (95% CI 0.445-2.222); *p*=0.9898. Angina pectoris: 3 (1.2%), 2 (0.8%) Transient ischemic attack: 0 (0%), 1 (0.4%) Neither grp had PCI or CABG, ACS (excluding MI). *Blood pressure:* Pts in Pio grp had significant reduction in diastolic blood pressure from BL (no change in systolic blood pressure). Pts in no Pio grp had no changes. Data NR. *Weight, BMI, abdominal circumference:* No changes. Data NR. *Adverse events:* Any event, # pts/# events (% pts): 33 (14.1%), 10 (5.3%); *p*=0.0001 39 total events occurred in 33 pts in Pio grp; 13 events occurred in 10 pts in the no Pio grps. Individual events included: Peripheral oedema: 12 (5.1%), 0 (0%) Cancer: 3 (1.3%), 5 (2.0%) Cataracts: 0 (0%), 1 (0.4%) Other events NR.	
Home et al. (2015)[57] Newcastle University, Newcastle upon Tyne, UK; Bangalore Diabetes Centre, Bangalore, Karnataka, India;	n=685 pts Pio + Met + Glim grp: 288 pts Albiglutide + Met + Glim grp: 281 pts	Pts randomised using an interactive voice response system at a 5:5:2 ratio to albiglutide, Pio, or PBO. Randomisation was stratified by HbA1c, hx of MI, and age.	Note that outcomes for pts receiving albiglutide are not summarised, as albiglutide is not a comparator of interest in this short report.	Results suggest that adverse events are common across tx grps, w/ tx-related adverse events occurring at a numerically higher rate for Pio vs. PBO as add-ons to Sulf +

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GlaxoSmithKline, King of Prussia, PA, US; GlaxoSmithKline, Stockley Park, UK HARMONY 5 trial 234 centers in US, Germany, Hong Kong, India, Peru, Philippines, Russia, Spain, or UK Randomised double-blind trial comparing Pio + Met + Glim, albiglutide + Met + Glim, and PBO in pts w/ ongoing Met. *F/u:* 52 wks *Time frame:* NR *Funding source:* GlaxoSmithKline	(Note that this comparator is outside the scope of this report, and outcomes are not summarised.) PBO + Met + Glim: 116 pts *Power analysis:* Based on changes in % HbA1c. Assuming expected change of 0.5%, albiglutide vs. PBO comparison has ≥90% power w/ 213 albiglutide pts and 85 PBO pts. For non-inferiority analysis of albiglutide w/ respect to Pio, 213 pts/grp estimated to give ≥93% power w/ a non-inferiority margin of 0.30%. Modified ITT population analysed. Included all pts receiving study drug w/ both BL and f/u data. *Pt characteristics (Pio grp, albiglutide grp, PBO grp):* % female: 46.6%, 50.2%, 39.1% Mean age: 55.7, 54.5, 55.7 Mean weight, kg: 91.0, 90.9, 89.9 Mean BMI, kg/m^2: 32.22%, 32.4%, 31.8% Mean duration of diabetes, yrs: 9.2, 8.5, 9.3 Mean % HbA1c: 8.29%, 8.19%, 8.26% % w/ prior MI: 5.1%, 3.7%, 3.5% *Inclusion criteria:* Pts aged ≥18 yrs w/ T2DM and inadequate	All pts received Met open label at the pre-study dose. All pts received 4 mg/day Glim, stabilised during 6-8 run-in stabilisation period before administration of study drugs. Dose could be reduced or discontinued in the event of severe or recurrent hypoglycaemia. All pts received an albiglutide or PBO injection, and Pio or PBO tablet. PBO and albiglutide injection devices were identical. Entire planned tx period is 156 wks, including 52 wks of tx (primary endpoint) and an additional 112 wks of f/u (not described here). *Intervention:* Pio (30 mg/day), uptitrated to a maximum dose of 45 mg/day to achieve desired glycaemic control (47.3% of pts). Final mean dose 37.1 mg/day. Pio provided in addition to Met, Glim, and injection PBO. *Comparator 1:* Subcutaneous albiglutide (30 mg/wk) uptitrated to a maximum dose of 50 mg/wk to achieve desired glycaemic control (59.5% of pts). Final mean dose 41.9 mg/wk. Albiglutide provided in addition to Met, Glim, and tablet PBO.	*Data reported as Pio + Sulf + Met grp, PBO + Sulf + Met grp.* *Study completion*: Modified ITT population, # pts (% pts): 273/288 (95%), 115/116 (99%) Reasons for exclusion: Did not receive allocated tx, lacking either BL or endpoint HbA1c measurements. Discontinued tx: 54/288 (18.8%), 35/116 (30.2%) Reasons: Adverse events, protocol violations, non-compliance, loss to f/u, withdrew consent (most common), investigator decision, sponsor decision or other. *Weight:* Pio grp gained weight (mean 4.4 kg), PBO grp lost weight (mean 0.4 kg); $p<0.001$ *CV events:* 43 (15.5%), 10 (8.7%) Authors note hypertension was most commonly reported event, further details NR. *Other adverse events, # pts (% pts):* Any event: 212 (76.5%), 80 (69.6%) On-therapy serious adverse events: 25 (9.0%), 7 (6.1%) On-therapy fatal adverse events: 3 (1.1%), 1 (0.9%) On-therapy related adverse events: 60 (21.7%), 16 (13.9%)	Met (21.7% vs. 13.9% of pts). Rates of CV events, serious adverse events, and hypoglycaemia rates were numerically higher for Pio vs. PBO, though the statistical and clinical significance of this is unclear. Weight gain was statistically significantly greater for Pio vs. PBO. *Limitations:* Study not powered to detect differences in adverse events, no statistical comparisons of adverse event rates btwn grps; pts permitted to change medication doses during study; higher proportion of pts receiving PBO discontinued tx than other grps (30% vs. 18%). *Study quality:* Fair *Conflicts of interest:* Authors report relationships w/ commercial entities.

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	glycaemic control w/ current regimen of Met (≥1500 mg/day) + Sulf (equivalent to ≥4 mg/day of Glim) for ≥3 mos; BMI 20.0-45.0 kg/m^2, % HbA1c 7.0%-0.0%, fasting C-peptide ≥0.26 nmol/L, creatinine clearance >60 mL/min. *Exclusion criteria:* Exclusion criteria included a hx of cancer (except non-melanoma skin cancers) not in remission for 3 yrs, treated diabetic gastroparesis, current symptomatic biliary disease, hx of pancreatitis, prior significant GI surgery, recent clinically significant CV disease; extreme abnormalities of liver functions, circulating lipase, amylase, or plasma triglycerides.	This is not a comparator of interest for this report, and outcomes related to this grp are not summarised. *Comparator 2:* PBO injection and PBO tablet only. Outcomes and comparisons are reported for this comparator. *Outcome measure(s):* Adverse events. Hypoglycaemic events were considered those as classified by the American Diabetic Association. Note that intermediate outcomes are also reported (e.g. HbA1c) but are not summarised here. All major CV outcomes were blindly adjudicated by 2 independent committees.	On-therapy adverse events leading to withdrawal: 19 (6.9%), 6 (5.2%) Hypoglycaemia: 87 (31.4%), 13 (11.3%) Severe hypoglycaemia: 3 (1.1%), 0 (0%) GI events: 72 (26.0%), 20 (17.4%) Nausea: 12 (4.3%), 4 (3.5%) Diarrhoea: 15 (5.4%), 3 (2.6%) Vomiting: 5 (1.8%), 1 (0.9%) Pancreatitis: 0 (0%), 0 (0%) Thyroid cancer: 0 (0%), 1 (0.9%) *Death:* 3 (1.1%), 1 (0.9%) Pio grp deaths 1 infection, 2 cancer. PBO grp deaths from infection. Not considered tx related.	
Vacarro et al. (2017)[63] TOSCA.IT study group under the mandate of the Italian Diabetes Society 57 centers in Italy Multicentre open-label, blinded endpoint RCT comparing Pio w/ Sulf as an add-on to Met in pts w/ T2DM. *F/u:* 57.3 mos *Time frame:* September 18, 2008 – January 14, 2014	n=3028 pts randomised to: Pio + Met grp: 1535 pts Sulf + Met grp: 1493 pts *Power and futility analyses:* Initial: Based on 3.5% rate of primary endpoint, study was designed to have an 80% power to detect a 20% reduction in the primary endpoint (based on results of PROactive trial). Assuming 15% attrition, 5172 pts required for randomisation.	Pts randomised 1:1 using permuted blocks randomisation, achieved centrally via interactive telephone system, and stratified by geographic location and prior CV events. Drugs were provided open label; primary outcome was adjudicated by an independent committee blinded to grp assignments. Met doses were unchanged during study period. Add-on drugs were titrated as	*Data reported as Pio grp; Met grp* *Study completion:* Did not complete trial: 148/1535 pts (9.6%); 112/1493 (7.5%) Reasons included withdrawal of consent, loss to f/u, poor compliance, personal reasons, pt or clinician decision, adverse events, or unknown. Premature permanent withdrawal of drugs: 32/1535 (28%), 238/1493 (16%); p<0.0001 *Primary CV composite, # pts (% pts):* 105/1535 (6.8%), 108/1493 (7.2%) HR 0.96 (95% CI 0.74-1.26); p=0.79	Results suggest that the incidence of CV events, mortality, and other adverse events were similar for Pio + Met and Sulf + Met w/ >4 yrs f/u in pts w/ T2DM. All outcomes were largely similar btwn tx grps, though hypoglycaemic events were less frequent in the Pio + Met grp. *Limitations:* Pts and treating physicians not blinded; high rate of drug discontinuation that was statistically significantly higher for Pio +

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Funding source: Italian Medicines Agency	Modified: Due to low recruitment and low attrition rates, protocol was amended in 2012. 3371 pts required to detect 20% reduction in primary endpoint w/ 80% power, assuming a 3.5% occurrence of the endpoint and 5% loss to f/u. Futility analysis: Study discontinued May 23, 2017, after a futility analysis showed a low probability of observing a significant positive result. *ITT analysis:* Included all randomly assigned pts w/ BL data and without protocol violations. Pts completing or discontinuing trial without an outcome were censored from day of last visit. *Pt characteristics (Pio grp, Sulf grp):* % female: 41%; 42% BMI, mean ±SD: 30.2±4.4; 30.4±4.5 % smokers: 18%, 17% Disease duration, mean yrs ±SD: 8.4±5.6, 8.5±5.8 % HbA1c, mean ±SD: 7.67±0.5%, 7.69±0.51% % w/ prior CV disease: 12%, 10% % w/ prior acute MI: 7%, 6% % w/ prior stroke: 2%, 1% % w/ prior ACS: 3%, 3% % w/ prior carotid artery revascularisation: 1%, 1%	appropriate by study investigators. *Intervention:* Pio (15-45 mg) as an add-on to Met. *Comparator:* Glib (2% of pts; 5-15 mg), Glic (50% of pts; 30-120 mg), or Glim (48% of pts; 2-6 mg) as an add-on to Met. *Assessments:* 1, 3, and 6 mos post-randomisation; every 6 mos thereafter. *Outcome measure(s):* Primary: Composite first occurrence of all-cause death, nonfatal MI, nonfatal stroke, or urgent coronary revascularisation. Key secondary: Composite of ischemic CV disease (first occurrence of sudden death; fatal and nonfatal MI; fatal and nonfatal stroke; leg amputation above the ankle; revascularisation of coronary, leg, or carotid arteries. Expanded composite outcome: First occurrence of all-cause death, nonfatal MI, nonfatal stroke, heart failure, revascularisation of coronary, leg, or carotid arteries. Other secondary outcomes: Individual components of	*Key secondary composite, # pts (% pts):* 74/1535 (5%), 83/1493 (6%) HR 0.88 (95% CI 0.65-1.21); *p*=0.44 Note that in a post hoc on-tx analysis (rather than ITT analysis), the differences btwn grps were significant (3% vs. 5%; *p*=0.03 favoring Pio). *Expanded composite outcome*: 163/1535 (11%), 157/1493 (11%) HR 1.03 (95% CI 0.82-1.28); *p*=0.81 *All-cause death:* 55/1535 (4%), 50/1493 (3%) HR 1.10 (95% CI 0.75-1.61); *p*=0.63 *Nonfatal MI:* 21/1535 (1%), 24/1493 (2%) HR 0.87 (95% CI 0.48-1.55); *p*=0.63 *Nonfatal stroke:* 16/1535 (1%), 20/1493 (1%) HR 0.79 (95% CI 0.41-1.53); *p*=0.49 *Urgent coronary revascularisation:* 31/1535 (2%), 34/1493 (2%) HR 0.91 (95% CI 0.56-1.48); *p*=0.70 *Heart failure:* 19/1535 (1%), 12/1493 (1%) HR 1.57 (95% CI 0.76-3.24); *p*=0.22 *New or worsening nephropathy:* 282/1535 (23%), 270/1493 (23%) HR 1.03 (95% CI, 0·89-1·19); *p*=0.37 *Serious adverse events:* 208/1535 (14%), 195/1493 (13%); *p*=0.73 *Malignant neoplasms:* Any: 78/1535 (5%), 71/1493 (5%); *p*=0.74	Met vs. Sulf + Met; study discontinued early due to a low occurrence of the primary endpoint, decision followed a futility analysis. *Study quality:* Fair *Conflicts of interest:* Authors report multiple relationships w/ commercial entities.

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	% w/ prior coronary artery revascularisation: 7%, 7% % w/ antihypertensive drugs: 70%, 70% % w/ lipid lowering drugs: l58%, 57% % w/ antiplatelet drugs: 42%, 38% *Inclusion criteria:* Men and women aged 50-75 yrs, T2DM for ≥2 yrs, on stable tx w/ full dose Met (2-3 g/day), HbA1c 7%-9%. *Exclusion criteria:* Acute CV events in prior 6 mos; serum creatinine >132 µmol/L.	composite, adverse events, serious adverse events (defined as death, life-threatening episodes, episode requiring hospital admission or prolongation of existing hospital stay, persistent or substantial disability). Hypoglycaemic events were defined as documented blood glucose <3.3 mmol/L.	Lung: 9 (0.5%), 3 (0.2%); *p*=0.15 Colorectal: 12 (0.8%), 9 (0.6%); *p*=0.66 Breast: 3 (0.2%), 4 (0.3%); *p*=0.72 Bladder: 8 (0.5%), 8 (0.5%); *p*=1.00 Pancreatic: 2 (0.1%), 6 (0.4%); *p*=0.17 Other: 44 (2.9%), 41 (2.7%); *p*=0.91 *Pathological fractures:* 6/1535 <1%), 4/1493 (<1%); *p*=0.75 *Oedema:* 7/1535 (<1%), 3/1493 (<1%); *p*=0.34 *Respiratory, thoracic, and mediastinal disorders:* 16/1535 (1%), 5/1493 (<1%); *p*=0.03 *Prescription of rescue insulin therapy:* 164/1535 (11%) vs. 233/1493 (16%); *p*<0.0001 *Weight changes:* Reported graphically, differences NS btwn grps (*p*=0.09). Authors note BMI changed slightly during first 2 yrs of tx, then leveled off by end of study in both grps. *Hypoglycaemic events:* Severe: 1/1535 (<1%; 2 total events), 24/1493 (2%; 33 total events); *p*<0.0001 Moderate: 147/1535 (10%; 515 total events, 484/1493 (32%; 1868 total events); *p*<0·0001 *Blood pressure:* Blood pressure was similar btwn grps throughout study period. Data NR.	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
Asakura et al. (2018)[52] 106 hospitals and clinics in Japan PPAR study Randomised open-label comparison of Pio vs. no Pio in pts w/ well-controlled T2DM and prior MI. *F/u:* Minimum of 2 yrs, median 1813 days (5 yrs) *Time frame:* May 2005 – June 2014 *Funding source:* Grants of Japan Heart Foundation for PPAR study	n=630 pts randomised to: Pio grp: 318 pts Other tx grp: 312 pts *Power analysis:* Based on estimated occurrence of primary composite endpoint over 2 yrs, sample size originally calculated to be 3000 pts (1500/grp). Following an interim review, a total of 330 pts per grp and 81 total events gave 80% power to detect a tx effect. Target # of pts for inclusion was 720, targeted # of CV events for primary endpoint was 81 (whichever came first). Recruitment was stopped at 630 after 7 yrs when 81 events were obtained. ITT population excluded pts who declined to participate, duplicate entries, or pts w/ site quality data. *Pt characteristics (Pio grp, no Pio grp):* % female: 13.7%, 14.8% Mean age, yrs: 66, 66 Mean BMI, kg/m^2: 24.8, 24.8 Mean % HbA1c: 5.9%, 5.8% % w/ hypertension: 79.4%, 78.3% % w/ dyslipidemia: 81.4%, 81.2% % smokers: 57.4%, 59.9% % w/ prior stroke: 5.9%, 3.3%	Pts randomly assigned 1:1 using a web-based system and computer-generated random numbers, w/ permuted blocked randomisation. Additional drugs were administered as needed throughout the trial to achieve glycemic control. *Intervention:* Pts received Pio starting at 15 mg/day, increased to 30 mg if well tolerated or reduced as needed for adverse events. It was unclear if the Pio grp underwent lifestyle changes. *Comparator:* Other drugs, including Sulf, in addition to lifestyle changes (weight reduction, diet, regular exercise), only. *Outcome measure(s):* Primary outcome: Time to first CV composite endpoint of CV death, hospitalisation for nonfatal MI, nonfatal unstable angina, tx w/ PCI or CABG, and cerebral infarction. Secondary outcomes: All-cause death, individual components of primary composite. The definition of hypoglycaemia was not clear. Intermediate outcomes were also reported but are not summarised.	*Data reported as Pio grp; no Pio grp:* *Study completion, # pts (% pts):* ITT population: 313/318 (98.4%), 311/312 (99.7%) Lost to f/u: 16/312 (5.1%); 24/318 (7.5%) Reasons include withdrawal of consent, death, protocol violation, loss to f/u, or other. *Compliance rate:* >80% for Pio *Blood pressure:* Blood pressure was not significantly different btwn grps or changed from BL. *Primary outcome (CV death or nonfatal CV event):* Overall occurrence, # pts (% pts): 44 (14.1%), 44 (14.2%) HR 1.005 (0.662-1.526); *p*=0.98 Kaplan-Meier curve: Data presented graphically. NS btwn Pio vs. no Pio. HR 0.98 (95% CI 0.662-1.526); *p*=0.98 Individual components of composite, # pts (% pts): CV death: 0 (0%), 1 (0.2%) MI: 7 (2.2%), 1 (0.3%) Unstable angina: 6 (1.9%), 3 (1.0%) Coronary revascularisation: 30 (9.6%), 36 (11.5%) Cerebral infarction: 1 (0.3%), 3 (1.0%) *All-cause death:* 5 (1.6%), 7 (2.3%) HR 0.722 (95% CI 0.229-2.274);p*P*=0.58	Results suggest that there were no differences in CV events for pts w/ well-controlled T2DM and prior MI receiving Pio vs. no Pio in addition to other medications and lifestyle modifications. *Limitations:* Pts and investigators not blinded; pts permitted to alter drugs during trial, modified ITT analysis. *Study quality:* Good *Conflicts of interest:* Authors report relationships w/ commercial entities.

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
	Concomitant medication at the time of entry: % ACE inhibitor or ARB: 76.4%, 76.24% % statin: 84.0%, 80.7% % calcium channel blocker: 30.4%, 33.1% % beta-blocker: 55.9%, 59.5% % diuretics: 16.3%, 15.4% % anti-platelet drugs: 92.7%, 92.9% % anti-coagulant drugs: 7.0%, 10.0% % vasodilators: 17.3%, 17.7% % anti-ulcer drugs: 61.7%, 68.8% % nicorandil: 16.0%, 21.5% Note that concomitant drug use changed over the course of the study. *Inclusion criteria:* Pts w/ clinically overt MI and T2DM. Aged 20-79 yrs, FPG <126 mg/dL or 75 g oral glucose tolerance test value >200 mg/dL, HbA1c levels <6.5%. *Exclusion criteria:* Acute MI in prior wk; T1D; scheduled PCI or hx of CABG, severe liver or kidney injury, hx of allergy or drug hypersensitivity, arteriosclerosis obliterans w/ Fontaine stage III or worse, inability to comply w/ study.	Event adjudication committee and data and safety monitoring board were blinded.	*All CV death*: 0 (0%), 1 (0.2%) HR 0.334 (95% CI 0.004-30.794); *p*=0.64 *All MI:* 1 (2.2%), 1 (0.3%) HR 5.049 (95% CI 0.786-32.415); *p*=0.09 *Unstable angina:* 6 (1.9%), 3 (1.0%) HR 1.876 (95% CI 0.477-7.380); *p*=0.37 *Coronary revascularisation:* 43 (13.7%), 40 (12.9%) HR 1.083 (95% CI 0.704-1.666); *p*=0.72 *Cerebral infarction:* 1 (0.3%), 3 (1.0%) HR 0.431 (95% CI 0.051-3.662); *p*=0.44 *ACS (MI + unstable angina):* 13 (4.2%), 4 (1.3%) HR 3.058 (95% CI 1.020-9.165); *p*=0.05 *Subgroup analysis:* NS interaction for sex, age, BMI, hypertension, dyslipidemia, arteriosclerosis, or use of hypertensive medications. *Adverse events:* Note that data are reported as the # of events/total # of pts Any event: 127/313 (40.6%), 123/311 (39.5%) GI disorders: 8/313 (2.5%), 7/311 (2.2%) Hepatic disorders: 2/313 (0.6%), 2/311 (0.6%) Respiratory disorders: 2/313 (0.6%), 4/311 (1.3%)	

Authors/Study Design	Study Population	Treatment	Results	Conclusions/Limitations/ Quality/Comments
			Any benign or malignant disorder: 5/313 (1.6%), 11/311 (3.5%) Bladder cancer: 0/313 (0%), 1/311 (0.3%) Metabolic, endocrine, nutritional disorders: 15/313 (4.8%), 20/311 (6.4%) Hypoglycaemia: 0/313 (0%), 1/311 (0.3%) Nervous system disorders: 2/313 (0.6%), 9/311 (2.9%) Ophthalmological disorders: 2/313 (0.6%), 3/311 (1.0%) Infectious disorders: 6/313 (1.9%), 4/311 (1.3%) Renal and urinary disorders: 2/313 (0.6%), 4/311 (1.3%) Cardiac disorders: 51/313 (16.3%), 41/311 (13.2%) Heart failure: 7/313 (2.2%), 2/311 (0.6%) Vascular disorders: 5/313 (1.6%), 5/311 (1.6%) Oedema: 2/313 (0.6%), 10/311 (3.2%)	

Appendix Table 10. Key Question 3. Cochrane Collaboration Tool for Assessing Risk of Bias in RCTs

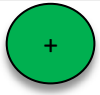
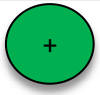
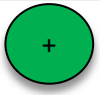
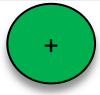
Key: ITT, intention to treat; NR, not reported

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
Across 13 studies	6 low risk + 7 unclear risk ? 0 high risk -	8 low risk + 5 unclear risk ? 0 high risk -	9 low risk + 0 unclear risk ? 4 high risk -	7 low risk + 6 unclear risk ? 0 high risk -	7 low risk + 4 unclear risk ? 2 high risk -	12 low risk + 1 unclear risk ? 0 high risk -	0 low risk + 13 unclear risk ? 0 high risk -	
Hanefeld et al. (2004)[56]	? (Details of randomisation NR)	? (Details of allocation concealment NR)	+ (Double blind, though details NR)	? (Not stated whether outcome assessors were blind)	+ (ITT analysis)	+ (All planned outcomes reported)	? (Conflict of interest)	Fair
Schernthaner et al. (2004)[61]	+ (Block randomisation and a computer generated list)	+ (Generated list administered with a telephone randomisation and resupply service)	+ (Double blind, though details NR)	? (Not stated whether outcome assessors were blind)	+ (ITT analysis)	+ (All planned outcomes reported)	? (Funding NR, no conflict of interest statement)	Good

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
Charbonnel et al. (2005)[54]	? (Details of randomisation NR)	? (Details of allocation concealment unclear)	+ (Double blind, though details NR)	? (Not stated whether outcome assessors were blind)	+ (ITT analysis)	+ (All planned outcomes reported)	? (Conflict of interest)	Fair
Dormandy et al. (2005)[55]	+ (Randomised permuted blocks.)	+ (Randomised with a central interactive voice response system)	+ (Double blind, though details NR)	+ (Independent endpoint adjudication committee; all investigators and study personnel were blind)	+ (ITT analysis)	+ (All planned outcomes reported)	? (Conflict of interest)	Good
Matthews et al. (2005)[59]	? (Details of randomisation NR)	? (Details of allocation concealment unclear)	+ (Double blind, though details NR)	? (Not stated whether outcome assessors were blind)	? (Modified ITT analysis, >15% attrition)	+ (All planned outcomes reported)	? (Conflict of interest)	Fair
Nissen et al. (2008)[60]	+	+	+	+	-	+	?	Fair

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
	(Block randomisation with a block size of 4)	(Interactive voice response system)	(Double blind, though details NR)	(Independent blinded endpoint adjudication committee, all pts and study personnel were blind to treatment assignment)	(>30% attrition, though sensitivity analysis performed)	(All planned outcomes reported)	(Conflict of interest)	
Bolli et al. (2009)[53]	+ (Randomisation numbers generated to ensure unbiased assignment using automated central telephone system)	+ (Automated central telephone system, randomisation numbers were concealed from patients and investigators)	+ (Investigators and patients were blinded)	+ (Independent endpoint adjudication committee)	? (ITT analysis, but study completion NR)	+ (All planned outcomes reported)	? (Conflict of interest)	Good
Kaku et al. (2009)[58]	? (Details of randomisation NR)	? (Details of allocation concealment unclear)	- (Open label)	+ (Independent blinded endpoint adjudication committee)	+ (ITT analysis)	? (Details of individual macrovascular events not reported)	? (Conflict of interest)	Fair
Tolman et al. (2009)[62]	?	+	+	?	-	+	?	Poor

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
	(Details of randomisation NR)	(Treatments were assigned via interactive voice response service vendor)	(Double blind, though details NR)	(Not stated whether outcome assessors were blind)	(>60% non-completion)	(Outcomes reported)	(Conflict of interest)	
Yoshii et al. (2014)[64]	? (Details on randomisation NR)	? (Details of allocation concealment unclear)	- (Open label)	? (Not stated whether outcome assessors were blind)	+ (ITT analysis)	+ (All planned outcomes reported)	? (Conflict of interest)	Fair
Home et al. (2015)[57]	? (Details of randomisation NR)	+ (Patients were randomised with interactive voice response system)	+ (Double blind)	+ (All major outcomes were blindly adjudicated by 2 independent committees)	? (ITT analysis performed, but discontinuation was high and imbalanced between groups)	+ (All planned outcomes reported)	? (Conflict of interest)	Fair
Vacarro et al. (2017)[63]	+ (Permuted blocks)	+ (Interactive telephone system)	- (Open label)	+ (Outcomes adjudicated by independent	? (ITT analysis performed, but discontinuation was high and	+ (All planned outcomes reported)	? (Conflict of interest)	Fair

Citation	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Quality Rating
	Random Sequence Generation	Allocation Concealment						
				blinded committee)	imbalanced between groups)			
Asakura et al. (2018)[52]	 (Permuted blocks)	 (Web-based system)	 (Open label)	 (Outcomes adjudicated by independent blinded committee)	 (ITT analysis)	 (All planned outcomes reported)	 (Conflict of interest)	Good

Appendix Table 11. Key Question 3. SOE Table

Key: CI, confidence interval; GI, gastrointestinal; grp(s), groups; HR, hazard ratio; meds, medications; Met, metformin; NS, no statistically significant difference; PBO, placebo; Pio, pioglitazone; RCT(s), randomised controlled trial(s); SOE, strength of evidence; Sulf, sulfonylurea

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Composite Outcomes	6 RCTs reported composite endpoints comprising all-cause mortality and various macrovascular events [52 55 58 60 63 64]. Limited evidence from 1 study favored Pio over PBO, and the remaining studies reported NS differences between grps receiving Pio vs. no Pio (3 studies) or Pio vs. Sulf as an add-on to Met or other meds (2 studies). *Components of composites varied across studies.* 1 favored Pio over PBO 5 NS between grps *Findings by comparison:* Pio + other meds vs. other meds ± PBO (4 studies): [52 55 58 64] 1 study favored Pio over PBO for a secondary composite (HR, 0.84; 95% CI 0.72-0.98; *p*=0.027) 3 NS between grps *Pio + other meds vs. Sulf + other meds (1 study): [60]* NS between grps *Pio + Met vs. Sulf + Met (1 study):* [63] NS between grps	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
All-cause mortality	11 RCTs reported outcomes related to mortality [52 55-64]). There was no evidence suggesting that all-cause mortality differed between grps receiving Pio vs. no Pio (5 studies), Sulf as an add-on to Met or other meds (5 studies), or Met only (1 study). *Across 11 studies:* Range across Pio grps: 0.003%-6.8% Range across comparator grps: 0%-7.1% 3 NS between grps 8 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (4 studies): [52 55 58 64] 0.4%-6.8% vs. 0.3%-7.1% Pio + other meds vs. Sulf + other meds (2 studies): [60 62] 0.1% and 1.1% vs. 0.6% and 0.7% Pio + Met vs. Sulf + Met (2 studies): [59 63] 0% and 4% vs. 0.6% and 3% Pio + Sulf vs. Met + Sulf (1 study): [56] 0.003% vs. 0.006% Pio + Sulf + Met vs. PBO + Sulf + Met (1 study): [57] 1.1% vs. 0.9% Pio vs. Met (1 study): [61] 0.5% vs. 0.3%	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Myocardial Infarction	6 RCTs reported the incidence of myocardial infarction [52 55 60 62-64]. There was no evidence suggesting that the incidence of myocardial infarction differed between Pio grps vs. grps receiving no Pio (3 studies) or Sulf as an add-on to Met or other medications (3 studies). *Across 6 studies:* Range across Pio grps: 0.7%-4.6% Range across control grps: 0.3%-5.5%. 4 NS between grps 2 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (3 studies): [52 55 64] 2.1%-4.6% vs. 0.3%-5.5% Pio + other meds vs. Sulf + other meds (2 studies): [60 62] 0.7% and 0.5% vs. 1.1% and 1.5% Pio + Met vs. Sulf + Met (1 study): [63] 1% vs. 2%	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Stroke	7 RCTs reported the incidence of stroke [52 53 55 60 62-64]. There was no evidence that the occurrence of stroke differs between Pio vs. no Pio (3 studies), Sulf as an add-on to Met or other drugs (3 studies), or vildagliptin + Met (1 study). *Across 7 studies:* Range across Pio grps: : 0%-3.3% Range across control grps: 0.33%-4.1% 4 NS between grps 3 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (3 studies) [52 55 64] 0.3%-3.3% vs. 1.0%-4.1% Pio + other meds vs. Sulf + other meds (2 studies) [60 62] 0% and 1% vs. 0.36% and 1% Pio + Met vs. Sulf + Met (1 study) [63] 1% vs. 1% Pio + Met vs. vildagliptin + Met (1 study) [53] 0.7% vs. 0.33%	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Coronary Revascularisation	5 RCTs reported the incidence of coronary revascularisation [52 55 60 63 64]. There was no evidence suggesting that this outcome differs by treatment type. Rates of coronary revascularisation were similar for Pio vs. no Pio (3 studies) or Sulf as an add-on medication (2 studies). *Across 5 studies:* Range across Pio grps: 0%-13.7% Range across control grps: 0%-12.9% 4 NS between grps 1 no statistical comparisons made *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (3 studies) [52 55:Yoshii, 2014 #361] 0%-13.7% vs. 0%-12.9% Pio + other meds vs. Sulf + other meds (1 study) [60] 10.7% vs. 11% Pio + Met vs. Sulf + Met (1 study) [63] 2% vs. 2%	High	0	0	0	-1	0	0	0	0	Moderate

Heart Failure	6 RCTs [52 55 56 59 60 63] and 1 post hoc study [67] report the incidence of heart failure. Limited evidence from 1 study suggests that heart failure occurred more often for patients receiving Pio vs. PBO [55]. The remaining studies reported no differences between Pio vs. Sulf [60 63], or did not report statistical comparisons. **1 post hoc study**[67] *Across 6 studie:s* Range across Pio grps: 0.6%-11% Range across control grps: 0.6%-8% 1 favored PBO over Pio 2 NS between grps 3 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (2 studies) [52 55] 2.2% and 11% vs. 0.6% and 8% 1 study favored PBO + other meds over Pio + other meds (p<0.0001) Pio + other meds vs. Sulf + other meds (1 study) [60] 1.5% vs. 1.8% Pio + Met vs. Sulf + Met (2 studies) [59 63] 1% and 1.6% vs. 1% and 0.6% Pio + Sulf vs. Met + Sulf (1 study) [56] 0.6% vs. 0.9% Pio + insulin vs. PBO + insulin (1 post hoc study) [67] 13.5% vs. 10.5%, P<0.05	High	0	0	0	-1	0	0	0	0	Moderate
Any adverse event	10 RCTs reported the overall occurrence of any adverse event [52-54 56-59 61 62 64]. Limited evidence from 1 study suggested higher adverse event rates for Pio vs. no Pio [64]. The remaining 9 studies did not report statistical comparisons, and adverse event rates were largely similar between grps across studies. *Across 10 studies:* Range across Pio grps: 14.1%-97.6% Range across control grps: 5.3%-96.9% 1 favored no Pio over Pio (p=0.0001)	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
	9 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (3 studies) [52 58 64] 14.1% - 97.6% vs.5.3% - 96.9% 1 study favored PBO + other meds over Pio + other meds (14.1% vs. 5.3%; *p*<0.0001) Pio + other meds vs. Sulf + other meds (1 study) [62] 81.7% vs. 83.7% Pio + Met vs. Sulf + Met (1 study) [59] 55.5% vs. 58.1% Pio + Met vs. vildagliptin + Met (1 study) [53] 68.2% vs. 67.8% Pio + Sulf + Met vs. PBO + Sulf + Met (1 study) [57] 76.5% vs. 69.6% Pio + Sulf vs. Met + Sulf (1 study) [56] 59.9% vs. 61.9% Pio vs. Sulf (1 study) [65] 75% vs. 71% Pio vs. Met (1 study) [61] 53% vs. 58%										

Any serious adverse event	9 RCTs reported the overall occurrence of any serious adverse event [53 55-59 61-63]. There was a trend toward lower adverse event rates for Pio vs. Sulf and/or Met in 3 studies [56 59 61] and vildagliptin + Met in 1 study [53], though statistical comparisons were not reported. The remaining studies have similar rates between grps. *Across 9 studies:* Range across Pio grps: 4.1%-46% Range across control grps: 6.1%-48% 2 NS between grps 7 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (2 studies) [55 58] 20.1% and 46% vs. 21.8% and 48% Pio + other meds vs. Sulf + other meds (1 study) [62] 15.1% vs. 16.6% Pio + Met vs. Sulf + Met (2 studies) [59 63] 4.4% and 14% vs. 6.4% and 13% Pio + Met vs. vildagliptin + Met (1 study) [53] 4.1% vs. 8.9% Pio + Sulf + Met vs. PBO + Sulf + Met (1 study) [57] 9.0% vs. 6.1% Pio + Sulf vs. Met + Sulf (1 study) [56] 6.6% vs. 9.7% Pio vs. Met (1 study) [61] 4.9% vs. 7.4%	High	0	0	0	-1	0	0	0	0	Moderate
Withdrawal due to adverse events	7 RCTs reported the rates of study discontinuation due to adverse events [55-57 59-62]. There is no evidence suggesting that rates of discontinuation differed between Pio vs. Sulf and/or Met (5 studies) or no Pio (2 studies). *Across 7 studies:* Range across Pio grps: 6.9%-11.1%	High	0	0	0	-1	0	0	0		Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
	Range across control grps: 4.4%-12.5% 1 NS between grps 6 no statistical comparisons *Findings by comparison:* Data reported as range across pio grps vs. range across comparator grps Pio + other meds vs. other meds + PBO (1 study) [55] 9.0% vs. 7.7% Pio + other meds vs. Sulf + other meds (2 studies) [60 62] 11.1% and 13.9% vs. 12.5% and 11.7% Pio + Met vs. Sulf + Met (1 study) [59] 6.9% vs. 6.7% Pio + Sulf + Met vs. PBO + Sulf + Met (1 study) [57] 6.9% vs. 5.2% Pio + Sulf vs. Met + Sulf (1 study) [56] 8.8% vs. 10% Pio vs. Met (1 study) [61] 7% vs. 7%										

Any GI disorder	7 RCTs reported the occurrence of GI illness [52 53 56 57 59 61 62]. None of the studies reported statistical comparisons between treatment grps, though 4 active-controlled studies reported numerically lower rates of GI events for Pio grps vs. comparator grps [53 56 59 61]. *Across 5 studies:* Range across Pio grps: 2.5%-26% Range across control grps: 2.2%-33.6% 7 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds (1 study) [52] 2.5% vs. 2.2% Pio + other meds vs. Sulf + other meds (1 study) [62] 8.8% vs. 7.6% (diarrhoea) 7.3% vs. 8.0% (vomiting) Pio + Met vs. Sulf + Met (1 study) [59] 3.8% vs. 5.1% Pio + Met vs. vildagliptin + Met (1 study) [53] 14.5% vs. 20% Pio + Sulf + Met vs. PBO + Sulf + Met (1 study) [57] 26.0% vs. 17.4% Pio + Sulf vs. Met + Sulf (1 study) [56] 12.2%, 23.4% Pio vs. Met (1 study) [61] 3.2% vs. 11.1% (diarrhoea) 2.3% vs. 4.2% (nausea)	High	0	0	0	-1	0	0	0	0	Moderate
Liver toxicity	3 RCTs reported rates of liver toxicity [52 61 62]. There was no evidence for variations by treatment grp (Pio vs. no Pio, Met, or Sulf). *Across 3 studies:* Range across Pio grps: 0.3%-0.6% Range across control grps: 0.2%-1.0%	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
	3 no statistical comparisons *Findings by comparison:* Data reported as range across pio grps vs. range across comparator grps Pio + other meds vs. other meds (studies) [52] 0.6% vs. 0.6% Pio + other meds vs. sulf + other meds (1 study) [62] 0.5% vs. 1.0% Pio vs. Met (1 study) [61] 0.3% vs. 0.2%										

Respiratory infection or inflammation	6 RCTs reported rates of respiratory infections or inflammation [52 53 55 61-63]; 1 study favored PBO over Pio for the occurrence of pneumonia [55] and 1 favored Sulf over Pio [63]. The remaining studies did not report statistical comparisons between Pio vs. no Pio, Met, vildagliptin + Met, or Sulf. *Across 6 studies:* Range across Pio grps: 0.6%-15.2% Range across control grps: <1%-15% 2 favored comparator grps over Pio grps 4 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (2 studies) [52 55] 0.6% vs. 1.3% (upper respiratory infection) 2% vs. 1%; *p*=0.047 favoring PBO over Pio (pneumonia) Pio + other meds vs. Sulf + other meds (1 study) [62] 7.8% vs. 7.7% (bronchitis) 15.2% vs. 15% (upper respiratory infection) 9.3% vs. 8.6% (sinusitis) 6.4% vs. 10.3% (cough) Pio + Met vs. Sulf + Met (1 study) [63] 1% vs. <1%; *p*=0.03 favoring Sulf + Met (upper respiratory infection) Pio + Met vs. vildagliptin + Met (1 study) [53] 7.1% vs. 5.4% (nasopharyngitis) Pio vs. Met (1 study) [61] 1.8% vs. 2.3% (bronchitis 2.4% vs. 3.7% (influenza) 4.2% vs. 3.2% (nasopharyngitis) 2.5% vs. 1.5% (pharyngitis)	High	0	0	0	-1	0	0	0	0	Moderate
Pain (arthralgia, back pain, or limb pain)	3 RCTs reported the occurrence of pain [53 61 62]. There is no evidence that pain outcomes differed by treatment type (Pio vs. Sulf, Met, or vildagliptin + Met). *Across 3 studies* Range across Pio grps: 1.5%-11.3% Range across control grps: 2.0%-10.9%	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
	3 no statistical comparisons *Findings by comparison:* Data reported as range across pio grps vs. range across comparator grps Pio + other meds vs. Sulf + other meds (1 study) [62] 11.3% vs. 10.9% (arthralgia) 7.5% vs.7.5% (back pain) 8.5% vs.7.6% (limb pain) Pio + Met vs. vildagliptin + Met (1 study) [53] 5.4% vs. 5.1% (back pain) Pio vs. Met (1 study) [61] 1.5% vs. 2.0% (arthralgia) 2.3% vs. 2.8% (back pain)										

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Headache	3 RCTs reported the incidence of headache [53 61 62]. There is no evidence for differences by treatment type, though only 1 study was available for each comparison (Pio vs. Sulf, Met, or vildagliptin + Met). *Across 3 studies:* Range across Pio grps: 4.4%-6.7% Range across control grps: 2.3%-7.6% 3 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. Sulf + other meds (1 study) [62] 6.7% vs.7.6% Pio + Met vs. vildagliptin + Met (1 study) [53] 6.1% vs. 6.4% Pio vs. Met (1 study) [61] 4.4% vs. 2.3%	High	0	0	0	-1	0	0	0	0	Moderate

Hypoglycaemia	11 RCTs [52-60 62 63] and 3 post hoc studies [67 74 75] reported outcomes related to hypoglycaemia. Pio was favored over Sulf in 2 studies [60 63] and PBO was favored over Pio in 1 study [55]. The remaining studies did not report statistical comparisons, though 4 studies reported numerically less frequent hypoglycaemia for Pio vs. Sulf [54 56 59 62]. *Across 11 studies:* Range across Pio grps: 0%-28% Range across control grps: 0.3%-37.0% 2 favored Pio grp over comparator grp 1 favored comparator grps over Pio grps 3 post hoc studies favored PBO over Pio 8 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (3 studies) [52 55 58] 0%-28% vs. 0.3%-37.0% 1 study favored PBO + other meds over Pio + other meds (28% vs. 20%, $p<0.0001$) Pio + other meds vs. Sulf + other meds (2 studies) [60 62] 3.8% and 15.2% vs. 11.4% and 37% 1 study favored Pio over Sulf (15.2% vs. 37%, $p<0.001$) Pio + Met vs. Sulf + Met (2 studies) [59 63] 1.3% and 10% vs. 11.2% and 32% 1 study favored Pio over Sulf (10% vs. 32%, $p<0.0001$) Pio + Met vs. vildagliptin + Met (1 study) [53] 0.3% vs. 0.4% Pio + Sulf + Met vs. PBO + Sulf + Met (1 study) [57] 31.4% vs. 11.3% Pio + Sulf vs. Met + Sulf (1 study) [56] 11.3% vs. 15.6% Pio vs. Sulf (1 study) [65] 3.5% vs. 10.1%	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
	Pio + Sulf + Met vs. PBO + Sulf + Met (1 post hoc study) [75]27% vs. 20%; *p*<0.001 favoring PBO Pio + Sulf vs. PBO + Sulf (1 post hoc study) [74] 21% vs. 13%; *p*<0.001 favoring PBO Pio + insulin vs. PBO + insulin (1 post hoc study) [67] 42.1% vs. 29.0%; *p*<0.001 favoring PBO										

Oedema	12 RCTs [52-56 58-64] and 3 post hoc studies [67 74 75] reported outcomes related to oedema; 1 study favored Sulf over Pio [60], and there was a trend in 7 additional studies favoring no treatment [55 58 64], Sulf and/or Met [54 56 61 62] over Pio. *Across 12 studies:* Range across Pio grps: 0.6%-21.6% Range across control grps: 0%-13% 1 study favored Sulf over Pio 3 post hoc studies favored PBO over Pio 1 NS between grps 10 no statistical comparisons (though there was a trend toward comparator favored over Pio) *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (4 studies) [52 55 58 64] 0.6%-21.6% vs. 0%-13% Pio + other meds vs. Sulf + other meds (2 studies) [60 62] 8.0% and 17.8% vs. 3.4% and 11.0% 1 study favored sulf over Pio (17.8% vs. 11.0%/*p*=0.02) Pio + Met vs. Sulf + Met (2 studies) [59 63] <1% and 7.6% vs. <1% and 3.5% Pio + Met vs. vildagliptin + Met (1 study) [53] 11.1% vs. 10.8% Pio + Sulf vs. Met + Sulf (1 study) [56] 10.7% vs. 2.8% Pio vs. Met (1 study) [61] 4.5% vs. 1.7% Pio vs. Sulf (1 study) [65] 8.7% vs. 4.5% Pio + Sulf + Met vs. PBO + Sulf + Met (1 post hoc study)[75] 29% vs. 17%; *p*<0.001 favoring PBO Pio + Sulf vs. PBO + Sulf (1 post hoc study)[74]	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
	22% vs. 11%; *p*<0.001 favoring PBO Pio + Met vs. PBO + Met (1 post hoc study)[74] 27% vs. 15%; *p*<0.001 favoring PBO Pio + insulin vs. PBO + insulin (1 post hoc study) [67] 30.8% vs. 18.2%; *p*<0.001 favoring PBO										

Weight changes	12 RCTs [53 55-65] and **3** post hoc studies [67 74 75] reported outcomes related to changes in weight. Evidence suggests Pio is associated with greater weight gain than other treatments. Grps receiving Pio had statistically significantly greater weight gain than grps receiving no Pio (3 studies) [55 57 58] or vildagliptin (1 study) [53]; 6 additional studies reported numerically greater weight gain for Pio vs. Sulf and/or Met, though statistical analyses were not reported [56 59-62 65]. *Across 12 studies:* Range across Pio grps: 2.6 gain – 5.2 kg gain Range across control grps: 1.7 kg loss – 1.9 kg gain 4 favored comparator over Pio 1 NS between grps 3 post hoc studies favored PBO over Pio 7 no statistical comparisons (though there was a trend toward comparator favored over Pio) *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO (3 studies) [55 58 64] 1 study: 3.6 kg gain vs. 0.4 kg loss (p<0.0001 favoring PBO) 1 study: Data NR, other meds favored over Pio (p<0.01) 1 study: Data NR, reported no weight changes Pio + other meds vs. Sulf + other meds (2 studies) [60 62] 1 study: 5.2 kg gain vs. 0.9 kg gain 1 study: Gain in both grps, 2 kg higher for Pio Pio + Met vs. Sulf + Met (2 studies) [59 63] 1 study: 2.5 kg gain vs. 1.2 kg gain 1 study: Data NR, NS differences between grps Pio + Met vs. vildagliptin + Met [53] 2.6 kg gain vs. 0.2 kg gain; p<0.0001 favoring vildagliptin Pio + Sulf + Met vs. PBO + Sulf + Met (1 study) [57] 4.4 kg gain vs. 0.4 kg loss; p<0001 Pio + Sulf vs. Met + Sulf (1 study) [56] 3.7 kg gain vs. 1.7 kg loss Pio vs. Met (1 study) [61]	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
	1.9 kg gain, 2.5 kg loss Pio vs. Sulf (1 study) [65] 2.8 kg gain, 1.9 kg gain Pio + Sulf + Met vs. PBO + Sulf + Met (1 post hoc study)[75] Higher weight gain for Pio vs. PBO, *p*<0.001 Pio + Sulf vs. PBO + Sulf (1 post hoc study)[74] Higher weight gain for Pio vs. PBO, *p*<0.001 Pio + Met vs. PBO + Met (1 post hoc study)[74] Higher weight gain for Pio vs. PBO, *p*<0.001 Pio + insulin vs. PBO + insulin (1 post hoc study)[67] 4.2 kg vs. 00.1 kg; *p*<0.0001 favoring PBO										

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Overall Malignancy rates	5 RCTs reported malignancy rates [52 55 57 63 64]. Rates were similar between grps across studies. *Across 5 studies:* Range across Pio grps: 0%-5% Range across control grps: 0%-5% 1 NS between grps 4 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO ([52 55 64] 1.3%-4% vs. 2.0%-4% Pio + Met vs. Sulf + Met [63] 5% vs. 5%; *p*=0.74 Pio + Sulf + Met vs. PBO + Sulf + Met [57] 0% vs. 0.9%	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Blood Pressure	8 RCTs reported outcomes related to changes in blood pressure [52 55 56 59-61 63 64]. Pio was favored over no Pio in 2 studies [55 64] and over Sulf in 1 study [60]; 5 additional studies reported that there were no differences between Pio vs. no Pio, Sulf, and/or Met. *Across 8 studies:* (quantitative data NR consistently) 3 favored Pio over comparators 5 reported no differences btwn grps *Findings by comparison:* Data were not consistently reported in the same manner across studies. Qualitative results are described. *Pio + other meds vs. other meds ± PBO [52 55 64]* 2 studies favored Pio 1 reported no changes or differences *Pio + other meds vs. Sulf + other meds (1 study) [60]* Pio favored over Sulf (p<0.03) *Pio + Met vs. Sulf + Met (2 studies)* [59 63] No changes or differences between grps, data NR *Pio + Sulf vs. Met + Sulf (1 study)* [56] No changes from baseline in either grp, data NR *Pio vs. Met (1 study)* [61] No changes from BL in either grp, data NR	High	0	0	0	-1	0	0	0	0	Moderate

Outcome	Findings	Starting SOE (Quality)	Decrease SOE					Increase SOE			SOE for Outcome
			Overall Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose Response	Associated Despite Confounders	
Fracture	4 fair-quality RCTs reported the occurrence of bone fractures [58 60 62 63]; 1 study reported higher fracture rates for patients receiving Pio vs. Sulf [60]. The remaining 3 studies reported no difference between Pio vs. Sulf or Pio vs. no Pio. *Across 4 studies:* Range across Pio grps: <1%-6.1% Range across control grps: 0%-6.1% 1 favored sulf over Pio 1 NS between Pio + Met vs. Sulf + Met 2 no statistical comparisons *Findings by comparison:* Data reported as range across Pio grps vs. range across comparator grps Pio + other meds vs. other meds ± PBO [58 60 62] 2.3%-6.1% vs. 0%-6.1% 1 favored sulf over Pio (3% vs. 0%; 95% CI NR; *p*=0.004) Pio + Met vs. Sulf + Met [63] <1% vs. <1%; *p*=0.75	High	-1	-1	0	-1	0	0	0	0	Low
Nephropathy	3 RCTs reported nephropathy rates [52 58 63]; 1 study reported that there was NS difference between Pio vs. Sulf as add-ons to Met [63]. Statistical comparisons were not provided in 2 studies [52 58]. *Across 3 studies:* Range across Pio grps: 0.6%-23% Range across control grps: 1.3%-23% 1 NS btwn Pio + Met vs. Sulf + Met 2 no statistical comparisons Pio + Met vs. Sulf + Met (1 study) [63] 23% in both grps, HR, 1.03; 95% CI 0.89-1.19; *p*=0.37	High	0	0	0	-1	0	0	0	0	Moderate

9.5 APPENDIX V. SYSTEMATIC REVIEWS

Appendix Table 12. Systematic Reviews Evaluating the Effectiveness and Safety of Glinides

Key: AHRQ, Agency for Healthcare Research and Quality; f/u, follow-up; grp(s), group(s); Met, metformin; Nat, nateglinide; OR, odds ratio; pt(s), patient(s); RCT(s), randomized controlled trial(s); Repa, repaglinide; SMD, standardised mean difference; Sulf, sulfonylurea; T2DM, type 2 diabetes mellitus; tx, treatment

Citation	Purpose of Review	Publication Dates Searched Included Literature	Results	Authors' Conclusions
Bennett, 2011 [3] Note: This is an archived AHRQ review that was updated in 2016 [5 79]. The 2016 update did not evaluate meglitinides, citing that they represent a small fraction of diabetes drugs currently in use.	Evaluate the benefits and harms of Met, second-generation Sulf, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists as monotherapy and in combination, for the tx of adults w/ type 2 diabetes.	**Search dates:** Inception to April 2010. **Repaglinide includes:** Marbury, 1999[41] (include) Wolffenbuttel, 1999[43] (include) Raskin, 2009 [195] (exclude, not comparator of interest) Monami, 2008[196] (exclude sample size) Lund, 2007 [197] (exclude sample size) Moses, 1999 [198] Derosa, 2003[38] (include) Raskin, 2004 [199] (exclude, not combination of interest) Jovanovic, 2004 [200](exclude, f/u) Jibran, 2006 [40] (include) Madsbad, 2001 [201] (exclude, wrong comparator) Landgraf, 1999 [202] (exclude, f/u) Wolffenbuttel, 1993 [203] (exclude, sample size and f/u) Dimic, 2009 [204] (exclude, sample size and f/u) **Nat includes:** Horton, 2000 [46] (include) Schwarz, 2008 [188] (include) Gerich, 2005 [45] (include)	**HbA1c** *Met vs. meglitinides (not stratified by drug type):* 3 RCTs reported similar effects on HbA1c for Met vs. meglitinides (Repa or Nat). Pooled quantitative analyses were not performed. *Met vs. Met + Nat:* 3 RCTs favored Met+Nat over Met (range of between-grp differences: -0.5% to -1.08%). Pooled quantitative analyses were not performed. *Sulf vs. Repa:* Pooled mean difference of 0.1% (95% CI -0.2% to 0.3%), slightly favoring Repa, based on 7 RCTs. *Met + Sulf vs. Met + Nat:* 2 RCTs had conflicting results (possibly reflecting dosing differences); 1 RCT favored Met+Nat and 1 RCT found no difference between grps. Pooled quantitative analyses were not performed. **Hypoglycaemia (not stratified by drug type)** *Meglitinides vs. Sulf:* OR 0.8; 95% CI 0.6-1.1 *Meglitinides vs. Met:* OR 3.0; 95% CI 1.8-5.2 **Weight** *Repa vs. Sulf:* 0.01 kg mean difference; 95% CI −1.0 kg to 1.0 kg **Other outcomes** Evidence for other outcomes (e.g. mortality, cardiovascular morbidity) was insufficient to draw conclusions, and meta-analyses were not conducted. Authors note that there is a gap in the literature for evidence regarding the comparative effectiveness of	Authors conclude that the evidence supports the use of Met as a first-line agent for diabetes tx. Evidence for meglitinides was largely insufficient to draw conclusions.

Citation	Purpose of Review	Publication Dates Searched Included Literature	Results	Authors' Conclusions
		Nakamura, 2006 [157] (exclude, data insufficient to evaluate outcome of interest) Marre, 2002 [47] (include) Derosa, 2009 [44] (include) Horton, 2004 [187] (exclude, post hoc of included study without novel data) Vakkilainen 2002 [159] (exclude, no outcomes of interest)	monotherapy and combination therapy comparisons of meglitinides.	
Jia, 2019 [2]	Compare the efficacy of hypoglycaemic drugs for T2DM by network meta-analysis of RCTs.	**Search dates:** Inception to January 8, 2019 **Includes:** Wolffenbuttel, 1999[43] (include) Jovanovic, 2000[205] (exclude, f/u) Madsbad, 2001[201] (exclude, comparator) Moses, 2001[206] (exclude, f/u) Del Prato, 2003[207] Derosa, 2003[37] (include) Derosa, 2003[38] (include) Mari, 2005[156] (exclude, f/u) Gonzalez-Clemente, 2008[51] (exclude, f/u) Bao, 2009[208] (exclude, sample size) Bellomo Damato, 2011[209] (exclude, f/u) Fang, 2014[210] (exclude, sample size) Ma, 2014[211] (exclude, f/u)	**HbA1c** *Nat vs. placebo:* Mean difference -0.51% (95% CI -0.90 to -0.12%); *p*<0.0001 favoring Nat, based on 3 RCTs *Repa vs. placebo:* Mean difference -1.61% (95% CI -2.57% to -0.65%); *p*<0.0001 favoring Repa based on 2 RCTs *Repa vs. gliclazide (Sulf):* Mean difference 0.01% (95% CI -0.13 to 0.16); *p*=0.8457 based on 1 RCT *Repa vs. glimepiride (Sulf):* Mean difference -0.10% (95% CI 0.09 to -0.11); *p*<0.0001 favoring Repa based on 1 RCT *Repa vs. glyburide (Sulf):* Mean difference 0.00 (95% CI-0.02 to 0.02); *p*=1 *Repa vs. Met:* Mean difference 0.37%, 95% CI 0.11- 0.62; *p*=0.005 favoring Repa based on 3 RCTs	Authors conclude that Repa and Met are the most efficacious oral drugs for first-line monotherapy for pts w/ T2DM.
Xie, 2019 [14]	Compare the short-term efficacy and safety of Repa + Met vs. glimepiride + Met.	**Search dates:** Inception to August 2018 **Includes:** (all excluded from our analysis for f/u , 8 also excluded for sample size) Yu, 2010	Note that SMDs lower than 0 and ORs <1 indicate that Repa + Met is favored over glimepiride + Met **HbA1c** SMD -0.06; 95% CI -0.27 to 0.15; *p*=0.55 **Adverse events** OR 0.55; 95% CI 0.26-1.16; *p*=0.12	Authors conclude that Repa in combination w/ Met may have benefits over Sulf (glimepiride) in combination w/ Met for tx of type 2 diabetes.

Citation	Purpose of Review	Publication Dates Searched Included Literature	Results	Authors' Conclusions
		Ren and Ge, 2006 Li, 2012 Kong, 2016 Li, 2016 Li, 2009 Wang, 2011 Tian, 2012 Cheng, 2006 Dimic, 2009 Zhao, 2012	**Hypoglycaemia** OR 0.64; 95% CI 0.22-1.88; *p*=0.42	

Appendix Table 13. Systematic Reviews Evaluating the Effectiveness and Safety of Pioglitazone

Key: AHRQ, Agency for Healthcare Research and Quality; CI, confidence interval; DPP-4, dipeptidyl peptidase-4 (DPP-4); f/u, follow-up; GLP-1, glucagon like peptide 1; grp(s), group(s); HbA1c, glycated haemoglobin; HR, hazard ratio; Met, metformin; OR, odds ratio; Pio, pioglitazone**;** pt(s), patient(s); RCT(s), randomised controlled trial(s); RR, risk ratio; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione

Citation	Purpose of Review	Publication Dates Searched Included Literature	Results	Authors' Conclusions
Bolen, 2016 [5] AHRQ comparative effectiveness review	Comparative effectiveness review of medications for adults w/ T2DM; key questions designed to evaluate intermediate outcomes, all-cause mortality, macrovascular morbidity, microvascular morbidity, and adverse events.	**Search dates:** Inception to April 2015. Update of 2011 review. 219 studies published in 249 articles were included. Studies of pioglitazone included RCTs and observational trials. Agarwal, 2005 [212] (exclude, wrong comparator) Alba, 2013[213] (exclude, sample size and f/u) Bergenstal, 2010 [214] (exclude, sample size and f/u) Comaschi, 2007 [215] (exclude, sample size and f/u) DeFronzo, 2012 [216] (exclude, f/u) Einhorn, 2000 [217] (exclude, sample size and f/u) Erem, 2014 #347 [218] (exclude sample size)	**HbA1c (not stratified by drug type)** The majority of comparisons did not stratify by Pio vs. rosiglitazone. Overall findings are summarised. *TZD vs. Sulf*: -0.04%; 95% CI -0.13% to 0.06% (based of 15 RCTs of Pio or rosiglitazone) *TZD vs. DPP-4 inhibitors:* 3 RCTs reported no clear between-grp differences in HbA1c (range -0.48% to 0.23%). No pooled analyses were performed. The strength of the evidence was insufficient. *Pio vs. GLP-1 receptor agonists:* 2 RCTs reported mixed results for Pio vs. exenatide; 1 study reported mean between-grp differences (-0.1%; 98.3% CI -0.15% to 0.35%), and 1 study favored exenatide (0.3%; 95% CI 0.0%-0.6%). Pooled	The authors conclude that the evidence supports the use of Met as first-line therapy based on outcomes related to HbA1c, weight, and cardiovascular mortality, and safety.

Citation	Purpose of Review	Publication Dates Searched Included Literature	Results	Authors' Conclusions
		Esposito, 2011 [219] (exclude, sample size and f/u) Genovese, 2013 [192] (exclude, sample size and f/u) Hanefeld, 2004 [56] (include) Hsiao, 2009 [220] (exclude, observational) Jain, 2006 [221] (exclude, sample size) Kaku, 2009 [58] (include) Kawai, 2008 [222] (exclude, sample size and f/u) Lawrence, 2004 [223] (exclude, sample size and f/u) Lee, 2013 [162] (exclude, sample size) Maffioli, 2013 [224] (exclude, sample size) Pantalone, 2009 [225] (exclude, observational) Pavo, 2003 [226] (exclude, sample size and f/u) Perez, 2009 [227] (exclude, sample size and f/u) Pfutzner, 2011 [228] (exclude, sample size and f/u) Rosenstock, 2010 [229] (exclude, f/u) Russell-Jones, 2012 [230] (exclude, f/u) Schernthaner, 2004 [61] (include) Shihara, 2011 [231] (exclude, sample size and f/u) Tan, 2004 [232] (exclude, f/u) Umpierrez, 2006 [233] (exclude, sample size and f/u) van der Meer, 2009 [168] (exclude, sample size and f/u) Xu, 2015 [234] (exclude, sample size and f/u) Yamanouchi, 2005 [235] (exclude, sample size)	analyses were not performed and the strength of the evidence was insufficient. *Met vs. Met + TZD:* 14 RCTs of Pio or rosiglitazone favored Met + TZD over Met alone. Results were not stratified by drug type. Pooled between-grp difference for all studies had marked heterogeneity. *Met + TZD vs. Met + Sulf:* 8 RCTs of Pio or rosiglitazone, pooled between-grp difference of -0.06%; 95% CI -0.19% to 0.06%; *p*=0.121). Results were not stratified by drug type. *Met+TZD vs. Met + GLP-1 receptor agonist:* 1 RCT favored Met + exenatide over Met + Pio (mean difference 0.3%; 95% CI 0.05%-0.55%). **All-cause mortality** *Pio vs. Met:* OR 0.91 (95% CI 0.22-3.72); Low-strength evidence from 4 RCTs suggests neither treatment is favored. *Pio vs. sitagliptin:* Low-strength evidence that neither is favored, based on 2 RCTs. *Other comparisons:* Evidence from other comparators was insufficient to grade. **Macrovascular events** *Pio vs. Met:* Moderate strength of evidence suggested that neither treatment is favored, 3 RCTs and 2 observational studies. *Pio vs. Sulf:* Low-strength evidence favored Pio over Sulf for short-term cardiovascular disease, 1 RCT and 1 cohort study. *Pio + Met vs. exenatide + Met:* Low-strength evidence favored exenatide + Met over Pio + Met, 1 RCT. *Pio vs. DPP-4:* Low-strength evidence suggests neither treatment is favored for heart failure,	

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			Other comparisons: Evidence from other comparators was insufficient to assess. **Microvascular morbidity** *Pio + Met vs. DPP-4 inhibitor + Met:* Low-strength evidence suggests neither is favored for outcomes related to nephropathy, 1 RCT. *Pio + Met vs. GLP-1 receptor agonist + Met:* Low-strength evidence suggests that GLP-1 receptor agonist + Met is favored over Pio + Met for nephropathy, 1 RCT. **Weight gain** *Pio vs. DPP-4 inhibitors:* Moderate-strength evidence favoring DPP-4 inhibitors, 2 RCTs. *Pioglitazone vs. GLP-1 receptor agonists:* Moderate-strength evidence favored GLP-1 receptor agonists, 2 RCTs. No other evidence stratified by rosiglitazone vs. Pio, though glitazones had less favorable weight outcomes than Met and Sulf. **Hypoglycaemia** *Pio vs. DPP-4 inhibitors:* Low-strength evidence suggested that neither is favored, 3 RCTs. *Pio vs. GLP-1 receptor agonists:* Low-strength evidence favored Pio over GLP-1 receptor agonists for mild, moderate, or total hypoglycaemia. Low-strength evidence suggested that neither was favored for severe hypoglycaemia, 2 RCTs. No other evidence stratified by rosiglitazone vs. Pio. In summary, glitazones were favored over Sulf for hypoglycaemic episodes, and had mixed findings compared w/ Met (alone and in combination). **Gastrointestinal events** Pio vs. sitagliptin: Low-strength evidence suggests that neither is favored, 2 RCTs.	

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			Pio vs. exenatide: Low-strength evidence favors Pio, 2 RCTs. Pio + Met vs. GLP-1 + Met: Moderate-strength evidence favored Pio, 1 RCT. **Other events** Low-strength evidence suggests Pio was favored over a GLP-1 agonist for pancreatitis. Low-strength evidence favored a DPP-4 inhibitor + Met combination over Pio + Met for short-term risk of pancreatitis. Low-strength evidence favored a GLP-1 receptor agonist + Met combination over Pio + Met for short-term risk of pancreatitis. Low-strength evidence suggested neither Pio nor exenatide are favored for systemic hypersensitivity reactions. Data for other outcomes and comparators were either insufficient, or results were pooled from studies of Pio and studies of rosiglitazone.	
de Jong, 2017 [86]	Assess the effects of pioglitazone treatment on the secondary prevention of cardiovascular disease.	**Search dates:** Inception to 25 September 2017. The analysis included studies reporting cardiovascular outcomes in patients w/ T2DM or other diagnoses receiving pioglitazone. Included both active and placebo-controlled trials. **Included studies:** Hong, 2015 [236] (exclude, sample size) Kaneda, 2009 [237] (wrong population) Kernan, 2016 [100] (wrong population) Lee, 2013 [162] (exclude, sample size) Nishio, 2006 [238] (exclude sample size) Nissen, 2008 [60] (included) Suryadevara, 2012 [239] (exclude sample size) Takagi, 2009 [240] (exclude sample size) Tanaka, 2015 [241] (exclude sample size)	Note that results were not analysed separately for studies of pts w/ type 2 diabetes vs. pre-diabetes or impaired glucose tolerance. Outcomes are reported for Pio vs. usual care, placebo, or active comparator: **HbA1c** Not reported. **Major adverse cardiac events** RR 0.74; 95% CI 0.60-0.92 **Myocardial infarction** RR 0.77; 95% CI 0.64-0.93 **Stroke** RR 0.81; 95% CI 0.68-0.96 **All-cause mortality**	Authors conclude that Pio is associated w/ a decreased risk of major adverse cardiac events, stroke, and myocardial infarction in pts w/ T2DM, pre-diabetes, or impaired glucose tolerance and vascular disease. Pio was associated w/ an increased risk of heart failure, and there was no association for risk for all-cause mortality.

Citation	Purpose of Review	Publication Dates Searched Included Literature	Results	Authors' Conclusions
		Dormandy, 2005 [55] (include)	RR 0.94; 95% CI 0.81-1.08 **Heart failure** RR 1.33; 95% CI 1.14-1.54	
Li, 2017 [19]	Perform a meta-analysis w/ a dose-response analysis to assess the risk of bladder cancer associated w/ Pio use.	**Search dates:** Inception to August 2015 **Includes (observational studies):** Lewis, 2015 Levin, 2014 Lee, 2014 Jin, 2014 Wei, 2013 Origasa, 2013 Hsiao, 2013 Fujimoto, 2013 Vallarino, 2012 Neumann, 2012 Mamtani, 2012 Axoulay, 2012 Dormandy, 2005	**Bladder cancer risk (ever use vs. never use of Pio)** HR 1.16; 95% CI 1.06-1.25	Authors conclude that Pio is associated w/ a mild increase in the risk of bladder cancer among pts w/ T2DM.
Liao, 2017 [85]	To evaluate the effect of pioglitazone in people w/ insulin resistance, pre-diabetes, and type 2 diabetes.	**Search dates:** 1966 – 17 May 2016 The analysis included studies reporting cardiovascular outcomes in pts w/ T2DM or other diagnoses receiving Pio. Included both active and placebo-controlled trials. **Includes:** Dormandy, 2005 [55] (include) DeFonzo, 2011[101] (wrong population) Mazzone, 2006 [242] (exclude sample size) Kernan, 2016 [100] (wrong population) Tanaka, 2015 [241] (wrong population) Lee, 2013 [162] (exclude sample size) Nissen, 2008[60] (include) Yoshi, 2014[64] (include) Kaku, 2009 [58]	Outcomes represent an analysis of studies of pts w/ T2DM, excluding studies of pts w/ pre-diabetes or impaired glucose tolerance. **HbA1c** Not reported. **Major adverse cardiac events** RR 0.83; 95% CI 0.72-0.97; *p*=0.02 **Myocardial infarction** RR 0.80; 95% CI 0.62- 1.03; *p*=0.08 **Stroke** RR 0.78; 95% CI 0.60-1.02; *p*=0.07	Authors report that Pio was associated w/ reduced risk of MACE in pts w/ type 2 diabetes, and a trend toward decreased risk of myocardial infarction or stroke. The risk of heart failure, bone fracture, oedema, and weight gain were increased w/ Pio, though a separate analysis of these outcomes in pts w/ T2DM was not reported.
Cho, 2018 [18]	Evaluate the efficacy and safety of Pio and sodium-glucose cotransporter 2 inhibitors as additions to	**Search Dates:** Inception to December 2016 **Includes (pioglitazone):** Rosenstock, 2002 [243] (exclude, f/u)	Authors performed a network meta-analysis using indirect comparisons between Pio and sodium glucose cotransporter 2 inhibitors. Outcomes of interest are summarised below.	Authors conclude that Pio and sodium glucose cotransporter 2 inhibitors are both feasible add-on oral medications to insulin

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	insulin therapy for the management of T2DM.	Mattoo, 2005 [244] (exclude, sample size and f/u) Berhanu, 2007 [245] (exclude, sample size and f/u) Charbonnel, 2010 [67] (included) Galle, 2012 [246] (exclude, sample size and f/u) Kharazmkia, 2014 [247] (exclude, sample size and f/u)	**HbA1c** Sodium-glucose cotransporter 2 inhibitors and pio had similar HbA1c reductions (weighted mean difference -0.01%; 95% CI -0.25% to 0.22%; *p*=0.896) **Weight changes** Sodium glucose cotransporter 2 inhibitors were associated w/ greater weight reduction than Pio (-4.54 kg; 95% CI -5.67 to -3.41 kg; *p*<0.001). **Hypoglycaemia** No differences between grps, but authors report a trend toward higher risk for Pio (relative risk 1.15; 95% CI, 0.97-1.35; *p*=0.102)	therapy in pts w/ inadequately controlled T2DM.
Pavlova, 2018 [87]	Evaluate the association between Pio and bone fractures.	**Search Dates:** 2000 – 15 February 2016 **Includes:** Bray 2013 [248] (exclude, sample size) Jain, 2006 [221] (exclude, sample size) Nissen, 2008 [60] (include) DeFonzo 2009 [249] (exclude, wrong population) Seufert , 2008 [250] (exclude, data from 2 RCTs that are included in the body of evidence [56 59], novel/nonduplicate data of interest not reported) Dormandy, 2009 [251] (exclude, review)	**Risk of bone fracture for Pio** OR 1.18; 95% CI 0.82-1.71; *p*=0.38 No association between risk of fracture and Pio therapy duration or pt gender.	Authors conclude that Pio treatment is not associated w/ an increased risk of bone fracture.
Tang, 2018 [21]	Evaluate the risk of bladder cancer associated w/ Pio and identify modifiers that affect the results.	**Search Dates:** Inception to 25 August 2016 **Includes:** *RCTs:* Dormandy, 2005 (include) Kernan, 2016 (exclude, wrong population) *Observational studies:* Azoulay, 2012 Chang, 2012	**Risk of bladder cancer from RCTs** OR 1.84; 95% CI 0.99-3.42; *p*=0.511 **Risk of bladder cancer from observational studies** OR 1.13; 95% CI 1.03-1.25; *p*=0.095	Authors conclude that evidence suggests that Pio may increase the risk of bladder cancer in a manner that may be dose and time dependent. They suggest that pts w/ long-term or high-dose Pio use should undergo regular monitoring.

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		Mamtani, 2012 Song, 2012 Tseng, 2012 Hsiao, 2013 Origasa, 2013 Vallarino, 2013 Wei, 2013 Jin, 2014 Kuo, 2014 Lee, 2014 Levin, 2014 Lewis, 2015 Erdmann, 2016 Han, 2016 Korhonen, 2016 Tuccori, 2016		
Mehtala, 2019 [20]	Evaluate the risk of bladder cancer in Pio-treated pts w/ T2DM.	**Search dates:** Inception to 30 September 2016 **Includes (observational studies):** Azoulay, 2012 Chang, 2012 Song, 2012 Hsaio, 2013 Kuo, 2014 Han, 2016 Jin, 2014 Lewis, 2015 Mamtami, 2012 Neumann, 2012 Tseng, 2012 Wei, 2013 Vallarino, 2013 Lee, 2014 Levin, 2015 Korhonen, 2016 MacKenzie, 2016 Tuccori, 2016	**Risk of bladder cancer for Pio use vs. no Pio use** OR 1.16; 95% CI 1.04-1.28	Authors conclude that there is a small but statistically significant association between the use of Pio and bladder cancer (vs. never use of Pio). The authors note that causality is not established and that it is not possible to rule out alternative explanations for these findings.
Hidayat, 2019 [88]	A meta-analysis of observational studies to	**Search dates:** Inception to February 2019 **Includes (Pio):**	**Risk of fracture for Pio** OR 1.38; 95% CI 1.23-1.54	Authors conclude that Pio is associated w/ an increased risk

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	evaluate the association between the use of Met, insulin, Sulf, or TZD and the risk of fracture.	Dormuth, 2009 Solomon, 2009 Colhoun, 2012 Aubert, 2010 Bilik 2010		of fracture, and suggest that there is compelling evidence to discourage its use among pts w/ high fracture risk.
Alam, 2019 [4]	Perform a systematic review and meta-analysis of the comparative safety and efficacy of Pio monotherapy vs. monotherapy w/ alternative oral antidiabetic drugs in pts w/ type 2 diabetes.	**Search dates:** Inception to May 2018 **Includes**: Mori, 2017 [252] (exclude, sample size and f/u) Esteghamati, 2015 [253] (exclude, sample size and f/u) Esteghamati, 2014a [254] (exclude, sample size and f/u) Esteghamati, 2014b [255] (exclude, sample size and f/u) Alba, 2013 [213] (exclude, sample size and f/u) Perez Monteverde, 2011 [256] (exclude, sample size and f/u) Hu, 2010 [257] (exclude, sample size and f/u) Rosenstock, 2010 [229] (exclude, f/u) Erem, 2008 [218] (exclude, sample size and f/u) Cooper, 2008 [258] (exclude, sample size and f/u) Rosenstock, 2007 [259] (exclude, f/u) Perriello, 2006 [260] (exclude, sample size and f/u) Ramachandran, 2004 [261] (exclude, sample size and f/u) Tan, 2004 [232] (exclude, sample size) Jonavic, 2004 [200] (exclude, sample size and f/u) Goke 2002 [262] (exclude, sample size and f/u)	Outcomes of interest are summarised below, w/ findings reported as Pio relative to comparators. **HbA1c** Pio had similar HbA1c reductions as comparators (mean difference 0.05%; 95% CI −0.21 to 0.11; *p*=0.56) **Blood pressure** Pio had a 1.05 mm Hg greater improvement vs. comparators (95% CI -4.29-2.19; *p*=0.52) **Hypoglycaemia** Pio favored over comparators (RR 0.51; 95% CI 0.33-0.80; *p*=0.003) **Oedema** Pio associated w/ increased risk (RR 2.21; 95% CI 1.48-3.31; *p*=0.0001) **Weight** Pio was associated w/ greater weight gain (mean difference 2.06 kg; 95% CI 1.11-3.01; *p*<0.0001) **Cardiovascular events** RR 1.47 95% CI 0.42-5.17; *p*=0.55 **Vascular disorders** RR 0.33; 95% CI 0.01 -8.01; *p*=0.49 **Upper respiratory tract infections** RR 1.09; 95% CI 0.67-1.76; *p*=0.33 **Nervous system disorders**	The authors conclude that Pio is favorable for treatment of T2DM based on findings related to hyperglycaemia, lipid metabolism, and blood pressure. The authors suggest that Pio should be prescribed based on individual pt needs.

Citation	Purpose of Review	Publication Dates Searched Included Literature	Results	Authors' Conclusions
			RR 0.89; 95% CI 0.56-1.40; *p*=0.61 **Diarrhoea** RR 0.56; 95% CI 0.12-2.60; *p*=0.46 **Musculoskeletal and connective tissue disorders** RR 1.49; 95% CI 0.19-11.69; *p*=0.71 **Abnormal liver function parameters** RR 0.96; 95% CI 0.29-3.26 **Vomiting** RR 2.89; 95% CI 0.12-69.4; *p*=0.48 **Nausea** RR 0.32; 95% CI 0.01-7.71; *p*=0.48 **Breast cancer** RR 0.32; 95% CI 0.01-7.71; *p*=0.48 **Colon cancer** RR 3.02; 95% CI 0.12-73.55; *p*=0.50 **Non-cardiac chest pain** RR 3.02; 95% CI 0.12-73.55; *p*=0.50	