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Pioglitazone for Type 2 Diabetes Mellitus and Pre-Diabetes: A Review of Safety

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Abbreviations

ACAR	acarbose
ADA	American Diabetes Association
AE	adverse event
ALE	aleglitazar
ALO	alogliptin
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews 2
BMD	bone mineral density
BMI	body mass index
CAD	coronary artery disease
CI	confidence interval
CRD	University of York Centre for Reviews and Dissemination
CV	cardiovascular
CVD	cardiovascular disease
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
EXE	exenatide
FDA	United States Food and Drug Administration
GLIC	gliclazide
GLIM	glimepiride
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycated hemoglobin A_{1c}
HF	heart failure
HOMA-IR	homeostatic model assessment of insulin resistant
HR	hazard ratio
ITT	intention-to-treat
LIN	linagliptin
LIR	liraglutide
MA	meta-analysis
MEDLINE	Medical Literature Analysis and Retrieval System Online
MEG	meglitinide
MeSH	medical subject headings
MET	metformin
MI	myocardial infarction
NMA	network meta-analysis
NNH	number needed to harm
NRS	non-randomized study
OAD	oral antidiabetic drugs
PIO	pioglitazone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
REP	repaglinide
ROS	rosiglitazone
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SIT	sitagliptin
SMD	standardised mean difference
SR	systematic review
SU	sulphonylurea
TIA	transient ischemic attack
TZD	thiazolidinediones
VIL	vildagliptin
WHO	World Health Organization

Context and Policy Issues

Diabetes mellitus is a group of metabolic disorders that result from deficiencies in insulin secretion, sensitivity, or both.[1] Type 2 diabetes mellitus ranges from predominant insulin resistance with relative insulin secretory deficiency, to insulin resistance with a predominant insulin secretory deficiency as the disease progresses.[1-3] There are several risk factors for type 2 diabetes, including a history of pre-diabetes, usually defined as having impaired fasting glucose (6.1 to 6.9 mmol/L), impaired glucose tolerance (noted by an oral glucose tolerance test results of 7.8 to 11 mmol/L), or an elevated glycated hemoglobin A_{1c} level (6% to 6.4%).[2]

In 2017, it was estimated there were 123,085 Canadians (95% confidence interval [CI], 109,119 to 137,118) newly diagnosed with type 2 diabetes,[4] raising the national burden of disease to an estimated 2,553,158 (95% CI, 2,295,152 to 2,857,046) prevalent cases.[5] Furthermore, it was estimated that 2.12% of total Canadian deaths (95% CI, 2.0% to 2.25%) in 2017 were attributable to type 2 diabetes.[6] This translates to an estimated 83,603 years of life lost (95% CI, 76,847 to 90,036) for 2017.[7]

The goals of therapy in type 2 diabetes are aimed at achieving stringent glycemic control within the normal range as early as possible.[2] In addition to diet and lifestyle measures, several classes of antidiabetic agents are approved in Canada: insulins, sulphonylureas (SUs), α-glucosidase inhibitors, biguanides, glucagon-like peptide-1 (GLP-1) receptor agonists, meglitinides (MEGs), thiazolidinediones (TZDs), sodium-glucose cotransporter 2 inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and a combination of these may often be necessary for optimal treatment.[1-3,8] This report will focus on a particular drug of the TZD class, pioglitazone (PIO), which is often considered as a therapeutic option when glycemic targets are not achieved with first-line drugs, such as metformin.[2] PIO works by binding to the peroxisome proliferator-activated receptor-γ, which is primarily located on adipose and vascular cells,[1] increasing their insulin sensitivity.[9]

In addition to its hypoglycemic effect, PIO has been shown to have favourable effects on reducing major adverse cardiovascular events (e.g., all-cause mortality, non-fatal myocardial infarction [MI], stroke).[10,11] Nevertheless, and as is the case with any drug therapy, the benefits associated with PIO ought to be weighed against possible risks to the patient. Because of previously reported concerns about adverse events (AEs) such as bladder cancer,[12-16] heart failure (HF),[10,17,18] edema,[10,19,20] fractures,[8,21] weight gain,[10] and ovulation in anovulatory women,[22] there remains uncertainty around the overall safety profile of PIO.

Previous CADTH reports on this topic include a 2010 comparison of the safety of PIO and rosiglitazone (ROS) for patients with type 2 diabetes.[23] The objective of the present report is to investigate the clinical evidence regarding the safety of PIO for patients with pre-diabetes or type 2 diabetes.

Research Question

What is the clinical evidence regarding the safety of pioglitazone for patients with type 2 diabetes or pre-diabetes?

Key Findings

Five relevant systematic reviews (four with meta-analysis and one with network meta-analysis), two randomized controlled trials, and six non-randomized studies were identified regarding the safety of pioglitazone for patients with pre-diabetes or type 2 diabetes.

In patients with pre-diabetes, evidence from one non-randomized study suggested that pioglitazone was associated with an increased likelihood of weight gain and edema when compared to placebo, while studies evaluating other safety outcomes generally found no significant differences between pioglitazone and comparators. Results in patients with type 2 diabetes were mixed, though there were often no significant differences from systematic reviews regarding several safety outcomes when comparing pioglitazone to other treatments for type 2 diabetes. However, the body of evidence was largely of low to moderate quality. As such, there remains some uncertainty around the overall safety profile of pioglitazone.

The limitations of the included studies (e.g., heterogeneity of the literature, and lack of blinding to treatment), should be considered when interpreting the results.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pioglitazone and type II diabetes. Search filters were applied to limit retrieval to health technology assessments, systematic reviews (SRs), meta-analyses (MAs), network meta-analyses (NMAs), randomized controlled trials (RCTs), or safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and May 12, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with type 2 diabetes mellitus or pre-diabetes
Intervention	Type 2 diabetes mellitus patients: pioglitazone or pioglitazone combined with other antihyperglycemic therapies Pre-diabetes patients: pioglitazone
Comparators	Type 2 diabetes mellitus patients: placebo, other antihyperglycemic therapies not combined with pioglitazone Pre-diabetes patients: placebo, no therapy, other antihyperglycemic therapies
Outcomes	Safety (e.g., adverse events, bone fractures, heart failure, shortness of breath, severe edema, bladder cancer)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, or they were duplicate publications. Articles published prior to 2019 were excluded due to the volume of relevant evidence identified from the literature search. SRs in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included SRs.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[24] for SRs, the "Questionnaire to assess the relevance and credibility of a network meta-analysis"[25] for NMAs, and the Downs and Black checklist[26] for randomized and non-randomized studies (NRSs). Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 581 citations were identified in the literature search. Following screening of titles and abstracts, 483 citations were excluded and 98 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 90 publications were excluded for various reasons, and 13 publications met the inclusion criteria and were included in this report. These comprised five SRs, two RCTs, and six NRSs. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[27] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Five SRs[28-32] (four with MAs[28,30-32] and one with NMA[29]), two RCTs,[33,34] and six NRSs[35-40] were identified and included in this review. Additional details regarding the characteristics of included publications are provided in Appendix 2, Table 2, and Table 3.

Three[28,29,32] SRs had broader inclusion criteria than the present review. Specifically, one SR[32] included studies in patients with all endocrine and metabolic disorders and the other two SRs[28,29] included studies where additional interventions and comparators were involved. Only the characteristics and results of the subset of relevant studies are described in this report.

Study Design

Three SRs[28-30] (one with NMA[29]) were published in 2020, and two SRs[31,32] were published in 2019. All of them searched multiple electronic databases for eligible RCTs published over pre-specified periods ranging from database inception to August 2019, except one[28] in which search period was unspecified. In the four SRs with MAs,[28,30-32] there were two,[28] 23,[30] 16,[31] and four[32] relevant primary studies. The SR with NMA[29] included eight primary studies,[41-48] of which two studies[41,42] directly involved PIO as intervention or comparator. The NMA used frequentist methods and a random effects model. Overall, the publications included 53 unique primary studies, with no overlap in primary studies included in each SR.

The two RCTs[33,34] were randomized open label parallel design trials, one which followed patients for 26 weeks[33] and the other for 52 weeks.[34]

Three[35,36,38] of the NRSs included in this report were retrospective cohort studies. A fourth NRS[40] was a secondary analysis of clinical trial data from an international multicenter double blinded trial.[11] The latter[11] was also included in a SR[30] retained in this review. A fifth NRS[37] was a cohort study using prospectively collected data, while the sixth[37] was a retrospective and prospective cohort study.[39] Three NRSs conducted a propensity-score matched analysis of the cohorts to address potential confounding variables,[35,36,39] while two used an analysis of variance,[38,40] and one did not report on such analyses.[37]

Country of Origin

The primary authors of the SRs were from China[28,30,32], Japan[29] and Malaysia.[31] The primary authors of the RCTs and NRSs were from Canada,[40] China,[38] Denmark,[37] Iran,[34] Korea,[33] Taiwan[35,36] and the United States of America.[39]

Among the two RCTs, one was a multicenter study conducted at eight sites in Korea,[33] and the other[34] was a single center Iranian study.

Patient Population

Five SRs[28-32] included studies of patients with type 2 diabetes. Two SRs also included studies of individuals with pre-diabetes[30] or with impaired glucose tolerance.[32] One SR[31] only included studies involving patients with type 2 diabetes without any comorbid diseases or diabetes associated complications. The number of patients in the analytical sample in the SRs ranged from 585[28] to 19,607.[30]

Two RCTs[33,34], and five NRSs[35-39] enrolled patients with type 2 diabetes. The Kim *et al.* (2020) RCT,[33] enrolled 135 patients with hemoglobin A_{1C} levels from 7.5% to 10% and with a body mass index (BMI) of 18.5 to 35 kg/m^2, and the baseline characteristics were balanced between groups.

The Khaloo *et al*. (2019) RCT[34] recruited 250 eligible patients (125 in each group) between the ages of 25 and 70 years. The patients in the PIO group had statistically significant differences in four baseline characteristics: sex (PIO: 55.5% females vs. sitagliptin [SIT]: 44.5%; P value = 0.04), disease duration (PIO: 14.3 years vs. SIT: 11.3 years; P value = 0.001), systolic blood pressure (SBP) (PIO: 129.1 mmHg vs. SIT: 135.7; P value = 0.001), and mean weight (PIO: 74.2 kg vs. SIT: 78.3 kg; P value 0.019).

One NRS[40] analysed patients with pre-diabetes from the participants of a multicenter RCT who were at least 40 years of age and had a transient ischemic attack (TIA) or stroke during the six months prior to randomization.[11] Pre-diabetes was defined as hemoglobin A_{1c} levels of 6.0% to 6.4% at baseline as per Diabetes Canada guidelines.[49] Among the 1,410 patients (PIO, n = 709; placebo, n= 701) included in the intention-to-treat (ITT) analysis relevant to the current report, mean age (PIO = 64.1 years; Placebo = 64.5 years), sex (PIO = 65.2 % males; placebo = 63.6% males) and co-morbidities were similar across the study arms.

Two NRSs[35,36] identified newly diagnosed type 2 diabetes patients from the National Health Insurance Database in Taiwan, through overlapping periods of enrollment. They enrolled 5,158[35] and 10,190[36] patients each, with mean age of 62[35] and 59[36] years respectively. The study by Cid Ruzafa and colleagues[37] identified eligible patients from the Danish health registers into an incident cohort (PIO, n = 80; comparator, n = 17,699) and a prevalent cohort (PIO, n=140; comparator, n=13,183) during the period of August 2011 to December 2015. Median age of the patients in each cohort arm ranged from 62.4 years to 67.2 years.[37]

The Miao *et al*. (2019) study,[38] conducted from July 2005 to June 2017, enrolled over 70,000 patients from the clinical data repository of a Chinese hospital, among which 13% were prescribed PIO at least once (PIO, n = 8,226).[38] The patients in the PIO group had statistically significant differences in several baseline characteristics (e.g., mean age, concurrent antidiabetic medications, and likelihood to have comorbidities; P value < 0.001 for each between group comparison).[38]

Interventions and Comparators

In one SR,[28] the antidiabetic drug aleglitazar (ALE) (not currently approved in Canada) was compared to PIO. In the NMA by Ida *et al*. (2020)[29] PIO was compared to placebo, conventional treatment, and other oral antidiabetic drugs (OAD) (e.g., liraglutide [LIR], exenatide [EXE], SIT, linagliptin [LIN], ROS, voglibose (not currently approved in Canada), and glimepiride [GLIM]) regardless of the use of dietary or exercise therapy. The SR by Alam and colleagues[31] compared PIO monotherapy with other FDA approved antidiabetic medications (e.g., metformin [MET], SUs, DPP-4 inhibitors, acarbose [ACAR], MEG). Lastly two SRs compared the effects of PIO to placebo[32] and any control (e.g., placebo, active comparator, usual care)[30] respectively.

In one RCT,[33] PIO 15 mg per day was compared to GLIM 2 mg per day along with existing MET and alogliptin (ALO) treatment in both groups. The dose of PIO and GLIM in both

groups could be increased after 12 weeks based on investigator's decision. The RCT by Khaloo *et al.*[34] compared PIO 30 mg per day to SIT 100 mg daily. MET 500 mg four times daily and gliclazide (GLIC) 80 mg thrice daily was given to patients in both groups.

Five NRSs, compared PIO use to PIO non-use (e.g., drugs other than PIO, drugs other than TZD, oral drugs other than PIO),[35,36,38] with insulin[37] and with LIN.[39] In the sixth NRS,[40] PIO (15 mg/day increased to 45 mg/day over three months, with patients given the highest tolerable dose) was compared to placebo.

Outcomes

The outcomes considered in the SRs were: all-cause mortality,[30] bladder cancer,[31] body weight,[28,32] cardiovascular events,[30,31] hospitalization for HF,[30] hypoglycemia,[28] left ventricular diastolic function,[29] peripheral edema,[28,31] abnormal liver function,[31] blood pressure,[31] bone mineral density (BMD),[32] BMI,[32] bone fracture,[32] laboratory findings (e.g., serum creatinine, albumin to creatinine ratio, urinary protein excretion),[28,30] musculoskeletal disorders (e.g., arthralgia, back pain, musculoskeletal pain),[31] upper respiratory tract infection,[31] and vascular disorders (arterial thrombosis and aortic stenosis).[31]

The outcomes of interests in the RCTs were: body weight,[34] blood pressure,[34] BMI,[34] waist circumference,[34] hip circumference,[34] and other AEs.[33,34]

The NRSs sought outcomes on: all-cause mortality,[35,40] cancer (e.g., hepatocellular carcinoma, bladder cancer, any cancer),[36,37,40] HF,[37,38] MI,[38,39] stroke,[38,39] unstable angina,[39] coronary revascularization,[39] cirrhosis,[36] esophageal varices,[36] hepatic failure,[36] body weight,[40] cardiovascular events,[40] hospitalization for HF,[40] edema,[40] bone fracture,[40] and haematuria.[37]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 4, and Table 5.

SRs

Strengths of all SRs[28-32] (four with MAs[28,30-32] and one with NMA[29]) included: clear objectives and inclusion criteria, reporting of key search terms and search strategies, and authors included statements on conflicts of interest.

While all SRs[28-32] performed a quality assessment of included studies using an appropriate tool, three SRs included high quality, low risk of bias studies in their analyses,[28,30,32] and two SRs included studies with high or unclear risk of bias in relation to random sequence generation and blinding of participants and personnel.[29,31]

While all studies performed study selection in duplicate, data extraction was reported to have been performed in duplicate for three SRs.[30-32] Three SRs did not report having an *a priori* protocol for their review.[28,29,32] These weaknesses of reporting decrease the confidence in the findings and the reproducibility of the SRs. None of the SRs provided a list of excluded studies; therefore, the accuracy and comprehensiveness of the exclusions could not be assessed. One SR[29] did not report exploring publication bias; therefore, it is unclear if the direction or strength of the findings are biased. Four SRs[28,29,31,32] did not adequately report the primary study results; therefore, the accuracy of data reporting and interpretation cannot be assessed.

The MA of one SR[31] had a small sample size (n = 2,681) and included nine (out of 16) studies that were assessed as having a high risk of bias in relation to their open-label study designs and selective reporting, decreasing overall confidence in the results.

With respect to the NMA,[29] a network diagram of the included primary studies was reported. There were no significant inconsistencies between direct and indirect comparisons in the design by treatment interaction model.[29] Systematic differences in treatment effect modifiers (e.g., BMI, age, number of comorbidities) were present between the different indirect treatment comparisons. These imbalances were not compared across the included studies and were not addressed in the analysis. Despite the presence of heterogeneity, authors did not perform additional analyses (e.g., subgroup analysis, meta-regression) to explore its origins.[29] While it was appropriate to have selected a random-effect NMA model,[29] authors did not justify its use.

RCTs

Strengths of all RCTs[33,34] included: clear descriptions of objectives, interventions, main outcomes, population characteristics, and eligibility criteria; and the major findings were described in a way that allowed verification of analyses and conclusions. Estimates of random variability were reported, and the data analyses were planned at the outset.

Both RCTs[33,34] performed safety endpoint analyses based on their ITT populations; however, one[33] did not specify how missing data were handled, while the other[34] indicated that missing data were handled using the "last observation carried forward" method. Furthermore, they both lacked the characterization of patients who withdrew or were lost to follow up. Both RCTs[33,34] were open label, meaning that patients and investigators were aware of their treatment group allocation. This may have introduced observer biases for certain outcomes like cancer or cardiovascular events; however, this unlikely to introduce bias for objectively measurable outcomes like death or fracture.

Patients in the Khaloo *et al.* (2019) RCT had statistically significant differences in four baseline characteristics: sex, disease duration, systolic blood pressure (SBP), and mean weight.[34] A lack of adequate adjustment for confounders that were not balanced at baseline may have introduced a bias in the analysis from which the main findings were drawn.

While the allocation of patients to the treatments groups was randomized in one RCT,[33] authors did not indicate their randomization method; therefore, the accuracy and comprehensiveness of the process could not be assessed. Also, the safety conclusions of the study were based on the analysis of treatment (i.e., per protocol) rather than ITT, meaning the comparisons among treatment groups may have been biased due to dropouts.[33]

NRSs

Several strengths were identified in all NRSs[35-40] including: clear descriptions of objectives, interventions, main outcomes, population characteristics, eligibility criteria. Propensity score matching was used in three studies,[35,36,39] minimizing the influence of principal confounders between groups; however, one study did not match by hemoglobin A_{1c} values,[35] while another did not match by duration of disease.[36] Four studies utilised a retrospective cohort design,[35-38] suffering no losses to follow up.

In one NRS,[37] the effects of the main confounders were not investigated nor were adjustments made in the final analyses; therefore it is unclear what impact, if any, the

confounding variables had on the results. One study[39] performed multiple observations over time, yet no statistical adjustments were made for multiplicity.

Summary of Findings

A detailed summary of findings is provided in Appendix 4, Table 6, and Table 7.

Clinical evidence regarding the safety of pioglitazone for patients with pre-diabetes

Death

Information regarding death outcomes with PIO in patients with pre-diabetes was available from one NRS.[40]

Among patients with pre-diabetes (using the American Diabetes Association [ADA] criteria),[50] authors reported no difference in all-cause mortality among PIO users compared with placebo.[40]

Cardiovascular outcomes

Information regarding cardiovascular outcomes with PIO in patients with pre-diabetes was available from one SR,[30] and one NRS.[40]

The SR[30] reported on major adverse cardiovascular events (i.e., the composite of non-fatal MI, non-fatal stroke, and cardiovascular death), non-fatal MI, non-fatal stroke, as well as hospitalization for HF among patients with pre-diabetes at baseline, with a history of established atherosclerotic cardiovascular disease (CVD) at baseline, reported no statistical differences between PIO and comparator groups (i.e., placebo, and not PIO). Similarly, results were not statistically significant in the group without a history of established atherosclerotic CVD at baseline between PIO and placebo.[30]

The NRS[40] was a secondary analysis of clinical trial data from a study[11] that was included in the SR[30] above. Authors reported statistically significant results favouring PIO over placebo among patients with pre-diabetes (using the World Health Organisation [WHO]/Diabetes Canada criteria),[49] for the outcomes of stroke or MI (ITT analysis; hazard ratio [HR] = 0.70, 95% CI, 0.51 to 0.95; P value = 0.02), and stroke (ITT analysis; HR = 0.68; 95% CI, 0.48 to 0.97; P value = 0.03).[40] However, among patients with pre-diabetes (using the ADA criteria),[50] authors reported no difference for the outcomes of HF causing hospitalization or death.[40] Similarly, in patients with pre-diabetes (using the WHO/Diabetes Canada criteria),[49] there were no differences in acute coronary syndrome, stroke, MI, or hospitalised HF.[40]

BMD

Information regarding BMD outcomes with PIO in patients with pre-diabetes was available from one SR.[32]

The SR[32] reported a mean difference in the change from baseline of BMD of the lumbar spine, favouring the comparators (–1.08; 95% CI, –2.04 to 0.13; P value = 0.03 [values as reported in the article]).

Fractures

Information regarding fracture outcomes with PIO in patients with pre-diabetes was available from one SR,[32] and one NRS.[40]

The SR reported on odds ratio of fractures and found there was no statistically significant difference between PIO and placebo.[32]

The NRS[40] reported statistically significant results favouring placebo over PIO among patients with pre-diabetes (using the ADA criteria),[50] for the outcomes of bone fracture causing hospitalization, surgery, or procedure (ITT analysis; PIO, n = 71 (4.9%) vs. placebo, n = 46 (3.2%); P value = 0.02; number needed to harm [NNH] = 59).

Weight

Information regarding weight change outcomes with PIO in patients with pre-diabetes was available from one NRS.[40]

The NRS[40] reported statistically significant results favouring placebo over PIO among patients with pre-diabetes (using the ADA criteria),[50] for the outcomes of weight change of 10% or more from baseline (ITT analysis; PIO, n = 382 (26.2%) vs. placebo, n = 182 (12.7%); P value < 0.001; NNH = 7).[40]

Edema

Information regarding edema outcomes with PIO in patients with pre-diabetes was available from one NRS.[40]

The NRS[40] reported statistically significant results favouring placebo over PIO among patients with pre-diabetes (using the ADA criteria),[50] for the outcomes of self-reported new or worsening edema (ITT analysis; PIO, n = 541 (37.2% vs. placebo, n = 360 (25.2%); P value < 0.001; NNH = 8).[40]

Other AEs

Information regarding other AEs with PIO in patients with pre-diabetes was available from one NRS.[40]

The NRS[40] reported no statistically significant results when comparing placebo with PIO among patients with pre-diabetes (using the ADA criteria),[50] for the outcomes of hospitalization or incident cancer.

Clinical evidence regarding the safety of pioglitazone for patients with type 2 diabetes mellitus

Death

Information regarding death outcomes with PIO in patients with type 2 diabetes was available from one SR,[30] and one NRS.[35]

In the SR,[30] authors reported outcomes for patients with type 2 diabetes, without a history of established atherosclerotic CVD at baseline. There was no statistical difference in relative risk (RR) between PIO and comparators (i.e., SUs, not PIO, MET 500 mg, MET 750 mg, MET 850 mg, GLIM, glyburide) on the outcomes of all-cause mortality.[30] The same SR[30] performed an additional analysis for patients with or at high risk of type 2 diabetes, without a history of established atherosclerotic CVD at baseline. On the outcome of all-cause mortality results were not statistically different between groups.[30]

Authors of the NRS[35] reported that PIO users had a statistically significantly lower risk of all-cause mortality (HR adjusted for sex, age, and baseline comorbidities: 0.47; 95% CI, 0.38 to 0.58; P value < 0.001), as well as lower risk of non-cardiovascular (CV) death (HR

adjusted for sex, age, and baseline comorbidities: 0.50; 95% CI, 0.38 to 0.66; P value < 0.001) compared with the use of antidiabetic drugs other than insulin and PIO. However, they reported no statistical differences on the incidence of CV death.[35]

Cardiovascular outcomes

Information regarding cardiovascular outcomes with PIO in patients with type 2 diabetes was available from three SRs,[29-31] two RCTs,[33,34] and four NRSs.[35,37-39]

The first SR[29] reported no statistical difference in left ventricular diastolic function in a direct comparison of PIO with ROS, as well as PIO with conventional treatment (not defined). When authors performed an NMA, they reported that PIO was statistically significantly worse than LIR for worsening left ventricular diastolic function (standardised mean difference [SMD] = –1.38; 95% CI, –2.11 to –0.65).[29] However, the same NMA found no difference when PIO was compared with placebo, EXE, SIT, or LIN.[29]

Another SR[30] reported outcomes for patients with type 2 diabetes, without a history of established atherosclerotic CVD at baseline. There were no differences in RR between PIO and comparators (i.e. SUs, not PIO, GLIM, glyburide) on the outcomes of: major adverse cardiovascular events (i.e., the composite of non-fatal MI, non-fatal stroke, and cardiovascular death), non-fatal MI, non-fatal stroke, hospitalization for HF, as well as cardiovascular death. The same SR[30] performed an additional analysis for patients with or at high risk of type 2 diabetes, without a history of established atherosclerotic CVD at baseline. On the outcomes of major adverse cardiovascular events (i.e., non-fatal MI, non-fatal stroke, or cardiovascular death), non-fatal MI, non-fatal stroke, hospitalization for HF, cardiovascular death, as well as overall effect (i.e., total of major adverse cardiovascular events, non-fatal MI, and non-fatal stroke), results were not statistically different between groups.

The third SR[31] reported no statistical difference between PIO and comparators (i.e., ACAR, GLIM, GLIC, and MET) in changes from baseline on outcomes of: blood pressure (systolic, diastolic, and overall), cardiovascular events, as well as vascular disorders.

In the first RCT, authors reported no statistically significant difference between PIO and GLIM in number of patients reporting palpitations.[33] While the second RCT[34] reported a statistically significant difference between the two treatment groups in increase in SBP from baseline, favouring PIO over SIT (PIO: 2.4 mmHg, standard deviation [SD] = 14.6; SIT 3 mmHg, SD = 15.4; P value < 0.001). However, it is important to highlight that baseline characteristics of patients with regards to their SBP were not balanced between groups (P value = 0.001); it is unclear whether this may have impacted these results. The same RCT[34] found no difference in diastolic blood pressure changes between groups.

The first NRS[35] reported no statistical differences between PIO users and non-users (i.e., use of antidiabetic drugs other than insulin and PIO) on the incidence of: hospitalized coronary artery disease (CAD), hospitalized stroke, and HF. A second NRS[37] reported an incidence of less than five cases of HF among 77 incident PIO users (incidence of nine per 1,000 person-years [95% CI, 2 to 34]) and less than five cases of HF among 133 prevalent PIO users (incidence of two per 1,000 person-years [95% CI, 0 to 13]) during the follow-up period.

A third NRS[38] reported a statistically significant difference favouring PIO users compared to non-users (i.e., use of other OADs) in the incidence of MI (RR adjusted for sex and age: 0.55; 95% CI, 0.37 to 0.80; P value = 0.002), as well as the incidence of HF (RR adjusted

for sex and age: 0.72; 95% CI, 0.55 to 0.95; P value = 0.021). However, authors reported no difference in incidence of stroke between groups.[38]

The fourth NRS[39] reported no statistical differences between PIO and LIN at last follow-up on outcomes of: MI, stroke, unstable angina, coronary revascularization, and composite (i.e., hospitalization for acute MI, ischaemic or haemorrhagic stroke, unstable angina, or coronary revascularization).

Fractures

Information regarding fracture outcomes with PIO in patients with type 2 diabetes was available from one RCT.[33]

Authors reported no statistical difference in the number of patients reporting a fracture between PIO and GLIM.[33] The number of events in the PIO group was two out of 69 patients (one cuneiform bone of the foot and one intertrochanteric section of femur after falling), while there were zero fractures out of 66 patients in the GLIM group.[33]

Weight

Information regarding weight change outcomes with PIO in patients with type 2 diabetes was available from one SR,[28] and two RCTs.[33,34]

In the SR,[28] authors performed a MA and reported no significant difference in percent weight change from baseline between ALE and PIO. Similarly, one RCT[33] reported no significant difference in number of patients reporting weight gain between PIO and GLIM.

While the second RCT[34] reported a statistically significant increase in body weight (PIO: 0.9 kg, SD = 1.5; SIT: –0.5 kg, SD = 1.1; P value < 0.001) and hip circumference (PIO: 2 cm, SD = 5.3; SIT: –0.7 cm, SD = 3.1; P value < 0.001), for the PIO group. Furthermore, the PIO group saw nine early study discontinuations, of 125 patients, due to weight gain.[34] However, authors reported no significant difference in changes from baseline with regards to BMI and waist circumference, measured at week 52.[34]

Edema

Information regarding edema outcomes with PIO in patients with type 2 diabetes was available from two SRs,[28,31] and two RCTs.[33,34]

In the first SR,[28] authors performed a MA and reported no difference in the odds ratio for edema events between ALE and PIO. Conversely, authors in the second SR with MA[31] found a statistically significant difference in the RR of peripheral edema (2.21; 95% CI, 1.48 to 3.31; P value = 0.0001) favouring the comparators (i.e., SIT, vildagliptin [VIL], GLIM, GLIC, repaglinide [REP], and ALO) over PIO.

Authors from one RCT[33] reported no significant difference between PIO and GLIM in the number of patients reporting edema. However, the PIO group in the other RCT saw six early study discontinuations, of 125 patients, due to edema, while none of the 125 patients in the SIT group discontinued the study.[34]

Hypoglycemia

Information regarding hypoglycemia outcomes with PIO in patients with type 2 diabetes was available from two SRs,[28,31] and one RCT.[33]

In the SR,[28] authors performed a MA and reported no difference in odds ratio of hypoglycemia events between ALE and PIO. Conversely, authors in the second SR with MA[31] found a statistically significant difference in the RR of hypoglycemia (0.51; 95% CI, 0.33 to 0.80; P value = 0.003) favouring PIO over the comparators (i.e., MET, VIL, REP, GLIC, GLIM, SIT).

Similarly, authors of the RCT reported a statistically significant difference in the number of patients reporting hypoglycemia, favouring PIO over GLIM (P value = 0.002).[33]

Cancer

Information regarding cancer outcomes with PIO in patients with type 2 diabetes was available from two SRs,[28,31] and one NRS.[37]

Authors of the first SR reported the absolute number of malignancy events (type not defined) for ALE (5/945), placebo (0/997), and PIO (1/148).[28] While authors of the second SR found no statistical difference in the RR of breast cancer between PIO and SIT, nor the RR of colon cancer between PIO and ALO.[31]

Authors of the NRS reported no new bladder cancer cases among incident PIO users and fewer than five new bladder cancer cases among prevalent PIO users. New bladder cancer cases among prevalent users of other agents were not reported.[37]

Renal function

Information regarding renal function outcomes with PIO in patients with type 2 diabetes was available from one SR,[28] one RCT,[33] and one NRS.[37]

In the SR,[28] authors performed a MA and reported a statistically significant difference between groups in the percent change from baseline in serum creatinine (P value < 0.00001) and estimated glomerular filtration rate (eGFR) (P value < 0.0004), favouring PIO over ALE.

Authors of the RCT,[33] reported no statistical difference in the number of patients reporting acute pyelonephritis between PIO and GLIM. Authors of the NRS, also reported no statistical difference between incident PIO users and prevalent PIO users in the number of uninvestigated cases of macroscopic haematuria (i.e., patients with a recording of haematuria, but without a subsequent laboratory urine assessment, or other investigation) during the follow-up period.[37]

Other AEs

Information regarding other AEs with PIO in patients with type 2 diabetes was available from one SR,[31] one RCT,[33] and one NRS.[36]

In the SR,[31] authors reported no statistically significant differences between PIO and comparators for the outcomes of: upper respiratory tract infections (comparators: REP, ALO, VIL, and SIT), nervous system disorders (comparators: SIT, REP, VIL, ALO), diarrhea (comparators: SIT, REP), musculoskeletal and connective tissues disorders (comparators: REP, ALO), asthenia (comparator: VIL), abnormal liver function parameters (comparator: GLIC), nausea (comparator: SIT), vomiting (comparator: SIT), and non-cardiac chest pain (comparator: ALO).

The RCT authors reported no statistically significant differences between PIO and GLIM for the outcomes of: upper respiratory infection, dizziness, headache, dyspepsia, diarrhea, itching, abdominal pain, ache, and myalgia.[33]

Authors of the NRS[36] reported a statistically significant difference in the incidence of cirrhosis favouring PIO users compared with non-TZD users (HR adjusted for sex, age, and baseline comorbidities: 0.35; 95% CI, 0.15 to 0.85; P value < 0.05).

Limitations

A number of limitations were identified in the critical appraisal as shown in Appendix 3, Table 4, and Table 5; however, additional limitations exist. The main limitations of this review are related to the heterogeneity of the study populations and the generalizability of the findings.

Heterogeneity was apparent in the baseline patient characteristics of primary studies included in the SRs,[28-32] and among the RCTs[33,34] and NRSs[35-40] included in this report (e.g., duration of type 2 diabetes, baseline hemoglobin A_{1c}, controlled or uncontrolled diabetes, number of comorbidities, number of concurrent antidiabetic medications). As PIO is generally not considered a first-line treatment in diabetes,[2] its use in more severe cases of diabetes brings with it additional confounders that should be considered, particularly with NRSs.

Another heterogenous aspect, affecting the pre-diabetes literature, was the lack of a standard definition of pre-diabetes (e.g., American definition, WHO definition, Canadian definition, homeostatic model assessment of insulin resistant [HOMA-IR]). As such, this reduces the ability to compare study findings.

Of note in the SRs, primary study data were often available only at the study characteristic level. Heterogeneity existed and was likely the result of differences in baseline characteristics of participants, sample size, or combination treatments. Although all the trials included in the SRs were randomized, minimising potential biases introduced by these limitations, it remains unclear whether any differences between outcomes were due to differences in these characteristics. An additional source of variability was the follow-up period (weeks[33,34,39] to years[35,36,40]) of the primary studies included in the SRs. As some outcomes such as cancer, HF, and fractures require months to years to develop, the reader should be mindful of the study durations when interpreting results of this report. Additionally, the doses of PIO interventions as well as those of comparator drugs varied from study to study. Therefore, caution should be exercised in interpreting and generalizing their findings.

Two SRs,[28,31] contained comparator drugs (e.g., VIL, ALE, currently not available in Canada, limiting the applicability of their findings to Canadian settings. One RCT[33,34] was of 26 week duration, which may not have been long enough to detect longer term outcomes such as fractures and cancer.

One study[40] was a secondary analysis of a subgroup of patients enrolled in a previous clinical trial that used the HOMA-IR score to measure insulin resistance. The use of the HOMA-IR score is not common in Canadian clinical settings; therefore, this study's results may have limited generalisability and application in clinical practice.

Except for one NRS,[40] participant adherence with treatment was not reported which introduces uncertainty with regards to the magnitude of effects reported. Furthermore, five

NRSs[35-39] queried large prescription databases for data on PIO dispensing, which does not necessarily corelate with patients actively taking the medication. Information bias, affecting the accuracy of outcome measurements, may have resulted from relying on dispensing information and the inability to ascertain the actual drug intake. Furthermore, depending on the comprehensiveness of administrative databases, some confounding factors that may change risk of outcomes such as CVD, cancer, and mortality (e.g., lipid profile, hemoglobin A_{1c}, renal function, hypoglycemia, diet and lifestyle, BMI, tobacco use) may not have been consistently available for inclusion in analyses, resulting in an underestimation of the reported risk.

The small number of PIO users in some included studies, resulted in high uncertainty around treatment effects, precluding meaningful inferences. In addition, while RCTs are a robust study design for establishing the safety and efficacy of pharmaceuticals, they generally exclude considerable portions of the potentially treatable population, thus limiting the generalizability of their findings.

Other potential safety issues of PIO (e.g., macular edema, ovulation in anovulatory women) were not examined in this report due to a lack of relevant data. This gap would suggest the need for future research.

Conclusions and Implications for Decision or Policy Making

This report identified safety evidence regarding the use of PIO in patients with pre-diabetes or type 2 diabetes. Five SRs[28-32] (four with MAs[28,30-32] and one with NMA[29]), two RCTs,[33,34] and six NRSs[35-40] were identified and included in this review.

The identified literature were heterogenous and revealed mixed conclusions regarding the safety of PIO in patients with pre-diabetes. No statistically significant difference was reported regarding PIO's potential effects on mortality[40] and major adverse cardiovascular events.[30] While lumbar spine BMD was worse for pre-diabetes PIO users,[32] no clear direction emerged regarding odds of fractures, with some studies finding no effect[32] and others favouring placebo.[40] However, an identified NRS in patients with pre-diabetes suggest that PIO was associated with an increased likelihood of weight gain and edema when compared to placebo.[40] Whether these increases would be considered clinically meaningful changes, particularly with respect to weight gain, was not discussed in the study. The same NRS reported no significant between group differences in hospitalization or incident cancer.[40]

With regards to the safety of PIO in patients with type 2 diabetes, the identified literature were heterogenous and revealed mixed conclusions. No clear direction emerged regarding the drug's potential effects on mortality, with one SR finding no effect[30] and one NRS favouring PIO in specific comparisons.[35] Results were mixed (some statistically significant and non-significant findings) regarding major adverse cardiovascular events (i.e., non-fatal MI, non-fatal stroke, or cardiovascular death),[30,35,39] blood pressure,[31,34] weight change,[28,33,34] edema,[28,31,33,34] renal function,[28,33,37] or incidence of HF among PIO users.[30,35,37,38] However, an NMA found that PIO was worse than LIR for decreasing left ventricular diastolic function, but found no difference when PIO was compared with placebo, EXE, SIT, or LIN.[29] There were no differences between PIO and GLIM in the incidence of fractures,[33] or between PIO and various comparators (e.g., ALE, MET, SUs, DPP-4 inhibitors, ACAR, MEG, insulin) for the incidence of cancer.[28,31,37] Two analyses of PIO found it to be less likely to cause hypoglycemia;[31,33] however, in a third analysis, the

odds depended on the comparator used.[28] As such, there remains some uncertainty around the overall safety profile of PIO.

The limitations of the included studies, especially heterogeneity (e.g., baseline characteristics, follow-up period, and lack of standard definition of pre-diabetes), should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. The lack of consensus in the identified literature suggests that more comparative studies are required in patients with pre-diabetes and type 2 diabetes.

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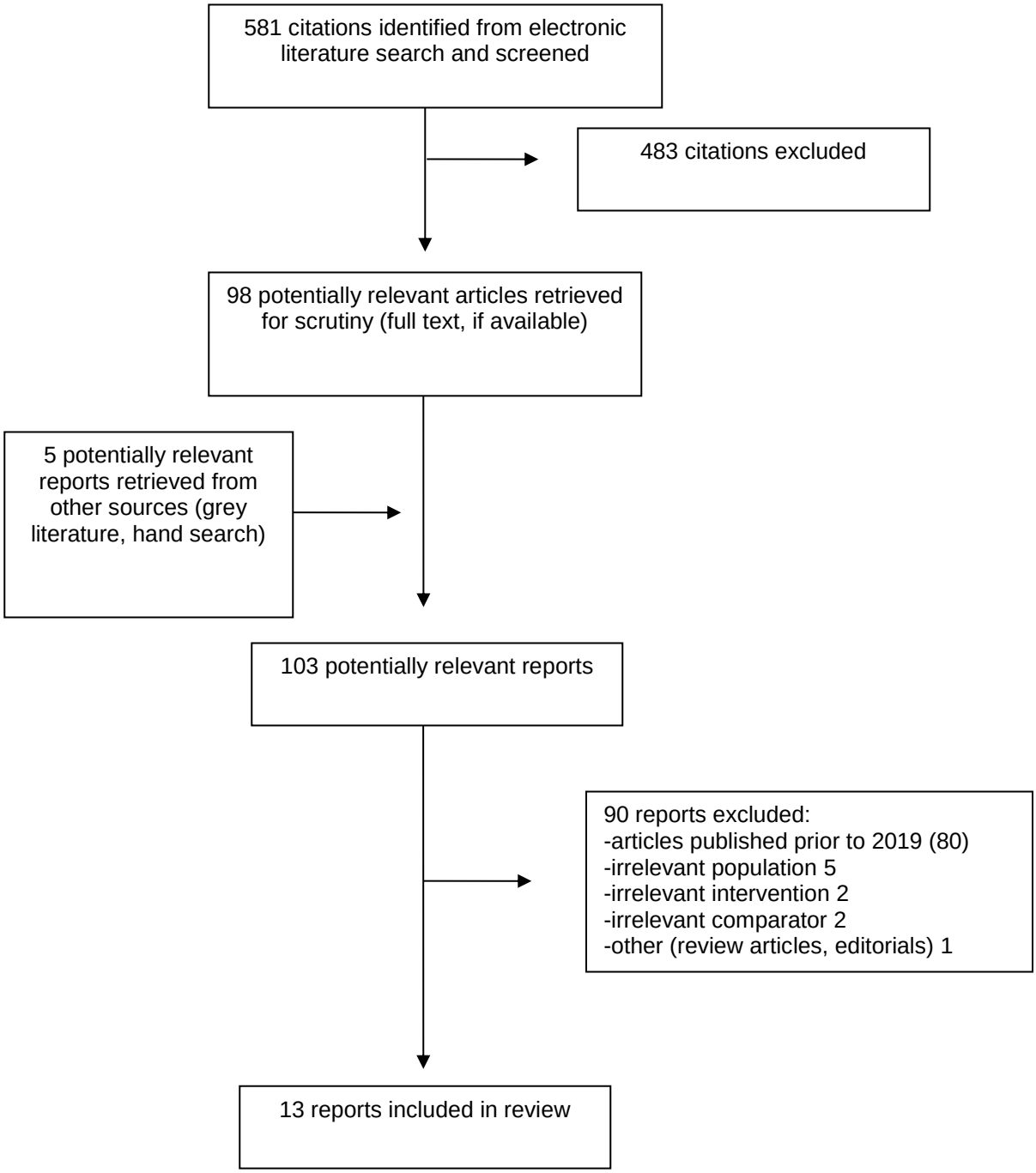
76. Grey A, Bolland M, Fenwick S, et al. The skeletal effects of pioglitazone in type 2 diabetes or impaired glucose tolerance: a randomized controlled trial. *Eur J Endocrinol.* 2014;170(2):255-262.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews, Meta-Analyses, and Network Meta-Analyses

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Han and Qu (2020)[28] **China** **Funding source**: • NR	**Study design**: SR and MA of relevant RCTs **Number of studies included**: seven **Number of relevant primary studies**: three	Patients with type 2 diabetes **Number of patients in relevant analytical sample**: 585 **Mean age of relevant analytical sample**: 58.9 years **Sex of relevant analytical sample**: 47.3% males	**Intervention**: • ALE **Comparator**: • PIO	**Outcomes**: Cardiovascular and safety related outcomes including: • Change in serum creatinine levels • Change in body weight • Hypoglycemia • Peripheral edema **Follow-up**: Ranged from 16 weeks to 52 weeks
Ida *et al.* (2020)[29] **Japan** **Funding source**: • NR	**Study design**: SR with NMA of relevant RCTs. **Number of studies included**: eight	Patients with type 2 diabetes, regardless of the use of dietary or exercise therapy **Overall number of patients**: 592 **Overall mean age**: 64 years **Overall sex**: 50% female **Overall mean time from diagnosis of diabetes**: 7.7 years	**Interventions**: • OADs • GLP-1 receptor agonists **Comparators**: • Each other • Placebo	**Outcomes**: • Left ventricular diastolic function **Follow-up**: • Mean duration of 18 weeks
Zhou *et al.* (2020)[30] **China** **Funding source**: • NR	**Study design**: SR with MA of relevant RCTs **Number of studies included**: 26 **Number of relevant primary studies:**23	Patients with or at high risk of type 2 diabetes	**Intervention**: PIO **Comparator**: any control (e.g., placebo, active comparator, usual care)	**Outcomes**: • Major adverse cardiovascular events (i.e., non-fatal MI, non-fatal stroke, or cardiovascular death) • Hospitalization for HF • Cardiovascular death • All-cause mortality • Urinary albumin to creatinine ratio • 24-hour urinary protein excretion level

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
				Follow-up range: two months to five years
Alam *et al.* (2019)[31] **Malaysia** **Funding source**: • Non-funded	**Study design**: SR with MA of relevant RCTs **Number of studies included**: 16 (all relevant)	Patients with type 2 diabetes without any comorbid diseases or diabetes associated complications **Number of patients in analytical sample**: 2,681 **Mean age of analytical sample**: • PIO group: ranged from 45.1 to 64.1 years. • Comparator groups: ranged from 44.4 to 65.1 years. **Sex of analytical sample**: 56.1% males **Mean duration of disease**: • PIO group: ranged from 2.3 to 6.5 years. • Comparator groups: ranged from 1.9 to 6.4 years	**Intervention**: PIO monotherapy **Comparator**: Other FDA approved OADs (e.g., MET, SUs, DPP-4 inhibitors, ACAR, MEG)	**Relevant outcomes**: • Blood pressure • Hypoglycemia • Peripheral edema • Upper respiratory tract infection • Vascular disorders (e.g., arterial thrombosis, aortic stenosis) • Musculoskeletal disorders (e.g., arthralgia, back pain, musculoskeletal pain) • Cardiovascular events • Bladder cancer • Abnormal liver function • Other AEs **Follow-up**: 12 weeks to 12 months
Zuo *et al.* (2019)[32] **China** **Funding source**: • Non-funded	**Study design**: SR with MA of relevant RCTs **Number of studies included**: six **Number of relevant primary studies**: four	Patients with type 2 diabetes or impaired glucose tolerance **Number of patients in relevant sample**: 684 **Mean age of relevant sample:** ranged from 32 to 64 years **Sex of analytical sample**: 48 to 62.2% of the patients in each group were males. One primary study[51] had only females.	**Intervention**: PIO (dose range: 30 mg/day to 45 mg/day) **Comparator**: Placebo	**Outcomes**: • BMD • BMI • Fat mass • Fracture rates **Follow-up**: Ranged from 26 weeks to 33.6 months

ACAR = acarbose; AE = adverse event; ALE = aleglitazar; BMD = bone mineral density; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; FDA = US Food and Drug Administration; GLP-1 = glucagon-like peptide-1; HF = heart failure; MA = meta-analysis; MET = metformin; MI = myocardial infarction; NMA = network meta-analysis; NR = not reported; OAD = oral antidiabetic drugs; PIO = pioglitazone; RCT = randomized controlled trial; SR = systematic review; SU = sulphonylureas.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Randomized Controlled Trials				
Kim *et al.* (2020)[33] **Korea** **Funding Source**: • Takeda Pharmaceuticals Korea Company	Multicentre, randomized, open-label, parallel design, phase IV trial (NCT02426294), between March 2015 and April 2018.	Patients with type 2 diabetes, a HbA_{1c} of 7.5% to less than 10%, aged 19 to 80 years, and a BMI of 18.5 to 35 kg/m^2. **Number of patients**: N = 135 • PIO, n = 69 • GLIM, n = 66 **Mean age (SD)**: • PIO, 60.7 years (9.1) • GLIM, 58.5 years (10.4) **Sex**: • PIO, 34 males (49.3%) • GLIM, 30 males (45.5%)	**Intervention**: PIO 15 mg per day (after 12 weeks the doses could be doubled based on the investigator's decision), in addition to existing MET and ALO therapy **Comparator**: GLIM 2 mg per day (after 12 weeks the doses could be doubled based on the investigator's decision), in addition to existing MET and ALO therapy	**Relevant outcomes**: • AEs **Follow-up**: 26 weeks
Khaloo *et al.* (2019)[34] **Iran** **Funding Source**: • None received	Randomized, open-label, parallel assignment clinical trial (NCT03125694), between February 2015 and April 2017.	Patients with type 2 diabetes, who had inadequate glycemic control, aged 25 to 70 years. **Number of patients**: N = 250 • SIT, n = 125 • PIO, n = 125 **Mean age (SD)**: • SIT, 60.8 years (8.1) • PIO, 62.7 years (8.2) **Sex**: • SIT, 57 females (44.5%) • PIO, 71 females (55.5%)	**Intervention**: SIT 100 mg daily, in combination with MET 500 mg four times a day and GLIC 80 mg three times a day. **Comparator**: PIO 30 mg daily, in combination with MET 500 mg four times a day and GLIC 80 mg three times a day.	**Outcomes**: • Blood pressure • Weight • Waist circumference • Hip circumference • BMI • AEs **Follow-up**: 52 weeks

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Non-Randomized Studies				
Yen *et al.* (2020)[35] **Taiwan** **Funding Sources**: • Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004), • Taipei Veterans General Hospital (V105C-204), • China Medical University Hospital, • Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10601010036), • Taiwan Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), • Tseng-Lien Lin Foundation, Taichung, Taiwan, • Taiwan Brain Disease Foundation, Taipei, Taiwan, • Katsuzo and Kiyo Aoshima Memorial Funds, Japan.	Retrospective cohort study from January 2000 to December 2012	Newly diagnosed patients with type 2 diabetes, aged 30 to 100 years. **Number of patients in analytical sample**: 5,158 (2,579 in each cohort) **Mean age of analytical sample (SD)**: • PIO: 62.09 years (12.39 • Non-PIO: 61.98 years (13.06) **Sex of analytical sample**: • PIO: 47.23% female • Non-PIO: 47.62% female	**Intervention**: PIO use **Comparator**: PIO non-use (e.g., use of antidiabetic drugs other than insulin and PIO)	**Outcomes**: • All-cause mortality **Follow-up**: 13 years
Yen *et al.* (2020)[36] **Taiwan** **Funding Source**: • Ministry of Health and Welfare, Taiwan, Grant/Award Number: MOHW108-TDU-B-212-133004; • China Medical University Hospital; • Academia Sinica Stroke Biosignature Project, Grant/Award	Retrospective cohort study from January 2000 to December 2013	Newly diagnosed patients with type 2 diabetes, aged 30 to 80 years. **Number of patients in analytical sample**: 10,190 (5,095 in each cohort) Mean age of analytical sample (SD): • TZD: 59.0 years (10.9) • Non-TZD: 59.0 years (11.1)	**Intervention**: TZD use (i.e., PIO, ROS) **Comparator**: TZD non-use (e.g., use of antidiabetic drugs other than TZD)	**Outcomes**: • Cirrhosis • Hepatic decompensation • Oesophageal varices • Abdominal ascites • Hepatic encephalopathy jaundice • Hepatic failure • Hepatocellular carcinoma **Mean follow-up time (SD)**:

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Number: BM10701010021; • MOST Clinical Trial Consortium for Stroke, Grant/Award Number: MOST 107-2321-B-039-044; • Tseng-Lien Lin Foundation; • Katsuzo and Kiyo Aoshima Memorial Funds		**Sex of analytical sample**: • TZD: 47.8% female • Non-TZD: 46.9% female		• TZD: 3.84 years (2.71) • Non-TZD: 3.90 years (3.01)
Cid Ruzafa *et al.* (2019)[37] **Denmark** **Funding Source**: • Takeda Pharmaceutical Company Limited	Cohort study	**PIO Incident cohort**: Patients with a diagnosis of type 2 diabetes, and a first dispensing (i.e., no prior use) of PIO between August 11, 2011 to December 31, 2015. **PIO Prevalent cohort:** Patients with a diagnosis of type 2 diabetes and dispensing (i.e., with prior use) of PIO between August 11, 2011 to December 31, 2015. **Insulin incident and prevalent cohorts are similarly defined** **Number of patients**: • Incident PIO: 80 • Prevalent PIO: 140 • Incident insulin: 17,699 • Prevalent insulin: 13,183 **Median age in years (IQR)**: • Incident PIO: 62.4 years (55.5 to 69.3) • Prevalent PIO: 66.0 years (58.2 to 74.1) • Incident insulin: 67.2 years (58.4 to 75.4) • Prevalent insulin: 66.8 years (60.2 to 74.1)	**Intervention**: PIO **Comparator**: insulin	**Relevant outcomes**: • HF • Bladder cancer • Haematuria • Uninvestigated macroscopic haematuria (i.e., patients with a recording of haematuria, but without a subsequent laboratory urine assessment, or other investigation) **Follow-up**: • From their first prescription for PIO to the end of the study period

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Sex: • Incident PIO: 43.7% female • Prevalent PIO: 37.9% female • Incident insulin: 39.0% female • Prevalent insulin: 40.9% female		
Miao *et al.* (2019)[38] **China** **Funding Source:** • 2016 Industry Prospecting and Common Key Technology Key Projects of Jiangsu Province Science and Technology Department, Grant/Award Number: BE2016002-4; • 2016 Projects of Nanjing Science Bureau, Grant/Award Number: 201608003; • 2017 Projects of Jiangsu Provincial Department of Finance, Grant/Award Number: 2150510; • UTHealth Innovation for Cancer Prevention Research Training Program Predoctoral Fellowship (Cancer Prevention and Research Institute of Texas), Grant/Award No RP160015	Retrospective cohort study from July 2005 to June 2017	Adult patients with type 2 diabetes prescribed at least one OAD **Number of patients in analytical sample**: • PIO users: N= 8,226 • Non-PIO users: N= 63,557 **Mean age of analytical sample (SD)**: • PIO users: 55.1 years (13.4) • Non-PIO users: 57.9 years (14.4) • P value < 0.001 **Sex of analytical sample**: • PIO users: 51.64 % males • Non-PIO users: 55.87% males • P value < 0.001	**Intervention**: PIO use **Comparator**: PIO non-use (e.g., use of other OADs)	**Outcomes**: • MI • Ischemic stroke • HF **Follow-up**: From their first prescription for PIO to the end of the study period
Patorno *et al.* (2019)[39] **United States of America**	Retrospective and prospective cohort, from May 2011 to December 2015	Individuals who are commercially insured or who have insurance through a Medicare Advantage plan, aged 18 years or older, with a	**Intervention**: • LIN **Comparator**: • other DDP-4 inhibitors	**Outcomes**: • composite CV outcome (hospitalization for acute MI, ischaemic or

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding Source: • Research grant from Boehringer-Ingelheim. • National Institute on Aging (K08AG055670) • National Institute of General Medical Sciences (RO1GM1089990235 5263)		diagnosis of type 2 diabetes, and who are new users of the intervention or comparator **Overall cohort**: N = 62,984 **Number of patients in analytical sample**: N = 46,632 • LIN: n = 23,316 • PIO: n = 23,316 **Mean age of analytical sample (SD)**: • LIN: 55.27 years (11.74) • PIO: 55.23 years (11.64) **Sex of analytical sample**: • LIN: 40.76% female • PIO: 40.38% female	• PIO • Second-generation • SUs	haemorrhagic stroke, unstable angina, or coronary revascularization) • hospitalization for acute MI, ischaemic or haemorrhagic stroke, • unstable angina • coronary revascularization **Mean follow-up (SD)**: • LIN: 0.77 years (0.71) • PIO: 0.73 years (0.68)
Spence *et al.* (2019)[40] **Canada (secondary analysis); United States of America (original trial)** **Funding Source**: • National Institute of Neurological Disorders and Stroke (U01NS044876)	Secondary analysis of clinical trial data from a double blinded placebo controlled RCT[11] (NCT00091949)	Patients with pre-diabetes (based on WHO/Canadian definition)[49] who were at least 40 years of age, had a TIA or stroke during the six months prior to randomization and had insulin resistance. The study included patients who had >80% adherence to the intervention, and ITT sample of all patients. **Adherent sample:** Number of patients, N=685 • PIO, n=300 • Placebo, n= 385 Mean age (SD): • PIO: 64.21 years (9.97)	**Intervention**: PIO (dose increasing from 15mg/day to 45 mg/day over 3 months, with patients given the highest tolerable dose) **Comparator**: Placebo	**Primary outcomes**: • Recurrent stroke/MI **Secondary outcomes**: • Stroke • Acute coronary syndrome • Stroke/MI/Hospitalization for HF **Safety outcomes**: • Bone fracture • Weight gain • Edema • All-cause mortality • Cancer **Follow-up**: Five years

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Placebo: 64.98 years (10.26) Sex: • PIO: 74% males • Placebo: 69.4% males **ITT sample:** Number of patients, N= 1,410 • PIO, n=709 • Placebo, n= 701 Mean age (SD): • PIO: 64.1 years (10.49) • Placebo:64.48 years (10.67) Sex: • PIO: 65.2% males Placebo: 63.6% males		

AE = adverse event; ALO = alogliptin; BMI = body mass index; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; HbA_{1c} = glycated hemoglobin A_{1c}; GLIC = gliclazide; GLIM = glimepiride; HF = heart failure; IQR = interquartile range; ITT = intention-to-treat; LIN = linagliptin; MET = metformin; MI = myocardial infarction; NR = not reported; OAD = oral antidiabetic drug; PIO = pioglitazone; ROS = rosiglitazone; SD = standard deviation; SIT = sitagliptin; SU = sulphonylurea; TIA = transient ischemic attack; TZD = thiazolidinedione; WHO = World Health Organisation.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Network Meta-Analyses Using AMSTAR 2[24] and the ISPOR Questionnaire[25]

Strengths	Limitations
Han and Qu (2020)[28]	
• The research question was clearly described and included the components of population, intervention, comparator and outcome • The rationale of included study designs was justified • Multiple databases, and the reference lists of the key studies were searched for eligible studies. The authors reported publication restrictions. Key search words were described • Study search and selection were done in duplicate • The ROB in the included primary studies were assessed using the Cochrane ROB tool. The primary studies were reported to have low risk of bias • MA of the included studies was conducted using inverse variance -weighted average using random effects model. Sensitivity analysis were performed "when required" for the end points percent change in hemoglobin A1c and LDL-cholesterol, omitting one study per MA; however, reasons for omitting those studies were not provided • Heterogeneity was assessed using I^2 index • Publication bias was explored using Begg's test (none found) • The authors reported no conflicts of interest	• It was unclear whether a review protocol was established *a priori* • Unclear whether data extraction was done in duplicate • A list of excluded studies and reason for exclusion was not provided • Study results for each of the included studies were not described. Details like dosing and number of patients in the PIO arm was not described • Possible confounders like baseline comorbidities in the included studies were not reported and addressed • Although authors listed the trial registration numbers for the included studies, they did not report on their individual funding source
Ida *et al.* (2020)[29]	
• Inclusion criteria for the review has a clear population, intervention, comparator, and outcomes • Multiple databases were searched for eligible studies. The authors reported publication restrictions. Key search words were described • The ROB of included studies was assessed using the Cochrane ROB tool • Study selection was performed in duplicate • Authors included a statement on their conflict of interest (none) • A network diagram of the included primary studies was reported • Authors used a random-effect NMA model • Statistical methods were used that preserved within-study randomization	• An *a priori* protocol was not reported for the review • Data extraction was not reported as being performed in duplicate • A list of excluded studies was not provided • There was no report of exploring publication bias (e.g., funnel plot); therefore, it is unclear if the direction or strength of the study findings are biased • Individual study results are not reported, therefore the accuracy of data reporting cannot be assessed • Authors did not report on the source of funding of their study, nor for the included studies • Systematic differences in treatment effect modifiers (e.g., BMI, age, number of comorbidities) were present between the different treatment comparisons. • The impact of important patient characteristics on treatment effects was not reported • Although heterogeneity was present, authors did not perform additional analyses (e.g., subgroup analysis, meta-regression) to explore its origins
Zhou *et al.* (2020)[30]	
• Inclusion criteria for the review had a clear population, intervention, comparator, and outcomes	• Authors did not report their source of funding, nor the source of funding of included studies • A list of excluded studies was not provided

Strengths	Limitations
• Multiple databases were searched for eligible studies. The authors reported publication restrictions. Key search words were described • Authors indicate that a protocol was devised; however, it was not registered • The choice of included study designs was justified • Authors used a comprehensive literature search strategy and they included additional references identified via grey literature • Study selection and data extraction were performed in duplicate • Authors assessed the ROB for individual studies (using the Cochrane ROB tool) and the risk of bias for most studies included in the MA was assessed as low • Heterogeneity was considered minimal and likely impact on the results was low • Funnel plots and Egger test were used for exploring publication bias • Authors declared no conflict of interest	
Alam *et al.* (2019)[31]	
• The research question was clearly described and included the components of population, intervention, comparator and outcome • A predefined protocol was registered in PROSPERO (CRD42018088073) • The rationale of included study designs was justified • Multiple databases, registries, and the reference lists of the key studies were searched for eligible studies. Authors also reported appropriate exclusion criteria. Articles were searched without restrictions of language and publication year. Key search words and strategy were described • Study search, selection, and data extraction were done independently by two reviewers • Characteristics of eligible studies were described in detail: including setting, population, doses, baseline characteristics and duration • The ROB in the included primary studies were assessed using the Cochrane ROB tool. The ROB in the included studies were reported in detail • MA was conducted using appropriate weighted technique using a random effects model. Heterogeneity was quantified using Chi^2 statistics and I^2 values • Authors performed sub-group analyses to investigate possible impact of ROB on pooled effects • Publication bias was assessed using funnel plot. No publication bias was observed • The authors reported no conflicts of interest	• A list of excluded studies and reason for exclusion was not provided • Study results for each of the included studies were not described • Possible sources of heterogeneity were investigated using Galbraith plot, and several subgroup analyses were conducted. Despite this, authors reported that the source of heterogeneity could not be identified; therefore, it is unclear if this may have influenced study results
Zuo *et al.* (2019)[32]	
• The research question was clearly described and included the components of population, intervention, comparator and outcome	• It was unclear whether a review protocol was established *a priori*

Strengths	Limitations
• The rationale of included study designs was justified • Multiple databases and the reference lists of the key studies were searched for eligible studies. Authors also reported publication restrictions. Key search words were described • Study search, selection and data extraction was done independently by two authors • Characteristics of eligible studies were described in detail: including setting, population, doses, baseline characteristics and duration • The ROB in the included primary studies were assessed using the Cochrane ROB tool. The primary studies were reported to have low to moderate ROB • MA was done when comparable outcome measures were reported by more than one study. Random or fixed effects were used based on the heterogeneity assessed using I^2 index and Chi ^{2} statistic • If I^2 >50%, sub-group analysis and sensitivity analysis were done. There was no significant heterogeneity in the results • Authors reported that publication bias was not evaluated because of the small number of included studies • The authors reported no conflicts of interest	• A list of excluded studies and reason for exclusion was not provided • Study results for each of the included studies were not described • Funding source for the studies included in the review were not reported

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; BMI = body mass index; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MA = meta-analysis; NMA = network meta-analysis; NR = not reported; PIO = pioglitazone; PROSPERO = International prospective register of systematic reviews; ROB = risk of bias.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[26]

Strengths	Limitations
Randomized Controlled Trials	
Kim *et al.* (2020)[33]	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described, and eligibility criteria given • The major findings of the study were described in a way that allowed verification of analyses and conclusions • Estimates of random variability were reported • Data analyses were planned at the outset • The time period over which patients were recruited was specified • Length of follow up was consistent between the intervention and comparator groups	• Although the characteristics of the patient included in the study are clearly described for the ITT population, the characteristics of the per protocol population or of the withdrawals and dropouts were not provided. • Authors did not describe how missing data were handled • This study was open label. This may have introduced observer biases for subjective outcomes • The study was multicenter (university hospitals), which may not be representative of the usual primary care setting for patients with type 2 diabetes • Although the allocation of patients to the treatments groups was randomized, authors did not indicate their randomization method • The main conclusions of the study were based on the analysis of treatment (i.e., per protocol) rather than ITT • Authors did not mention personal conflicts of interest • Although the study's funding source (Takeda Pharmaceutical Korea Company) was declared, it is unclear if it may have influenced the editorial independence of the authors

Strengths	Limitations
Khaloo *et al.* (2019)[34]	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described, and eligibility criteria given • The major findings of the study were described in a way that allows verification of analyses and conclusions • Estimates of random variability were reported • Data analyses were planned at the outset • The time period over which patients were recruited was specified • Analyses were done according to ITT • Missing data were handled using the "last observation carried forward" method	• There was no characterization of the patients who withdrew • There was no mention of any patients lost to follow-up, nor was there any mention of adjusting the analyses for different lengths of follow-ups • This study was open label. This may have introduced observer biases for subjective outcomes • This was a single center study and may not be representative of treatment available for most of the source population, therefore limiting generalisability • Adherence to the intervention was not mentioned, therefore it is unclear if group contamination may have occurred
Non-Randomized Studies	
Yen *et al.* (2020)[35]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Distribution of principal confounders were well balanced due to propensity score matching • No loss to follow up due to retrospective cohort design • Appropriate statistical analysis • Authors declared no conflict of interest	• Unclear if observers were blinded • Actual probability values were not reported • 15,218 patients from the analysis set could not be matched (non-PIO, n = 15,169; PIO, n = 49), which could impact generalizability • An important confounder missing from propensity score calculations was hemoglobin A_{1c} values which reflects disease severity
Yen *et al.* (2020)[36]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Distribution of principal confounders were well balanced due to propensity score matching • No loss to follow up due to retrospective cohort design • Appropriate statistical analysis • Authors declared no conflict of interest	• Unclear if observers were blinded • Actual probability values were not reported • 86,792 patients from the analysis set could not be matched (never used TZD, n = 69,031; used TZD, n = 17,761), which could impact generalizability • An important confounder missing from propensity score calculations was duration of disease
Cid Ruzafa *et al.* (2019)[37]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • No loss to follow up due to retrospective cohort design • The source population is provided (entire population from Denmark), and authors adequately describe how participants were selected • Authors adjusted their analyses to account for different lengths of follow-up between patients • Compliance with the intervention was reliable, decreasing the probability of misclassification • Main outcomes measures were valid and reliable (presence of a diagnostic code) • Patients in the different intervention and control groups were selected from the same population	• Main findings are not presented in a way that allows the reader to verify the major analyses and conclusions • Although estimates of the random variability in the data are offered for the main outcomes, authors presented interquartile range for normally distributed data (laboratory test results) instead of SD, standard error, or CIs • The effect of the main confounders was not investigated nor was adjustments made in the final analyses • Authors reported the study's funding source (i.e., the drug manufacturer) as well as personal conflicts of interest (e.g., employees of the drug manufacturer); however, they did not discuss how these were managed. It is unclear if this may have influenced editorial independence

Strengths	Limitations
Miao *et al.* (2019)[38]	
• The objective of the study, patient characteristics, interventions, comparators and outcomes were clearly described • A list of principal confounders was given and were compared across the groups and adjusted for during the analysis • Main findings of the study were clearly described as simple outcome data. Study also provided estimates of random variability using SDs and CIs as appropriate. Actual probability values were reported when the P value was > 0.001 • No loss to follow up due to retrospective cohort design • The statistical analyses conducted were appropriate and predefined • Patients in the different intervention and control groups were selected from the same population over the same period of time • Potential confounders were adjusted for in the comparative analysis • Study authors had no conflict of interest to declare	• Participants and outcome assessors were not blinded • The baseline characteristics of the groups were different for potential confounders • An important confounder missing from propensity score calculations was hemoglobin A_{1c} values which reflects disease severity • The duration of exposure to the intervention and comparators were not similar • No other AEs were measured
Patorno *et al.* (2019)[39]	
• The objectives, patient characteristics, interventions, controls, and outcomes were well described • Authors reported the study's funding sources and declared that editorial independence was retained • Authors adjusted their analyses for different lengths of follow-up • Propensity score matching was utilized to minimize the influence of confounders between groups and no important confounder appeared to be missing from propensity score calculations • Main outcome measures used were valid and reliable • Patients from the intervention and comparator groups were recruited from the same population and over the same period of time	• Although the characteristics of the patient included in the study are clearly described, the characteristics of patient withdrawals and dropouts was not provided • Although patients were representative of the entire population of their dataset, they may not be representative of the type 2 diabetes population at large. For instance, uninsured individuals would not be represented in this study and this would limit its generalizability. • Since this is a database study, the patient's adherence to the intervention can not be fully ascertained. • No statistical adjustments were made for multiple testing over time • Authors reported the study's funding source (e.g., drug manufacturer) as well as personal conflicts of interest (e.g., employees of drug manufacturer); however, they did not discuss how these were managed. It is unclear if this may have influenced editorial independence • 236,108 patients initiating LIN or PIO from the analysis set could not be matched, which could impact generalizability.
Spence *et al.* (2019)[40]	
• The objective of the study, patient characteristics, interventions, comparators and outcomes were clearly described • The primary and secondary outcomes were clearly defined in the methods section • Potential confounders (e.g., smoking status, blood pressure, BMI) were listed and compared across treatment and placebo groups.	• Post-hoc analysis of a subgroup of patients enrolled in a previous RCT. • Patients lost to follow up were not clearly described • The treatment of missing data in the ITT analysis was not reported

Strengths	Limitations
• Main findings of the study are clearly described as simple outcome data. Study also provided estimates of random variability using SD and CIs as appropriate • Important AEs were reported. Actual probability values were reported when the P value was > 0.001 • The study was an international multicenter trial and was representative of the population of interest • The statistical analyses of the secondary analysis were appropriate and predefined with a statistical analysis plan • Adherence was formally assessed using pill counts • An ITT analysis was done	

AE = adverse event; BMI = body mass index; CI = confidence interval; ITT = intention-to-treat; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews, Meta-Analyses, and Network Meta-Analyses

Main study findings	Authors' conclusion
Han and Qu (2020)[28]	

Mean difference in percent change from baseline; MD (95% CI)
• **Serum creatinine, (**MA of two primary studies)[52,53]
  ○ ALE 150 mcg vs. PIO: 9.35% (5.32 to 13.38)
  ○ P value < 0.00001; I^2 = 0%
• **eGFR,** (MA of three primary studies)[52-54]
  ○ ALE 150 mcg vs. PIO: –13.30% (–20.68 to –5.92)
  ○ P value < 0.0004; I^2 = 82%
• **Body weight,** (MA of two primary studies)[52,53]
  ○ ALE 150 mcg vs. PIO: –0.32% (–1.11 to 0.47)
  ○ P value = 0.42; I^2 = 79%
 	
Odds ratios for events between ALE and PIO; OR (95% CI)
• **Hypoglycemia,** (MA of three primary studies)[52-54]
  ○ ALE 150 mcg vs. PIO: 1.82 (0.66 to 4.97)
  ○ P value = 0.24; I^2 = 26%
• **Edema,** (MA of three primary studies)[52-54]
  ○ ALE 150 mcg vs. PIO: 0.94 (0.30 to 2.91)
  ○ P value = 0.91; I^2 = 75%
 	
Number of malignancy events (not defined) reported:
• ALE: 5/945
• Placebo: 0/997
• PIO: 1/148
	"[..] efficacy end points are found to be associated with serious adverse side effects. The higher incidences of renal dysfunction, hypoglycemia, edema, and increased body weight were consistent in many studies. Moreover, in high CVD risk patients, the risk of heart failure, gut hemorrhage, and bone fractures was also higher with [ALE] treatment."[28] (p. 357)

Ida *et al.* (2020)[29]	

SMDs between PIO and various pairwise contrasts for the value obtained by dividing peak early diastolic transmitral flow velocity by the mitral annular early diastolic velocity, via tissue Doppler echocardiography; SMD (95% CI):
 	
• **Direct comparison**, with PIO as the reference (negative values indicate worsening left ventricular diastolic function relative to the comparator):
  ○ ROS: –0.19 (–0.81 to 0.43)
  ○ Conventional treatment (not defined): 0.03 (–0.41 to 0.46)
 	
• **NMA** of eight primary studies,[41-48] with PIO as the reference (negative values indicate worsening left ventricular diastolic function relative to the comparator):
  ○ Placebo: –0.44 (–1.24 to 0.36)
  ○ LIR: –1.38 (–2.11 to –0.65)
  ○ EXE: –1.07 (–2.23 to 0.09)
  ○ SIT: –0.54 (–1.11 to 0.04)
  ○ LIN: –0.47 (–1.21 to 0.28)
  ○ Voglibose: 0.62 (–0.10 to 1.34)
  ○ GLIM: 0.17 (–0.74 to 1.09)
	"The results showed that compared with placebo and OADs, only [LIR] significantly improved left ventricular diastolic function."[29] (p. 7)

Main study findings	Authors' conclusion
Zhou *et al.* (2020)[30]	

Relative risks of events, for PIO among patients <u>with or at high risk of type 2 diabetes</u>, <u>without</u> a history of established atherosclerotic CVD at baseline; RR (95% CI):
• **Overall** effect on major adverse cardiovascular events, non-fatal MI, and non-fatal stroke (MA of six primary studies)[55-60]
  ○ 0.90 (0.70 to 1.16)
  ○ I^2 = 0.0%
• **Major adverse cardiovascular events** (i.e., the composite of non-fatal MI, non-fatal stroke, and cardiovascular death), (MA of six primary studies)[55-60]
  ○ 0.94 (67 to 1.31)
  ○ I^2 = 0.0%
• **Non-fatal MI**, (MA of five primary studies)[55-57,59,60]
  ○ 0.93 (0.57 to 1.52)
  ○ I^2 = 0.0%
• **Non-fatal stroke**, (MA of four primary studies)[55-57,59]
  ○ 0.76 (0.42 to 1.36)
  ○ I^2 = 0.0%
• **Hospitalization for HF**, (MA of four primary studies)[55,57,59,60]
  ○ 1.51 (0.78 to 2.92)
  ○ I^2 = 0.0%
• **Cardiovascular death**, (MA of three primary studies)[55,58,60]
  ○ 1.79 (0.66 to 4.88)
  ○ I^2 = 0.0%
• **All-cause mortality**, (MA of six primary studies)[55,56,58-61]
  ○ 1.05 (0.74 to 1.51)
  ○ I^2 = 0.0%
 	
Relative risks of events, for PIO among patients with <u>type 2 diabetes</u> at baseline, <u>without</u> a history of established atherosclerotic CVD as baseline; RR (95% CI):
• **Major adverse cardiovascular events** (i.e., the composite of non-fatal MI, non-fatal stroke, and cardiovascular death), (MA of five primary studies)[55,56,58-60]
  ○ 0.92 (0.68 to 1.30)
  ○ I^2 = 0.0%
• **Non-fatal MI**, (MA of four primary studies)[55,56,59,60]
  ○ 0.90 (0.54 to 1.49)
  ○ I^2 = 0.0%
• **Non-fatal stroke**, (MA of three primary studies)[55,56,59]
  ○ 0.76 (0.42 to 1.36)
  ○ I^2 = 0.0%
• **Hospitalization for HF**, (MA of three primary studies)[55,59,60]
  ○ 1.55 (0.78 to 3.05)
  ○ I^2 = 0.0%
• **Cardiovascular death** (MA of three primary studies)[55,58,60]
  ○ 1.79 (0.66 to 4.88)
  ○ I^2 = 0.0%
• **All-cause mortality**, (MA of seven primary studies)[55,56,58-62]
  ○ 1.07 (0.75 to 1.52)
  ○ I^2 = 0.0%
 	
Relative risk of events, for PIO among patients with <u>pre-diabetes</u> at baseline, <u>without</u> a history of established atherosclerotic CVD as baseline; RR (95% CI):
• **Major adverse cardiovascular events** (i.e., the composite of non-fatal MI, non-fatal stroke, and cardiovascular death), (one primary studies)[57]
	"In conclusion, [PIO] should be considered in patients with or at high risk of [type 2 diabetes] for the prevention of cardiovascular endpoints, especially in patients with a history of established CVD who might benefit the most. Robust reductions in progression of renal disease are seen regardless of baseline renal function category. Nonetheless, [PIO] should be cautiously used in [type 2 diabetes] patients with symptomatic HF."[30] (p. 1,679)

Main study findings	Authors' conclusion
○ 1.97 (0.18 to 21.65) • **Non-fatal MI**, (one primary study)[57] ○ 1.97 (0.18 to 21.65) • **Hospitalization for HF**, (one primary study)[57] ○ 0.99 (0.06 to 15.70) **Relative risk of events, for PIO among patients with pre-diabetes at baseline, with a history of established atherosclerotic CVD at baseline; RR (95% CI)**: • **Major adverse cardiovascular events** (i.e., the composite of non-fatal MI, non-fatal stroke, and cardiovascular death), (MA of two primary studies)[11,63] ○ 0.75 (0.63 to 0.91) ○ I^2 = 26.3% • **Non-fatal MI**, (one primary study)[11] ○ 0.70 (0.48 to 1.02) • **Non-fatal stroke**, (MA of two primary studies)[11,63] ○ 0.81 (0.64 to 1.02) ○ I^2 = 37.0% • **Hospitalization for HF**, (one primary study)[11] ○ 1.21 (0.81 to 1.82)	
Alam *et al.* (2019)[31]	
Mean difference in change from baseline for blood pressure (MA of three primary studies)[64-66]; MD (95% CI) • Systolic BP: ○ PIO vs. comparator: –1.76 (–8.24 to 4.72) ○ P value = 0.59; I^2 = 67% • Diastolic BP: ○ PIO vs. comparator: –0.27 (–4.14 to 3.61) ○ P value = 0.89; I^2 = 59% • Total: ○ PIO vs. comparator: –1.05 (–4.29 to 2.19) ○ P value = 0.52; I^2 = 60% **Relative risk of AEs; RR (95% CI):** • **Peripheral edema**, (MA of seven primary studies)[67-73] ○ PIO vs. comparator: 2.21 (1.48 to 3.31) ○ P value = 0.0001; I^2 = 0% • **Hypoglycemia**, (MA of six primary studies)[67-71,74] ○ PIO vs. comparator: 0.51 (0.33 to 0.80) ○ P value = 0.003; I^2 = 0% • **Upper respiratory tract infections**, (MA of five primary studies)[67,68,71-73] ○ PIO vs. comparator: 1.09 (0.67 to 1.76) ○ P value = 0.74; I^2 = 0% • **Nervous system disorders**, (MA of five primary studies)[67,68,71,72] ○ PIO vs. comparator: 0.89 (0.56 to 1.40) ○ P value = 0.61; I^2 = 0% • **Diarrhea**, (MA of three primary studies)[67,71,72] ○ PIO vs. comparator: 0.56 (0.12 to 2.60) ○ P value = 0.46; I^2 = 0% • **Musculoskeletal and connective tissue disorders**, (MA of two primary studies)[71,73] ○ PIO vs. comparator: 1.49 (0.19 to 11.69) ○ P value = 0.71; I^2 = 39% • **Cardiovascular events**, (MA of three primary studies)[70,72,73] ○ PIO vs. comparator: 1.47 (0.42 to 5.17)	"Based on the findings of this [MA], we concluded that [PIO] monotherapy showed overall favourable risk-benefit balance. Specifically, [PIO] is an effective treatment option in managing [type 2 diabetes] patients due to its potential of ameliorating hyperglycaemia, adverse lipid metabolism and BP [..] Since hypoglycaemia is recognized as a potential cause of death, particularly due to cerebral damage, the low hypoglycaemic risk of [PIO] over other [antidiabetic] drugs will be advantageous in preventing mortality in [type 2 diabetes] patients. However, development of oedema and [body weight] gain due to [PIO] cannot be ignored. […] Whether [PIO] increases the risk of bladder cancer in [type 2 diabetes] patients remains unclear, but no signal for this [AE] was observed in the [MA]. Since [PIO] is the only insulin sensitiser among existing [antidiabetic] drugs and is the only TZD currently in use, we believe that the evidence from this [MA]

Main study findings	Authors' conclusion
○ P value = 0.55; I^2 = 0% • **Vascular disorders**, (MA of two primary studies)[72,73] ○ PIO vs. comparator: 0.33 (0.01 to 8.01) ○ P value = 0.49; I^2 = NA, (only one study contributed data) **Number of AEs and associated RR with PIO monotherapy vs. comparator monotherapies**: • **Asthenia** (n/N), (one primary study)[68] ○ PIO: 2/161 ○ Comparator: 3/153 ○ RR = 0.36; 95% CI, 0.11 to 3.74; P value = 0.61 • **Abnormal liver function parameters** (n/N), (one primary study)[70] ○ PIO: 5/140 ○ Comparator: 5/135 ○ RR = 0.96; 95% CI,0.29 to 3.26; P value = 0.95 • **Vomiting** (n/N), (one primary study)[67] ○ PIO: 1/54 ○ Comparator: 0/52 ○ RR = 2.89; 95% CI, 0.12 to 69.40); P value = 0.51 • **Nausea** (n/N), (one primary study)[67] ○ PIO: 0/54 ○ Comparator: 1/52 ○ RR = 0.32; 95% CI, 0.01 to 7.71; P value = 0.48 • **Breast cancer** (n/N), (one primary study)[67] ○ PIO: 0/54 ○ Comparator: 1/52 ○ RR = 0.32; 95% CI, 0.01 to 7.71; P value = 0.48 • **Colon cancer** (n/N), (one primary study)[73] ○ PIO: 1/163 ○ Comparator: 0/164 ○ RR = 3.02; 95% CI, 0.12 to 73.55; P value = 0.50 • **Non-cardiac chest pain** (n/N), (one primary study)[73] ○ PIO: 1/163 ○ Comparator: 0/164 ○ RR = 3.02; 95% CI, 0.12 to 73.55; P value = 0.50	support the ongoing role of [PIO] in managing patients with [type 2 diabetes]" [31] (p. 11)
Zuo *et al.* (2019)[32]	
Odds ratio of fractures, for PIO vs. placebo; OR (95% CI), (MA of two primary studies)[75,76] • PIO vs. placebo: 1.96 (0.47 to 8.10); P value = 0.35; I^2 = 5% **Mean difference in the change from baseline of BMD of the lumbar spine for PIO 30 mg/day, followed by 45 mg/day one month later; MD (95% CI),** (MA of two primary studies)[51,75] • PIO vs. placebo: –1.08 (–2.04 to 0.13), P value = 0.03 (as reported in the article); I^2 = 0%	"Our [MA] of RCTs elucidated that compared with placebo, [PIO] therapy reduced BMD and serum PTH levels and increased fat mass and BMI with no differences in serum BSAP and 25-OHD levels or fracture rates; 30 mg/d [PIO] was sufficient to reduce BMD of the lumbar spine. For patients receiving [PIO] therapy, it may be necessary to take action to improve their bone health." [32] (p. 3,595)

25-OHD = 25-hydroxyvitamin D; AE = adverse event; ALE = aleglitazar; BMD = bone mineral density; BMI = body mass index; BP = blood pressure; BSAP = bone-specific alkaline Phosphatase; CI = confidence interval; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; EXE = exenatide; GLIM = glimepiride; HDL = high density lipoprotein; HF = heart failure; LDL = low density lipoprotein; LIN = linagliptin; LIR = liraglutide; MA = meta-analysis; MD = mean difference; MI = Myocardial Infraction; NA = not applicable; NR = not reported; OAD = oral antidiabetic

drug; OR = odds ratio; PIO = pioglitazone; PTH = parathyroid hormone; RCT = randomized controlled trials; ROS = rosiglitazone; RR = relative risk; SIT = sitagliptin; SMD = standardised mean difference; TZD = thiazolidinedione.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Randomized Controlled Trials	
Kim *et al.* (2020)[33]	

Number of withdrawals from study due to AEs or serious AEs; n/N:
• PIO: 2/69
• GLIM: 0/66
 	
N**umber of patients reporting an AE; n/N (%):**
• **At least one AE**, occurring in a frequency of ≥ 2% in either treatment group
  ○ PIO: 64/69 (92.8)
  ○ GLIM: 58/66 (87.9)
  ○ P value = 0.504
• **Hypoglycemia**
  ○ PIO: 3/69 (4.4)
  ○ GLIM: 16/66 (24.2)
  ○ P value = 0.002
• **Upper respiratory infection**
  ○ PIO: 10/69 (14.5)
  ○ GLIM: 6/66 (9.1)
  ○ P value = 0.481
• **Dizziness**
  ○ PIO: 5/69 (7.3)
  ○ GLIM: 5/66 (7.6)
  ○ P value = 1.000
• **Headache**
  ○ PIO: 3/69 (4.4)
  ○ GLIM: 2/66 (3.0)
  ○ P value = 1.000
• **Weight gain**
  ○ PIO: 4/69 (5.8)
  ○ GLIM: 0/66
  ○ P value = 0.120
• **Dyspepsia**
  ○ PIO: 0/69
  ○ GLIM: 4/66 (6.1)
  ○ P value = 0.055
• **Acute diarrhea**
  ○ PIO: 2/69 (2.9)
  ○ GLIM: 1/66 (1.5)
  ○ P value = 1.000
• **Itching**
  ○ PIO: 3/69 (4.4)
  ○ GLIM: 0/66
  ○ P value = 0.245
• **Edema**
  ○ PIO: 3/69 (4.4)
  ○ GLIM: 0/66
	"In conclusion, the addition of [PIO] to [MET] plus [ALO] for patients with inadequately controlled [type 2 diabetes] resulted in a similar decrease in HbA1c levels to that induced by the addition of [GLIM]. However, in addition to the comparable level of glycemic control, [PIO] provided several better outcomes (improvements in lipid control, insulin resistance, and hypoglycemia risk). Therefore, [PIO] can be used effectively and safely as a third-line agent for managing patients whose [type 2 diabetes] is not adequately controlled using [MET] plus a DPP-4 inhibitor."[33] (p.75)

Main study findings	Authors' conclusion
○ P value = 0.245 • **Abdominal pain** ○ PIO: 2/69 (2.9) ○ GLIM: 0/66 ○ P value = 0.497 • **Ache** ○ PIO: 2/69 (2.9) ○ GLIM: 0/66 ○ P value = 0.497 • **Myalgia** ○ PIO: 2/69 (2.9) ○ GLIM: 0/66 ○ P value = 0.497 • **Palpitation** ○ PIO: 0/69 ○ GLIM: 2/66 (3.0) ○ P value = 0.237 • **Fractures** ○ PIO: 2/69 (2.9), (one cuneiform bone of the foot and one intertrochanteric section of femur after falling) ○ GLIM: 0/66 ○ P value = 1.000 • **Acute pyelonephritis** ○ PIO: 1/69 (1.5) ○ GLIM: 0/66 ○ P value = 1.00 **AEs that were rated as being possibly/probably/definitely related to the study drug; n/N (%)**: • **Adverse drug reaction (not defined)** ○ PIO: 8 (11.6) ○ GLIM: 23 (34.9) ○ P value = 0.003 • **Hypoglycemia** ○ PIO: 1 (1.5) ○ GLIM: 14 (21.2) ○ P value = 0.001 • **Dizziness** ○ PIO: 1 (1.5) ○ GLIM: 3 (4.6) ○ P value = 0.358 • **Weight gain** ○ PIO: 2 (2.9) ○ GLIM: 0 ○ P value = 0.497 • **Edema** ○ PIO: 2 (2.9) ○ GLIM: 0 ○ P value = 0.497	

Main study findings	Authors' conclusion
Khaloo *et al.* (2019)[34]	

Early study discontinuation; n/N:
• PIO: 13/125
  ○ Weight gain: 9/125
  ○ Edema: 6/125
• SIT: 15/125
  ○ Gastrointestinal upset: 9/125
  ○ Cost: 8/125
 	
Mean changes from baseline to week 52
• Weight; kg (SD):
  ○ PIO: 0.9 (1.5)
  ○ SIT: –0.5 (1.1)
  ○ P value < 0.001
• BMI; kg/m^2 (SD):
  ○ PIO: 2.3 (3.8)
  ○ SIT: –1.2 (2.8)
• Waist circumferences; cm (SD):
  ○ PIO: –6.6 (85.8)
  ○ SIT: –0.1 (4.3)
• Hip circumference; cm (SD):
  ○ PIO: 2 (5.3)
  ○ SIT: –0.7 (3.1)
  ○ P value < 0.001
• Systolic BP; mmHg (SD):
  ○ PIO: 2.4 (14.6)
  ○ SIT: 3 (15.4)
  ○ P value < 0.001
• Diastolic BP; mmHg (SD):
  ○ PIO: –0.6 (7.8)
  ○ SIT: –0.6 (8.9)
	"There were also some differences regarding body weight and SBP in favor of [SIT]. […] The current study confirmed that both [SIT] and [PIO] are effective treatment options in patients treated with [MET] and SU who require more intensive therapy."[34] (p. 856)

Non-Randomized Studies	
Yen *et al.* (2020)[35]	
All-Cause Mortality incidence; rate per 1,000 person-years: • Non-PIO: 30.26 • PIO: 15.02 • Adjusted HR (for sex, age, and baseline comorbidities): 0.47 (0.38 to 0.58), P value < 0.001 **CV death incidence; rate per 1,000 person-years:** • Non-PIO: 7.23 • PIO: 4.94 • Adjusted HR (for sex, age and baseline comorbidities): 0.78 (0.51 to 1.19) **Non-CV death incidence; rate per 1,000 person-years:** • Non-PIO: 19.74 • PIO: 9.11 • Adjusted HR (for sex, age and baseline comorbidities): 0.50 (0.38 to 0.66), P value < 0.001	"In conclusion, our study demonstrated that the combination of insulin and [PIO] lowered the all-cause mortality risk, and this combination therapy exerted beneficial effects on non-CV deaths compared with nonusers. [PIO] might be a beneficial complementary agent for insulin treatment."[35] (p. 408)

Main study findings	Authors' conclusion
Hospitalized CAD incidence; rate per 1,000 person-years: • Non-PIO: 14.09 • PIO: 12.10 • Adjusted HR (for sex, age and baseline comorbidities): 0.84 (0.64 to 1.11) **Hospitalized stroke incidence; rate per 1,000 person-years:** • Non-PIO: 15.78 • PIO: 15.72 • Adjusted HR (for sex, age and baseline comorbidities): 0.99 (0.77 to 1.28) **HF incidence; rate per 1,000 person-years:** • Non-PIO: 19.71 • PIO: 19.15 • Adjusted HR (for sex, age and baseline comorbidities): 0.99 (0.79 to 1.25)	
Yen *et al.* (2020)[36]	
Cirrhosis incidence; rate per 1,000 person-years: • PIO: 0.84, adjusted HR (for sex, age and baseline comorbidities): 0.35 (0.15 to 0.85), P value < 0.05 • Non-TZD: 1.95	"Our nationwide cohort study revealed that compared with TZD non-use, TZD use in type 2 diabetes could significantly lower the risk of cirrhosis."[36] (p. 1,096)
Cid Ruzafa *et al.* (2019)[37]	
Diagnoses of bladder cancer during follow-up period: • Incident PIO: zero • Prevalent PIO: less than five **Uninvestigated macroscopic haematuria during follow-up period:** • Incident PIO: zero • Prevalent PIO: zero **HF during follow-up period:** • Incident PIO: less than five out of 77 patients; incidence rate of nine per 1,000 person-years (95% CI, 2 to 34) • Prevalent PIO: less than five out of 133 patients without a history of HF; incidence rate of two per 1,000 person-years (95% CI, 0 to 13)	"In summary, based on the small numbers of [PIO] users in Denmark over a 4.4-year period, risk estimates of [bladder cancer] or HF or haematuria from exposure to [PIO] treatment are small and imprecise because of low occurrence."[37] (p. 138)
Miao *et al.* (2019)[38]	
MI ▪ Events; n (%) ○ Non-PIO: 256 (0.40%) ○ PIO: 30 (0.36%) ▪ Incidence; rate per 1,000 person-years: ○ Non-PIO = 2.55 ○ PIO = 1.24 ○ Adjusted RR (for sex and age): 0.55; 95% CI, 0.37 to 0.80; P value = 0.002	"The study findings also validated the favorable effects of [PIO] on the risk of MI in a provincial medical institution patient population, which may be helpful for personalized decision making in [type 2 diabetes] treatment."[38] (p. 689)

Main study findings	Authors' conclusion
○ Multivariable RR: 0.61; 95% CI, 0.42 to 0.90; P value = 0.012 **HF** ▪ Events; n (%) ○ Non-PIO: 387 (0.61%) ○ PIO: 59 (0.72%) ▪ Incidence; rate per 1,000 person-years: ○ Non-PIO = 3.86 ○ PIO = 2.44 ○ Adjusted RR (for sex and age): 0.72; 95% CI, 0.55 to 0.95; P value = 0.021 ○ Multivariable RR: 0.82; 95% CI, 0.62 to 1.08; P value = 0.150 **Stroke** ▪ Events; n (%) ○ Non-PIO: 52 (0.08%) ○ PIO: 5 (0.06%) ▪ Incidence; rate per 1,000 person-years: ○ Non-PIO = 0.52 ○ PIO = 0.21 ○ Adjusted RR (for sex and age): 0.46; 95% CI, 0.18 to 1.15; P value = 0.096 ○ Multivariable RR: 0.47; 95% CI, 0.18 to 1.18; P value = 0.106	
Patorno *et al.* (2019)[39]	
Outcomes at last follow-up: **Composite CV (hospitalization for acute MI, ischaemic or haemorrhagic stroke, unstable angina, or coronary revascularization)** • LIN: ○ 291 events ○ 16.3 per 1,000 person-years (95% CI, 14.51 to 18.26) ○ HR: 0.98 (95% CI, 0.84 to 1.15) • PIO: ○ 286 events ○ 16.8 per 1,000 person-years (95% CI, 14.97 to 18.88) ○ HR: reference **MI** • LIN: ○ 113 events ○ 6.29 per 1,000 person-years (95% CI, 5.23 to 7.56) ○ HR: 0.89 (95% CI, 0.69 to 1.15) • PIO: ○ 121 events ○ 7.07 per 1,000 person-years (95% CI, 5.92 to 8.45) ○ HR: reference **Stroke** • LIN: ○ 86 events	"In conclusion, in a prespecified analysis from a 5-year monitoring programme, involving >100 000 commercially insured patients with [type 2 diabetes], [LIN] had similar CV safety compared to other DPP-4 inhibitors and [PIO], and was associated with a reduced CV risk compared to sulphonylureas."[39] (p. 1,834)

Main study findings	Authors' conclusion
○ 4.78 per 1,000 person-years (95% CI, 3.87 to 5.90) ○ HR: 1.07 (95% CI, 0.79 to 1.46) • PIO: ○ 77 events ○ 4.50 per 1,000 person-years (95% CI, 3.60 to 5.63) ○ HR: reference **Unstable angina** • LIN: ○ 74 events ○ 4.11 per 1,000 person-years (95% CI, 3.27 to 5.16) ○ HR: 0.84 (95% CI, 0.61 to 1.15) • PIO: ○ 84 events ○ 4.91 per 1,000 person-years (95% CI, 3.96 to 6.08) ○ HR: reference **Coronary revascularization** • LIN: ○ 142 events ○ 7.91 per 1,000 person-years (95% CI, 6.71 to 9.32) ○ HR: 0.98 (95% CI, 0.78 to 1.24) • PIO: ○ 138 events ○ 8.08 per 1,000 person-years (95% CI, 6.84 to 9.55) ○ HR: reference	
Spence *et al.* (2019)[40]	
Relevant outcome rates and associated HR for patients with pre-diabetes (based on the WHO/Diabetes Canada criteria)[49] Number of patients: Adherence ≥ 80% sample: PIO = 300; Placebo = 385 ITT Sample: PIO = 709; Placebo = 701 • **Stroke or MI; proportion %:** ○ Adherence ≥ 80% sample: ▪ PIO: 8.3% ▪ Placebo: 11.7% ▪ HR = 0.68; 95% CI, 0.42 to 1.12; P value = 0.13 ○ ITT sample: ▪ PIO: 9.6% ▪ Placebo: 13.7% ▪ HR = 0.70; 95% CI, 0.51 to 0.95; P value = 0.02 • **Stroke; proportion %:** ○ Adherence ≥ 80% sample: ▪ PIO: 6.0%	"[PIO] appears to reduce the risk of recurrent stroke or MI, recurrent stroke, acute coronary syndrome, and diabetes in patients with insulin resistance and prior stroke / [TIA] and prediabetes, particularly in individuals who adhere to therapy. These benefits appear to outweigh the risks of fracture and fluid retention."[40] (p. 12)

Main study findings	Authors' conclusion
▪ Placebo: 8.8% ▪ HR = 0.66; 95% CI, 0.37 to 1.16; P value = 0.15 ○ ITT sample: ▪ PIO: 7.2% ▪ Placebo: 10.6% ▪ HR = 0.68; 95% CI, 0.48 to 0.97; P value = 0.03 • **Acute coronary syndrome; proportion %:** ○ Adherence ≥ 80% sample: ▪ PIO: 4.0% ▪ Placebo: 4.9% ▪ HR = 0.78; 95% CI, 0.38 to 1.61; P value = 0.5 ○ ITT sample: ▪ PIO: 4.1% ▪ Placebo: 5.4% ▪ HR = 0.76; 95% CI, 0.47 to 1.23; P value = 0.26 • **Stroke/MI/Hospitalized HF; proportion %:** ○ Adherence ≥ 80% sample: ▪ PIO: 9.0% ▪ Placebo: 11.7% ▪ HR = 0.74; 95% CI, 0.46 to 1.19; P value = 0.21 ○ ITT sample: ▪ PIO: 11.9% ▪ Placebo: 14.8% ▪ HR = 0.80; 95% CI, 0.60 to 1.07; P value = 0.13 **Number of AEs and associated NNH for patients with pre-diabetes (based on the ADA criteria)[50]** Number of patients: Adherence ≥ 80% sample: PIO = 644; Placebo = 810 ITT Sample: PIO = 1456; Placebo = 1429 ▪ **All-cause mortality; n (%):** ○ Adherence ≥ 80% sample ▪ PIO: 42 (6.5) ▪ Placebo: 57 (7.0) ▪ P value = 0.70 ▪ NNH: NA ○ ITT sample ▪ PIO: 108 (7.4) ▪ Placebo: 111 (7.8) ▪ P value = 0.72 ▪ NNH: NA ▪ **Hospitalization; n (%):** ○ Adherence ≥ 80% sample ▪ PIO: 262 (40.7) ▪ Placebo: 353 (43.6) ▪ P value = 0.27 ▪ NNH: NA	

Main study findings	Authors' conclusion
○ ITT sample ▪ PIO: 674 (46.3) ▪ Placebo: 703 (49.2) ▪ P value = 0.12 ▪ NNH: NA ▪ **Incident cancer; n (%):** ○ Adherence ≥ 80% sample ▪ PIO:33 (5.1) ▪ Placebo: 53 (6.5) ▪ P value = 0.25 ▪ NNH: NA ○ ITT sample ▪ PIO: 99 (6.8) ▪ Placebo: 110 (7.7) ▪ P value = 0.35 ▪ NNH: NA ▪ **Bone fracture (causing hospitalization, surgery or procedure); n (%):** ○ Adherence ≥ 80% sample ▪ PIO: 23 (3.6) ▪ Placebo: 23 (2.8) ▪ P value = 0.43 ▪ NNH: NA ○ ITT sample ▪ PIO: 71 (4.9) ▪ Placebo: 46 (3.2) ▪ P value = 0.02 ▪ NNH: 59 ▪ **HF (causing hospitalization or death); n (%):** ○ Adherence ≥ 80% sample ▪ PIO: 4 (0.6) ▪ Placebo: 2 (0.2) ▪ P value = 0.27 ▪ NNH: NA ○ ITT sample ▪ PIO: 39 (2.7) ▪ Placebo: 31 (2.2) ▪ P value = 0.37 ▪ NNH: NA ▪ **Weight gain (Weight increase of 10% of more from baseline); n (%):** ○ Adherence ≥ 80% sample ▪ PIO: 192 (29.8) ▪ Placebo: 97 (12) ▪ P value < 0.001 ▪ NNH: 6 ○ ITT sample ▪ PIO: 382 (26.2) ▪ Placebo: 182 (12.7) ▪ P value < 0.001 ▪ NNH: 7 ▪ **Edema (self-reported new or worsening); n (%):** ○ Adherence ≥ 80% sample ▪ PIO: 188 (29.2) ▪ Placebo:175 (21.6)	

Main study findings	Authors' conclusion
▪ P value < 0.001 ▪ NNH: 13 ○ ITT sample ▪ PIO: 541 (37.2) ▪ Placebo: 360 (25.2) ▪ P value < 0.001 ▪ NNH: 8	

ADA = American Diabetes Association; AE = adverse event; ALO = alogliptin; BP = blood pressure; CAD = coronary artery disease; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; GLIM = glimepiride; HbA_{1c} = glycated hemoglobin A_{1c}; HR = hazard ratio; ITT = intention-to-treat; LIN = linagliptin; MET = metformin; MI = myocardial infarction; NA = not applicable; NNH = number needed to harm; NR = not reported; PIO = pioglitazone; ROS = rosiglitazone; RR = relative risk; SBP = systolic blood pressure; SIT = sitagliptin; SU = sulphonylurea; TIA = transient ischemic attack; TZD = thiazolidinedione; WHO = World Health Organisation.

Appendix 5: Further Information

Additional References

Case reports

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