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Efficacy of metformin on glycemic control and weight in drug-naïve type 2 diabetes mellitus patients: a systematic review and meta-analysis of placebo-controlled randomized trials

Running title: Metformin in first-line therapy of T2DM

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Abstract

Aim of the study

Metformin is recommended as the first-line treatment of type 2 diabetes mellitus. Despite its common use, few studies have been conducted to precisely measure the efficacy of metformin versus placebo as a first-line treatment. This study aims to assess the precise effects of metformin monotherapy on glycemic control and weight in drug-naive patients with type 2 diabetes mellitus.

Methods

Medline and Cochrane databases were searched until March 19, 2016 to perform a systematic review and meta-analysis of placebo-controlled randomized trials evaluating metformin monotherapy in drug-naive patients with type 2 diabetes mellitus. Assessed outcomes include glycemic control (fasting plasma glucose, glycosated hemoglobin) and weight.

Results

Overall, 16 studies (1140 patients) were selected. Compared to placebo, metformin monotherapy was associated with decreased glycosated hemoglobin by 0.95% at 3 months (95% CI: 0.50 to 1.39, $I^2=87\%$) and 1.32% at 6 months (95% CI: 1.01 to 1.62, $I^2=71\%$), and decreased fasting plasma glucose by 1.92 mmol/L at 1 month (95% CI: 0.11 to 3.74, $I^2=88\%$), 1.79 mmol/L at 3 months (95% CI: 0.92 to 2.66, $I^2=88\%$) and 2.14 mmol/L at 6 months (95% CI: 1.17 to 3.12, $I^2=82\%$). No significant difference was demonstrated for the comparisons of weight due to relatively small number of studies retrieved from the literature resulting in insufficient statistical power.

Conclusion

This study provides the precise effects of metformin monotherapy regarding the decreases in fasting plasma glucose and glycosated hemoglobin that physician can expected in drug-naive patients with type 2 diabetes mellitus. No evidence was found for the effects on weight.

Keywords:

Type 2 diabetes mellitus; metformin; meta-analysis; randomized controlled trials

Abbreviations

95% CI: 95% confidence interval

BMI: Body Mass Index

FPG: Fasting Plasma Glucose

HbA1c: glycosated hemoglobin

LOCF: Last Observation Carried Forward

M1, M3, M6: one month, 3 months, 6 months

MD: Mean Difference

T2DM: Type 2 Diabetes Mellitus

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Introduction

Available since the 1950's, metformin is one of the oldest oral glucose lowering agent and is currently recommended worldwide as first-line treatment of type 2 diabetes mellitus (T2DM). As a non-insulin secretion modifying agent, metformin's mechanism of action is based on a reduction of hepatic glucose production, an increased muscle sensitivity to insulin, improved glucose uptake and peripheral utilization, and delayed intestinal glucose absorption [1]. In addition to its efficacy in controlling blood glucose levels, metformin shows a favorable effect on weight. Its safety profile is well known: frequent gastrointestinal disorders (abdominal pain, diarrhea), sometimes severe enough to lead to treatment cessation, and a risk of lactic acidosis with treatment overdose, in particular with impaired renal function.

Despite its common use, few clinical trials have been conducted to study the efficacy of metformin versus placebo as a first-line treatment, and only a few of which are recent. Hence, an accurate evaluation of the beneficial effects is currently lacking and precise measurements of metformin efficacy in the first months of treatment can play an important role in the decision of treatment initiation. The predominant use of metformin as a first-line T2DM pharmacotherapy is mainly based on the UKPDS 34 study (*United Kingdom Prospective Diabetes Study 34*) [2]. Published in 1998, this large randomized study aimed to evaluate the benefits of early intense glycemic control in T2DM. A total of 4209 recently diagnosed T2DM patients were randomly assigned to conventional treatment (dietary and lifestyle measures) or intensive blood-glucose control with pharmacotherapy (metformin, sulfonylureas or insulin monotherapy, or metformin associated with sulfonylureas). Only intense metformin monotherapy for obese patients was associated with a significantly reduced cardiovascular risk [2]. Since

then, numerous biases have been noted in this study, including the absence of double-blindness and placebo control [3]. Yet, to our knowledge, no further large methodologically sound studies have been conducted to verify the efficacy of metformin on cardiovascular morbidity and mortality.

In everyday practice, family physicians play a major role in screening and management of patients with T2DM. Indeed, a study of diabetic patients in France established that 82% of the patients had consulted only their family physician within a two-year follow-up period [4]. Likewise, data analysis of French National Health reimbursements for prescriptions filled at pharmacies shows that of the 31 million packages of metformin dispensed in 2015 (monotherapy or combined with other glucose lowering agents), 88% had been prescribed by a family physician [5]. In the age of evidence-based medicine, widespread access to information through the internet, and a shift from paternalistic medicine to patient empowerment with growing demands for evidence, it has become urgent to provide more accurate motivating arguments for endocrinologists and family physicians when initiating pharmacotherapy with metformin.

The aim of this study was to measure the efficacy of metformin as first-line treatment for T2DM patients based on changes in fasting plasma glucose (FPG), glycosated hemoglobin and weight, based on a systematic review of the literature and a meta-analysis of placebo-controlled randomized trials with metformin.

Materials and methods

This study was conducted in accordance with the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines [6].

Data sources and search strategy

We searched the Medline and Cochrane databases for placebo-controlled clinical trials evaluating metformin in diabetic patients. Boolean search strategy for both databases was: [(« diabetes mellitus » OR « type 2 diabetes ») and « metformin » and « placebo » and « clinical trial »]. Terms were searched in title or abstract in Medline and in title, abstract or keywords in the Cochrane database. The search was performed by one investigator (CPM) on March 19, 2016. No search filters were applied concerning language restrictions or date of publication.

Study selection

Included studies were randomized, placebo-controlled clinical trials, lasting 4 weeks or longer, with at least two parallel groups or a cross-over design including metformin monotherapy. Participants had to be adult drug-naïve patients with T2DM. Studies comparing metformin versus placebo were included regardless of dietary and lifestyle measures. No limit was set for metformin posology or dosage regimens. Studies comparing metformin versus another active agent and studies comparing metformin as an add-on treatment versus another active agent were excluded. One investigator performed the selection while identifying uncertainly relevant publications which were then revised by a second investigator. The final selection was discussed by the two investigators.

Endpoints

The primary endpoint was the changes in glycosated hemoglobin (HbA1c) at M3 and M6. Secondary endpoints initially included changes in fasting plasma glucose at one, three, and six months (M1, M3, and M6), fasting insulin levels, weight, and body mass index (BMI) but all outcomes were not available for all studies. Investigators required a minimum of at least three studies for the meta-analysis.

Data extraction

For each study, we extracted data concerning study design, patient characteristics, and relevant endpoints. As continuous variables, endpoints were reported for each group in terms of mean differences (MD) from baseline with standard deviations (SD) reported or calculated based on standard errors (SE) or 95% confidence intervals (95% CI). In three trials, only the *p-value* was available. Hence, an approximation was calculated based on the assumption that the SD was identical in the two compared groups, as recommended in the *Cochrane Handbook* [7]. In cross-over trials, results in the metformin group and the placebo group were compared in the same manner as in two parallel group trials. In multi-arm trials, only data from the two relevant arms, *i.e.* metformin and placebo, were studied. In trials with two arms of metformin at different dosages, only one arm was retained for the meta-analysis based on data availability and the metformin posology closest to common clinical practice.

Risk of bias assessment

Risk of bias was assessed independently by two investigators for each trial included in the study using the *Cochrane Collaboration risk-of-bias tool* which provides an overall

risk of bias assessment (“High”, “Low” or “Uncertain”) summarizing the study of seven specific risk of bias domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias [8]. Risk of bias assessments were compared and discrepancies were discussed between the investigators.

Statistical analysis

Results were pooled using mean differences and 95% CIs estimated based on the inverse-variance method in random-effects models.[7] Heterogeneity across trials was assessed with the I^2 statistic and was considered high if the values were above 50%. All statistical analyses were two-sided using a significance level of 0.05. Analyses were performed using *RevMan* software, version 5.3 (*Nordic Cochrane Center*, Copenhagen, Denmark).

Sensitivity analysis

A sensitivity analysis of primary endpoints was performed excluding the trials estimated as having a high risk of bias, including all cross-over trials.

Results

The selection of studies is detailed in Figure 1. Overall, 16 studies were selected, including 12 parallel trials and 4 cross-over trials. Five trials were multi-arm trials, two of which included two metformin arms with different dosages. Median study duration was 18 weeks (minimum: 4 weeks, maximum: 29 weeks). Risk of bias was estimated as high in 10 studies (62.5%), low in 3 studies (18.8%), and uncertain in 3 studies (18.8%). Table 1 presents the characteristics of included studies.

The present meta-analysis included 1140 patients (596 in the metformin group, 544 in the placebo group), 51% of whom were men. Mean age, BMI, duration of diabetes and HbA1c were respectively 55.2 years, 30.6 kg/m², 56.5 months and 8.19%.

Four trials were used for the analysis of fasting plasma glucose at M1 [9–12], 8 trials for fasting plasma glucose at M3 [10, 13–19], 6 trials for fasting plasma glucose at M6 [10, 14, 15, 20–22], 8 trials for HbA1c at M3 [10, 13–16, 18, 19, 23], 8 trials for HbA1c at M6 [10, 14, 15, 20–24], 4 trials for weight at M3 [13, 16, 18, 22], and 3 trials for weight at M6 [15, 21, 22].

Primary endpoint

In comparison with placebo, metformin was associated with a significant decrease in HbA1c by -0.95% at M3 (95% CI from -1.39 to -0.50; I² = 87%) and by -1.32% at M6 (95% CI from -1.62 to -1.01; I² = 71%) (Figure 2).

Secondary endpoints

In comparison with placebo, metformin was associated with a significant decrease in fasting plasma glucose by -1.92 mmol/L at M1 (95% CI from -3.74 to -0.11), by -1.79 mmol/L at M3 (95% CI from -2.66 to -0.92), and by -2.14 mmol/L at M6 (95% CI from -3.12 to -1.17). There was significant heterogeneity between trials, with I^2 at 88%, 88%, and 82% at M1, M3, and M6, respectively (Figure 3).

Among the other secondary endpoints, the only available was weight at M3 and M6. In comparison with placebo, metformin was not associated with a significant difference in weight at M3 ($MD = -0.44$ kg ; 95% CI from -1.38 to 0.51; $I^2 = 0\%$) or at M6 ($MD = -1.49$ kg; 95% CI from -6.79 at 3.80; $I^2 = 0\%$) (Figure 4).

Sensitivity analysis

The sensitivity analysis excluding studies with a high risk of bias (10 studies including 4 cross-over trials) did not significantly differ from the main analysis: metformin was associated with a significant decrease in fasting plasma glucose by -1.69 mmol/L at M3 (95% CI from -2.74 to -0.64; $I^2 = 94\%$), by -2.12 mmol/L at M6 (95% CI from -3.66 to -0.58; $I^2 = 91\%$), and in HbA1c by -0.90% at M3 (95% CI from -1.52 to -0.28; $I^2 = 92\%$) and by -1.35% at M6 (95% CI from -1.88 to -0.82; $I^2 = 80\%$). Sensitivity analysis was not computed for fasting plasma glucose at M1 and weight at M3 and M6 due to an insufficient number of studies.

Discussion

This systematic review and meta-analysis of randomized placebo-controlled clinical trials in drug-naive patients with T2DM provided precise measures of the effect of metformin in decreasing fasting plasma glucose and HbA1c at M3 and M6. No significant changes were observed for weight.

To our knowledge, this systematic review provides the most comprehensive assessment of the advantages of metformin as a first-line treatment versus placebo in drug-naive diabetic patients based on HbA1c, fasting plasma glucose, and weight. Despite the long-term use of metformin and the absence of filters on publication year and language in our study search, few studies were eligible for inclusion in the meta-analysis. Although our stringent inclusion criteria limited the number of eligible studies, it allowed for closer assessment of the theoretical effects physicians should expect when prescribing metformin as a first-line pharmacological treatment. Moreover, our analysis allowed for the study of endpoints at specific follow-up periods commonly used for patient follow-up in everyday clinical practice.

Several meta-analyses have been conducted on metformin efficacy with various control groups (placebo, diet-control only, other glucose lowering agent, absence of treatment) and/or including add-on therapy, and/or excluding drug-naive patients [25–31]. In a meta-analysis by Hirst *et al.* [25], the effect of metformin on HbA1c was compared with placebo, but also as an add-on therapy to another therapy, in all types of diabetes, and without specifying whether patients were drug-naive. Despite these differences, results did not significantly differ from our results; nevertheless Hirst *et al.* presented results for studies lasting at least 12 and 24 weeks without specifying the

exact follow-up duration. Sherifali *et al.* [26] evaluated the effect of different classes of glucose lowering agents on HbA1c versus placebo, but also as an add-on therapy in treatment-naïve patients or in patients already treated with another glucose lowering agent (including insulin), in groups of at least 50 patients. Biguanides were associated with a decrease of 1% at M3. In a meta-analysis of cardiovascular outcomes, Boussageon *et al.* [27] included studies comparing metformin to placebo or metformin as an add-on therapy, without excluding patients with previous pharmacological treatments. As we targeted relevant data for first-line treatment, *i.e.* in treatment-naïve patients, only two studies evaluating cardiovascular morbidity/mortality were included in our study. This emphasizes the small number of studies based on clinical criteria. In comparison to UKPDS 34, the cornerstone trial for metformin prescription [2], our study evaluating only double-blind placebo-controlled trials presented a reduced risk of bias.

Several limitations should be considered when interpreting our results. First, study inclusion may have been limited by the search using only Medline and Cochrane databases although it is unlikely that any major clinical trials were overlooked with our selection procedure. Furthermore, the relevance of uncertain publications was discussed by two investigators but the selection process was not formally performed independently by two reviewers. Nevertheless, all of the studies included in other meta-analyses and corresponding to our selection criteria were found with our search procedure. Second, the inclusion of four studies using the Last Observation Carried Forward (LOCF) technique to evaluate outcome measures may also have impacted the results. However, this could have theoretically resulted in under-estimating metformin efficacy. Third, dosages of metformin could not be compared in our study since dosages varied across or within some studies or were adapted to glycemic response during the

intervention. When several different dosages of metformin were studied, we only included the dosages similar to those commonly used in first-choice pharmacological treatment in order to remain true to everyday clinical practice. Fourth, the majority of included trials showed high risk of bias. In addition, reviewing selected articles did not allow for evaluation of the risk of a selective reporting bias. Hence, this risk was not calculated in our analysis of risk of bias assessment. Nevertheless, all studies were blinded and we found similar results in the sensitivity analysis when studies with a high risk of bias, including cross-over trials, were excluded. Fifth, statistical heterogeneity between studies was high in our comparisons ($I^2 > 50\%$), thereby indicating a large variability of results in the trials. Heterogeneity on metformin effects across trials could be explained, at least in part, by the differences regarding glycemic control or BMI in the study populations and by the different doses of metformin used. Hence, to take heterogeneity into account we used a random-effects model and our results reflect the mean results of the included trials. The few number of studies and missing information in trials did not allow the investigation of potential sources of heterogeneity such as baseline BMI, HbA1c and metformin dosage. Finally, most of the included trials have been published a long time ago (mainly in the 1990's). Furthermore, results based on outcomes reported at one, three and six months do not come from the same trials. However, we do not believe that these two potential limits had a significant impact in our results.

This study confirms the beneficial effects of metformin regarding glycemic parameters and provides accurate data on expected values during the first months of first-line treatment with metformin. Nevertheless, we compared metformin versus placebo in identical management and dietary and lifestyle conditions, and our results do not warrant unconditional pharmacological treatment of all new patients with T2DM.

Indeed, it has been well-demonstrated that diet control and lifestyle measures are beneficial in T2DM [32] without exposing patients to the disadvantages of drug intake (adverse effects, psychological impact, daily compliance...). Hence, the results of this study should be interpreted within the framework of the important beneficial effects achieved with improved diet control and lifestyle, and the essential role of family physicians in patient education.

It is of note that we only measured the intermediate efficacy criteria for metformin due to a lack of studies demonstrating the efficacy of metformin versus placebo as a first-line drug based on relevant clinical criteria. Fleming and DeMets [33] noted the difference between correlate and surrogate endpoints, and how difficult it can be to establish a clear causal link between surrogate endpoints and clinical outcomes. Physicians should provide patients with clear information, address patient's preferences, and discuss any uncertainties in the absence of tangible causal evidence. According to Guyatt *et al.* [34], the expression « clinically relevant », commonly used in evidence-based medicine, should be replaced with « patient-relevant », thereby emphasizing the importance of shared decision-making between physicians and patients, which is crucial in chronic illnesses.

Conclusion

The results of this meta-analysis confirm and clarify the expected effects of metformin as first-line treatment in lowering HbA1c and fasting plasma glucose in T2DM patients. These results need to be weighed against the lack of solid evidence of effectiveness on morbidity/mortality and the fact that drug initiation is potentially associated with lesser compliance for dietary and lifestyle which remain a necessary alternative or add-on approach. Further studies are needed to compare morbidity/mortality among the different pharmacological and non-pharmacological strategies, as well as the effects of metformin versus dietary and lifestyle control on the patient's quality of life instead of surrogate endpoints.

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Author contributions

Study concept and design: Piera-Mardemootoo, Lambert, Faillie

Acquisition of data: Piera-Mardemootoo

Analysis and interpretation of data: Piera-Mardemootoo, Faillie

Statistical analysis: Piera-Mardemootoo, Faillie

Drafting of the manuscript: Piera-Mardemootoo

Critical revision of the manuscript for important intellectual content: Piera-Mardemootoo, Lambert, Faillie

Study supervision: Faillie

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Tables

Table 1. Characteristics of studies or subgroups included in the meta-analysis

STUDIES					STUDY CHARACTERISTICS						PATIENT CHARACTERISTICS				
Authors	Year	Design	Risk of bias	Ref.	Intervention	Participants (M/P)	Length of trial	Inclusion criteria	Overweight	Available end points	Males (%)	Mean age (years)	BMI (kg/m ²)	Duration of diabetes (months)	HbA1c (%)
Boulé <i>et al.</i>	2011	Cross-over	High	(10)	Metformin 2000mg/day or Placebo, no diet	10/10	28 days	HbA1c ≤8%	NA	FPG M1	80	58	28.6	NA	6.5
Damsbo <i>et al.</i>	1998	Parallel-group	Unclear	(14)	Metformin 3000mg/day or Placebo, diet	9/9	3 months	Newly diagnosed, no prior exposure to antidiabetic medication	Yes	HbA1c M3, FPG M3, weight M3	72	52	31.8	NA	9.7
DeFronzo and Goodman (protocol 1)	1995	Parallel-group	Low	(11)	Metformin 2550mg/day or Placebo, diet	143/146	29 weeks	FPG ≥7.8mmol/L	Yes	HbA1c M3 and M6, FPG M1 M3 and M6	43	53	29.6	72	8.3
Grant	1996	Parallel-group	High	(15)	Metformin 3000mg/day or Placebo, no diet	27/23	24 weeks	FPG ≥6mmol/L	Yes	HbA1c M3 and M6, FPG M3 and M6	NA	NA	NA	NA	NA
Guo <i>et al.</i>	2014	Parallel-group	Unclear	(24)	Metformin 2000mg/day or Placebo	29/29	24 weeks	NA	NA	HbA1c M6	62	54	NA	NA	7.92
Haak <i>et al.</i> (subgroup)	2012	Parallel-group	High	(23)	Metformin 2000mg/day or Placebo, no diet	67/32	24 weeks	HbA1c 7.5-11%	NA	HbA1c M3 and M6	NA	NA	NA	NA	NA
Hällsten <i>et al.</i>	2002	Parallel-group	Unclear	(21)	Metformin 2000mg/day or Placebo + diet	13/14	26 weeks	FPG 6.1-11mmol/L	NA	HbA1c M6, FPG M3 and M6, weight M6	67	58.1	30.1	NA	6.59
Hoffmann and Spengler	1997	Parallel-group	Low	(16)	Metformin 3700mg/day or Placebo, diet	31/32	24 weeks	HbA1c 7-11%, no prior exposure to antidiabetic medication	NA	HbA1c M3 and M6, FPG M3 and M6, weight M6	41.4	58.1	26.8	34.2	9.55
Horton <i>et al.</i>	2004	Parallel-group	Low	(20)	Metformin 1500mg/day or Placebo, no diet	104/104	24 weeks	FPG ≤15mmol/L, HbA1c 6.8-11%, no prior exposure to antidiabetic medication	NA	HbA1c M6, FPG M3 and M6	65.9	57.2	29.7	47.4	8.25
Johnson <i>et al.</i>	1993	Cross-over	High	(17)	Metformin 2550mg/day or Placebo, diet	8/8	12 weeks	Newly diagnosed, no prior exposure to antidiabetic medication	NA	HbA1c M3, FPG M3, weight M3	62.5	58	30.1	NA	11.2
Lalor <i>et al.</i>	1990	Cross-over	High	(18)	Metformin 1500mg/day or Placebo. Diet NA	26/26	12 weeks	Blood glucose 11-20mmol/L	Yes	FPG M3	46	58	31.5	NA	NA
Lee and Morley (protocol 2)	1998	Parallel-group	High	(22)	Metformin 1700mg/day or Placebo, diet	24/24	24 weeks	NA	Yes	HbA1c M6, FPG M3 and M6, weight M3 and M6	0	60	39.8	42	8.2
List <i>et al.</i>	2009	Parallel-group	Low	(9)	Metformin XR 1500mg/day or Placebo. Diet NA	56/54	12 weeks	HbA1c 7-10%, no prior exposure to antidiabetic medication	NA	HbA1c M3, FPG M3, weight M3	51.8	53.5	32	NA	7.75
Mather <i>et al.</i>	2001	Parallel-group	High	(19)	Metformin 1000mg/day or Placebo. Diet ND	28/15	3 months	FPG >7mmol/L or blood glucose >11.1mmol/L + symptoms or OGTT >11.1mmol/L at 2 hours	NA	HbA1c M3, FPG M3	60.5	52.1	32.5	NA	6.94
Pedersen <i>et al.</i>	1989	Cross-over	High	(12)	Metformin 1500mg/day or Placebo, diet	10/10	4 weeks	NA	Yes	FPG M1	20	53	36.4	33.6	NA
Tessari <i>et al.</i>	1994	Parallel-group	High	(13)	Metformin 1700mg/day or Placebo, no diet	11/8	4 weeks	no prior exposure to antidiabetic medication	NA	FPG M1	47*	55.5*	28*	24-240	7.54*

BMI = body mass index, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, M = metformin, M1 = at 1 month, M3 = at 3 months, M6 = at 6 months, NA = not available, OGTT = oral glucose tolerance test, P = placebo, Ref = bibliographic reference,

*out of 17 patients

Figures

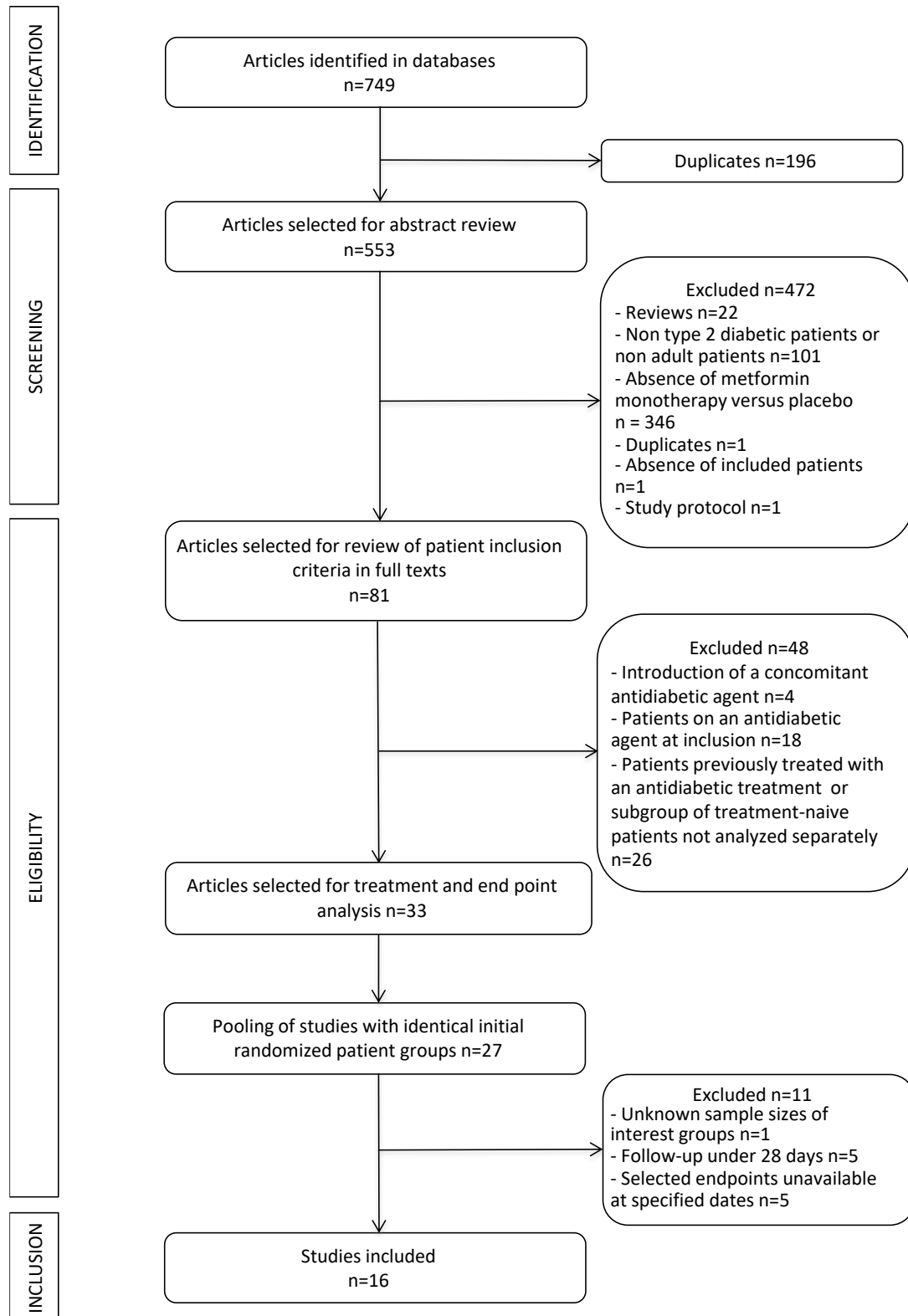
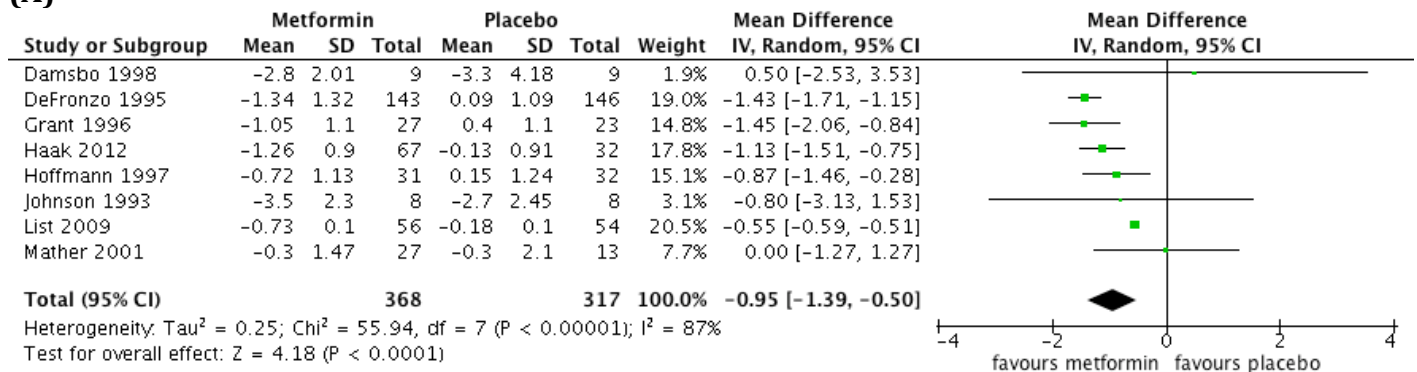


Figure 1. Flow chart of study selection

(A)



(B)

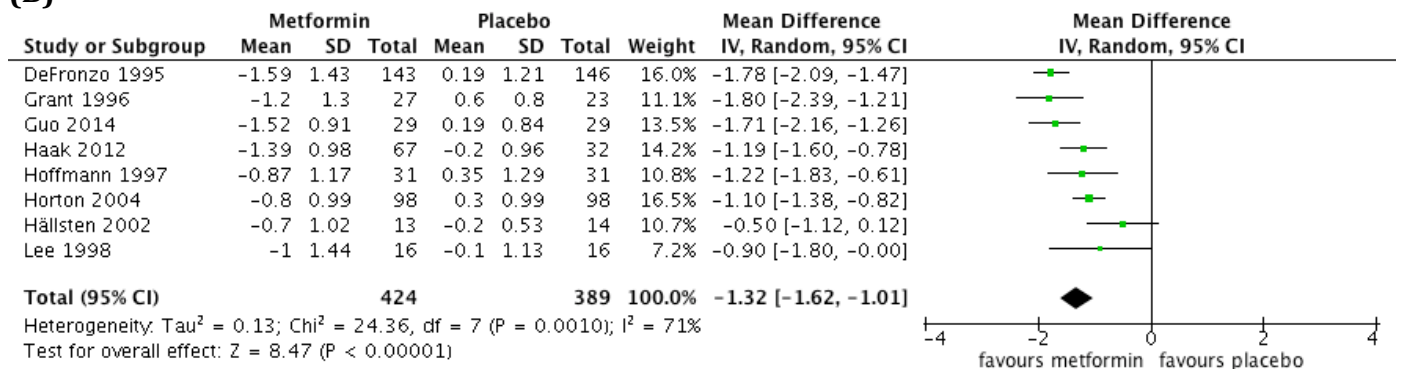
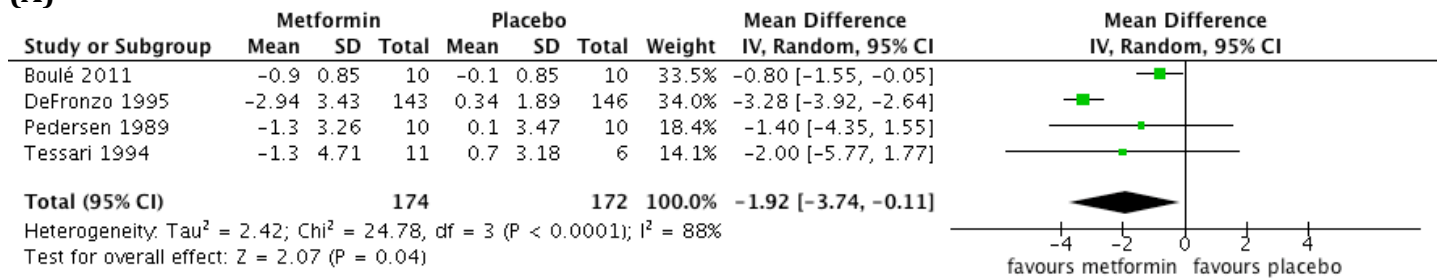
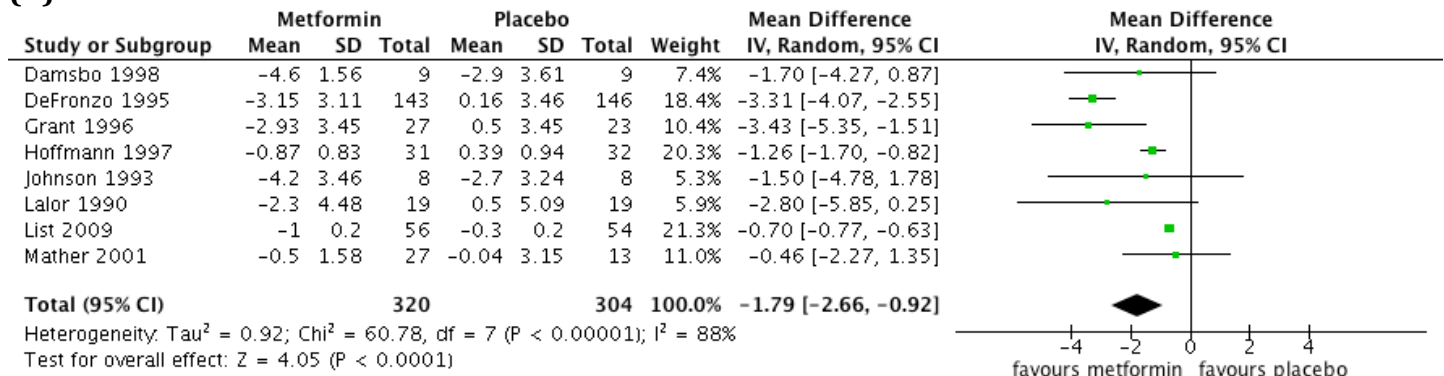


Figure 2. Forest plots with mean differences of change in HbA1c (%) from baseline at M1 (A) and M3 (B)

(A)



(B)



(C)

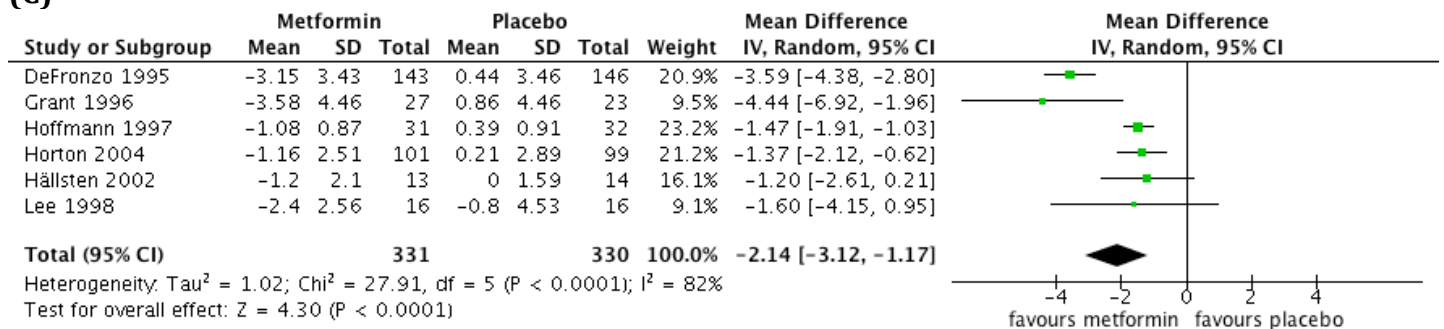
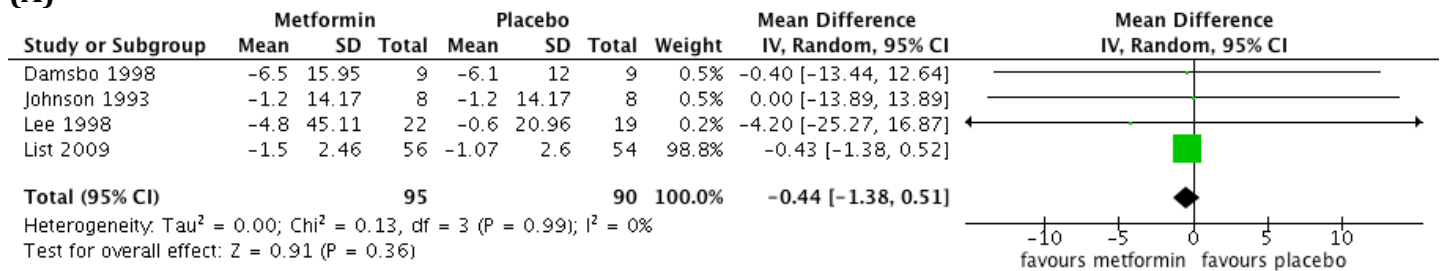


Figure 3. Forest plots with mean differences of change in fasting plasma glucose (mmol/L) from baseline at M1 (A), M3 (B), and M6 (C)

(A)



(B)

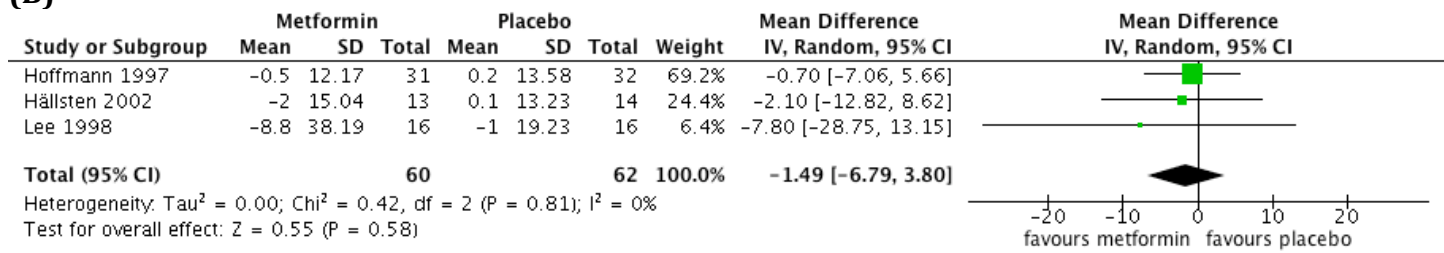


Figure 4. Forest plots with mean differences of change in weight (kg) from baseline at M3 (A) and M6 (B)

