Effect of pharmacological interventions on lipid profiles and C-reactive protein in polycystic ovary syndrome: a systematic review and meta-analysis

Running title: pharmacological interventions in PCOS

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Abstract

Context: Polycystic ovary syndrome (PCOS) is a heterogeneous condition affecting women of reproductive age. It is associated with dyslipidaemia and elevated plasma C-reactive protein (CRP), which increase the risks of cardiovascular disease (CVD).

Objective: To review the existing evidence on the effects of different pharmacological interventions on lipid profiles and CRP of women with PCOS.

Data sources: We searched PubMed, MEDLINE, Scopus, Embase, Cochrane Library, and Web of Science in April 2020 and updated the results in March 2021.

Study selection: The study included randomised controlled trials (RCTs) and follows the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)**.**

Data extraction: Two independent researchers extracted data and assessed for risk of bias using the Cochrane risk of bias tool. Covidence systematic review software were used for blinded screening and study selection.

Data synthesis: In 29 RCTs, there were significant reductions in triglycerides with atorvastatin vs placebo (MD: -0.21 mmol/L; 95% CI: -0.39, -0.03, I^2 = 0%, moderate grade evidence). Significant reductions were seen for LDL-C with metformin vs placebo (SMD:-0.41; 95%CI:-0.85, 0.02, I^2= 59%, low grade evidence). Significant reductions were also seen for total cholesterol with saxagliptin vs metformin (MD:-0.15 mmol/L; 95% CI: -0.23, -0.08, I^2= 0%, very low grade evidence). Significant reductions in C-reactive protein (CRP) were seen for atorvastatin vs placebo (MD:-1.51 mmol/L; 95% CI:-3.26-0.24, I^2=75%, very low-grade evidence).

Conclusion: There were significant reductions in the lipid parameters when metformin, atorvastatin, saxagliptin, rosiglitazone and pioglitazone were compared with placebo or other agents. There was also a significant reduction of CRP with atorvastatin.

Keywords: polycystic ovary syndrome (PCOS), LDL, HDL, triglycerides, total cholesterol, therapeutic agents , pharmacological therapy.

PROSPERO registration No: CRD42020178783

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous condition affecting up to 20% of women of reproductive age[1]. PCOS is characterised by signs and symptoms of androgen excess and an increase in cardiovascular risk[2].

The pathology behind this condition is unclear; however, it has been attributed to hormonal excess, environmental factors and increases in body weight[3]. Lipid abnormalities including elevated triglycerides (TGs), low density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and decreased high density lipoprotein cholesterol (HDL-C) are common in women with PCOS with up to 70 % of women with PCOS having dyslipidaemia[4,5]. Insulin resistance is also higher in obese women with PCOS, a feature of the metabolic syndrome associated with PCOS and, contributes to lipid disorders[6]. Hyperandrogenism is a feature of PCOS that is also associated with an adverse metabolic risk by increasing intra-abdominal fat deposition, which promotes the metabolic dysfunction seen in the PCOS[7]. Women with PCOS have significantly higher CRP which is an inflammatory marker and cardiovascular risk factor[8]. Dyslipidaemia and high levels of CRP are associated with an increased risk of cardiovascular disease (CVD)[9,10]. Moreover, anovulation has been found to be associated with higher TC, TGs, LDL-C and lower HDL-C in women with PCOS due to an increased release of the reactive oxygen species (ROS), which leads to ovarian damage and follicular atresia[11].

Lipid-lowering agents are occasionally used in PCOS for primary and secondary prevention of CVD. Besides lipid lowering these drugs can reduce oxidative stress and inflammation and improve other metabolic parameters in PCOS[12]. Statins can significantly reduce the levels of TC, TGs, LDL-C and CRP in women with PCOS[13]. Simvastatin and atorvastatin have synergistic effects on the lipid profiles and can improve the menstrual cyclicity of women with PCOS[14]. Therefore, this review aimed to evaluate and analyse the available evidence for the effectiveness of various therapeutic options for the treatment of dyslipidaemia seen in PCOS.

Methods

Protocol and registration

The protocol of this systematic review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews, PROSPERO (CRD42020178783) and reported following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[15].

Eligibility criteria

Only randomised controlled trials (RCTs) defined based on PICO (population, intervention, comparator and outcome) were included in this review. Eligibility criteria are presented in Table 1. Briefly, only RCTs included women aged 18 years and over and diagnosed with PCOS were eligible. RCTs that evaluated one pharmacological agent versus placebo, or comparing different pharmacological gents were eligible regardless of the design and methodology (open-labelled, double-blinded, parallel and crossover).

Literature search

A Literature search was performed in the medical databases; PubMed, EMBASE, MEDLINE, Scopus, Cochrane Library (CENTRAL) and Web of Science in April 2020 (L.Ö). A search update in PubMed was conducted in March 2021 (L.Ö), the search was not limited to specific dates. Search phrases were decided by professional in the medical filed (T.S & M.A) together with a medical librarian (L.Ö). All search terms were searched in a combination of title, abstract and Medical Subject Headings (MeSH) for optimal literature retrieval (supplementary materials). A filter for English language was applied. The search strings were later used to search in open grey, EU clinical trials and registry ClinicalTrials.gov. The full search strategy is shown in the supplementary material. All records identified in the literature search were uploaded to the systematic review software Covidence[16] for de-duplication and blinded screening followed by data extraction. All the selected references were managed by using EndNote[17]. Cabell's Predatory Report [18] was sought to ensure the non-predatory status of the included studies from open access journals.

Study selection

Two independent reviewers (M.A, and N.S) screened titles and abstracts of the retrieved studies with support of Covidence and assessed eligibility based on the inclusion/exclusion criteria. A full text evaluation was performed with agreement of both reviewers and disagreement was resolved by either consensus, discussion or by arbitration of a third reviewer (T.S). Studies included non-pharmacological agents and observational

studies were deemed ineligible and excluded. The study selection process together with the study identification, screening, and the reason for exclusion is shown in Figure 1.

Data extraction

Two independent reviewers (M.A and N.S) extracted information from the eligible studies. Information included countries of the RCTs, years of publications, design of the RCTs, type of the interventions and comparators, number of participants, duration of the RCTs, baseline aspects of the participants, and the reported outcomes. An overview of these characteristics is shown in Table 2. From all the reported outcomes total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP) were included.

Risk of bias assessment in the included studies

The Cochrane collaboration's tool was used to assess for the risk of bias (RoB) as suggested by Higgins et al[19]. The tool has six bias domains (selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias). Each RCT was assessed against these domains by two independent reviewers (M.A and N.S). Any disagreement was resolved by mediation of a third reviewer (S.T). This study followed the recommendations from the Cochrane handbook[20] and graded RoB as 'high RoB', 'low RoB', or 'unclear RoB'. The magnitude of RoB for the included RCTs and the calculated RoB for each specific domain in the RCTs are presented in Figure 1 and 2 in the supplementary material.

GRADE scoring

The robustness of evidence for each chosen outcome (CRP, LDL, HDL, triglycerides, total cholesterol) was examined following the recommendations from the Grading of Recommendations, Assessments, Development and Evaluation (GRADE)[21]. The GRADEpro GDT software was consulted to value the quality of the outcomes and to generate "Summary of findings table" in Table 1 in supplementary material. Initially, four points were given for each outcome. The points were then reduced in each outcome based on the presence of the following; the overall RoB for each RCT, inconsistency (significant heterogeneity), indirectness (significant

differences in the population, comparisons, and outcomes), imprecision (the size of the cohort, width and significance of the confidence intervals (CIs)). Based on these factors the overall GRADE scores were recorded for the outcome of each comparison as a high grade (at least 4 points), moderate grade (3 points), low grade (2 points) and very low-grade (1 point or less). All the grades of evidence are presented in Table 1 in the supplementary material.

Data analysis and evidence synthesis

The estimated pooled effects (mean difference [MD], standardised mean difference [SMD] and their 95 % confidence intervals [95% CIs]) on the variation between the comparison and intervention groups were quantified by using the random-effect model [20]. Where at least two effect estimates are reported a meta-analysis was conducted using the MD, inverse variance and random model presuming that the provide data for the continues outcome variables were normally distributed and reported using the same measuring scales otherwise SMD was used. Highly biased data or data presented as ranges were not considered for the meta-analysis. Whereas means and standard deviation (SD) of the post-intervention and changes from baseline values were included in the meta-analysis. Where data was reported as standard error (SE), CIs, *p*-values and *t* values, we used the RevMan calculator to transform them into means and standard deviations (SD). Where units of measurements were significantly varied, scales were converted to the most common measures. For RCTs with more than one intervention arm, we combined data from all arms based on the method recommended in the *Cochrane Handbook's* [20]. The meta-analysis was carried out using the Review Manager software (RevMan 5.4, The Cochrane collaboration) and differences with two-tailed p- values of ≤ 0.05 were considered statistically significant.

Assessment of heterogeneity

Heterogeneity for the outcomes across each RCT was evaluated using the I-squared (I^2) test statistics. Heterogeneity was reported as (may not be important if I^2 = 0-40 %), (might be moderate if I^2 =30-60 %), (may be substantial if I^2 = 50-90 %) and (may be considerable if I^2=75-100%)[20]. For statistically significant heterogeneity, the source was examined by omitting the RCT that showed significant effect from the meta-

analysis and the squared I^2 was re-examined. If significant heterogeneity still existed subgroup analysis was performed.

Subgroup analysis

Subgroup analysis was conducted and RCTs were grouped according to the dosages (mg/μg), frequencies of administration (once a day [QD], twice a day [BID] and trice a day [TDS]), and duration (weeks or months) of the therapeutic interventions.

Results

Characteristics of the included studies

Overall, 6326 records were found in the electronic database of which 3186 records were initially scanned for eligibility criteria based on titles and abstracts after duplicates were removed. In total, 814 full-text articles were acquired to examine their eligibility, of which 29 RCTs met the eligibility criteria and were therefore included in the meta-analysis (Figure 1).

The 29 RCTs were published until 2020, of which fifteen RCTs [22-35] diagnosed PCOS based on the Rotterdam criteria-2003[36], five RCTs [37-41] used the National Institute of Health 1990 (NIH, NICHD) criteria[42]; whereas no diagnostic criteria were given for the remaining RCTs (Table 2).

Interventions and comparisons details

Nine RCTs (31%) assessed the effect of metformin compared with placebo[22,25,31,33,41,43-46]. Five RCTs (17%) evaluated the effect of metformin compared with pioglitazone[29,30,35,47,48]. Two RCTs (6.8%) examined the effect of pioglitazone compared with placebo[23,49]. Two RCTs (6.8%) assessed the effect of rosiglitazone compared with metformin[27,38]. Two RCTs (6.8%) evaluated the effect of liraglutide compared with liraglutide added to metformin[37,39]. Two RCTs (6.8%) examined the effect of exenatide compared with metformin[26,34]. Two RCTs (6.8%) assessed saxagliptin compared with metformin[24,32]. Two RCTs (6.8%) evaluated metformin compared with simvastatin[40,50]. Three RCTs (10.3%) evaluated atorvastatin versus placebo[28,51,52].

Characteristics of the outcomes measured

All RCTs evaluated participants at baseline and post-intervention**.** Eleven RCTs (37.9%) reported changes in CRP[25-28,31,34,38,51,52].Twenty-six RCTs (89.6%) reported changes in total cholesterol[22-30,32-35,37-39,41,43-49,51,52].Twenty-seven RCTs (93.1%) reported changes in triglycerides[22-26,28-30,32-35,37,39-41,43-47,49-52].Twenty-six RCTs (89.6%) reported changes in HDL[22,24-30,32-35,37-40,43-46,48,50-52].Twenty-five RCTs (86.2%) reported changes in LDL[22,24-30,32,34,35,37-39,41,43-48,51,52].Table 2 shows the descriptive characteristics of the 29 RCTs included in this review.

Assessment of risk of bias in the included studies

The RoB item for each included RCT and the overall RoB are presented in Figures 1 and 2 in the supplementary material. Briefly, fifteen RCTs (51.72%) were judged to have a high risk of performance bias due to lack of blinding the participants[22,24-27,30,32,34,35,37,39,47,48].One RCT (3.4%) was judged to have a high risk of selective reporting bias[50]. Low risk of bias was judged for the majority of domains among the included RCTs, and an unclear RoB was also judged due to insufficient reporting.

We did not assessed for publication bias for the comparisons as there were fewer than 10 RCTs across each outcome.

Effects of interventions on the lipid profiles outcomes and CRP

The outcomes of the meta-analyses on the impact of pharmaceutical interventions compared with placebo are presented in Figures 2-6 and the comparison with other medications are shown in Table 3.

Lipid profiles

Total cholesterol

Atorvastatin versus placebo

In three RCTs, atorvastatin 20 mg QD significantly reduced the mean total cholesterol (SMD: -3.48; 95%CI: -5.74, -1.21, I^2 = 90%) (Figure 2-A) (very low-grade evidence).

Saxagliptin versus metformin

In two RCTs, saxagliptin 5 mg QD was compared with metformin 2000 mg QD significantly reduced the mean total cholesterol by 0.15 mmol/L (95% CI: -0.23, -0.08, I^2 = 0%) (Table 3)(very low-grade evidence).

The meta-analysis showed no effect on the mean total cholesterol when pioglitazone and metformin were compared with placebo (Figure 2-B and C). Similarly, no effect on mean total cholesterol was found when metformin alone or when metformin was added to liraglutide compared with pioglitazone, rosiglitazone, liraglutide and exenatide (Table 3).

Triglycerides

Atorvastatin versus placebo

In two RCTs, atorvastatin 20 mg QD significantly reduced the mean TGs by 0.59 mmol/L (95%CI: -0.72,-0.46, I^2= 0%*)* (Figure 3-A)(very low-grade evidence).

Pioglitazone versus placebo

In two RCTs, pioglitazone 30 mg QD significantly reduced the mean TGs by 0.21 mmol/L (95%CI: -0.39, -0.03, I^2 = 0%) when was compared with placebo (Figure 3-B) (very low-grade evidence).

The meta-analysis showed no effect on the mean TGs with metformin alone (Figure 3-C) or when metformin was added to liraglutide compared with pioglitazone, liraglutide, exenatide, saxagliptin and simvastatin (Table 3).

High-density lipoprotein cholesterol

Saxagliptin versus metformin

In two RCTs, saxagliptin 5 mg QD compared with metformin 2000 mg QD significantly reduced the mean HDL-C by 0.11 mmol/L (95%CI: -0.15, -0.06, I^2 = 7%) (Table 3) (very low-grade evidence).

The meta-analysis did not show any effect on the mean HDL-C when atorvastatin and metformin were compared with placebo (Figure 4-A and B). Similarly, no effect was observed with metformin alone or when metformin was added to liraglutide compared with pioglitazone, rosiglitazone, liraglutide, exenatide and simvastatin (Table 3).

Low-density lipoprotein cholesterol

Metformin versus placebo

In three RCTs, metformin 850 mg BID had no effect on the mean LDL-C (SMD: -0.65; 95%CI: -1.53, 0.22) and in four RCTs metformin 1500 mg QD was also associated with no effect in the mean LDL-C (SMD: -0.23; 95%CI: -0.71, 0.24). Overall, regardless of the administered doses metformin was associated with a significant reduction in the mean LDL-C when compared with placebo (SMD: -0.41; 95%CI: -0.85, 0.03, I^2 = 59%) (Figure 5-A) (low grade evidence).

Atorvastatin versus placebo

In two RCTs, atorvastatin 20 mg QD significantly reduced the mean LDL-C by 0.91 mmol/L(95%CI: -1.04-0.79, I^2 = 0%*)* when compared with placebo (Figure 5-B) (very low-grade evidence).

Rosiglitazone versus metformin

In one RCT, rosiglitazone 4 mg QD significantly reduced the mean LDL-C by 0.22 mmol/L (95%CI: -0.36 -0.08) when was compared with metformin 1000 mg QD. In one RCT, rosiglitazone 4 mg QD also significantly reduced the mean LDL-C by 0.48 mmol/L (95%CI: -1.19, 0.23) when was compared with metformin 850 mg BID. Overall, rosiglitazone 4 mg QD significantly reduced the mean LDL-C by 0.23 mmol/L (95%CI: -0.37-0.09, I^2 = 0%*)* when compared with various doses of metformin (Table 3) (very low-grade evidence).

The meta-analysis showed no effect on the mean LDL-C when metformin alone or when metformin was added to liraglutide compared with pioglitazone, liraglutide, exenatide and saxagliptin (Table 3).

C-reactive protein

Atorvastatin versus placebo

In two RCTs, atorvastatin 20 mg QD was associated with a significant reduction in the mean CRP by 1.51 mg/L (95%CI: -3.26-0.24; 65 participants, I^2 = 75%, p =0.09) (Figure 6-A) (very low-grade evidence).

However, the meta-analysis showed no effect on the mean CRP when metformin was compared with placebo (Figure 6-B), and no effect with either rosiglitazone or exenatide compared with placebo (Table 3).

Sensitivity analysis

The effect of each individual RCT on heterogeneity and the strength of the result was reviewed by conducting a sensitivity analysis. Thus, small sample sized RCTs and the one with an overall high RoB were eliminated from the meta-analysis while inspecting their impacts on the collective results. As a results, no substantial effect was found and thus, no RCT was removed from the meta-analysis.

Discussion

This systematic review provides an overview of the current evidence on the effect of pharmacological interventions on the lipids profile in women with PCOS. In the current review, we found that when metformin and atorvastatin were administered at various doses, compared with placebo, there were significant reductions in the mean CRP, TC, TGs, and LDL-C. Saxagliptin, pioglitazone and rosiglitazone also showed significant reductions in the mean TC, TGs and LDL-C when compared with metformin or with placebo.

Lipid profile outcomes and CRP

Metformin significantly reduced the mean TC, TGs, LDL, but no effect on HDL was seen. In a systematic review and meta-analysis of 12 RCTs, metformin showed a significant effect for LDL-C reduction, but no effect was seen for the other parameters of the lipid profiles[53]. However, an RCT that compared metformin with placebo reported a significant increase in the mean HDL-C and a decrease in the mean TC[54 55]. The lipid lowering mechanism of action of metformin is that it activates the AMP-activated protein kinase (AMPK),which regulates the sterol regulatory element binding protein-1 (SREBP-1) and inhibits the hepatic lipogenesis [56]. Statins reduce cholesterol production by competitively inhibiting the 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis[57].

Metformin at various therapeutic doses showed no effect on CRP when compared with other agents. The subgroup analysis also did not indicate any significant effect of Metformin at various doses and durations on CRP when compared with placebo. This is the converse to a meta-analysis of 20 RCTs[58] that assessed the effect of Metformin on CRP that reported a significant reduction in CRP. However, in the above study there was a significantly high level of heterogeneity among the studies; therefore, care ,must be taken when interpreting the results of the study. Dawson et al., in an open clinical trial of exenatide (5 mcg BID administered for 4 weeks then titrated to 10 mcg for 12 weeks) reported a significant reduction in CRP from baseline (8.5 ± 1.4 to 5.6 ± 0.8 mmol/L p = 0.001)[59]. Conversely, in this study we did not observe any effect for exenatide on CRP when compared with metformin. No effect on CRP was seen in this study when rosiglitazone was compared with metformin that differs to a study of rosiglitazone 4 mg QD administered for 12 months that showed a significant reduction in CRP[60].

The review was conducted based on a systematic search for the related databases and grey sources. It also included RCTs and crossover trials only with the exclusion of both observational and non-randomised studies.

To date, this is the most inclusive systematic review and meta-analysis of the effect of pharmacological interventions on lipid profiles in women with PCOS.

One of the limitations of this systematic review is that a language filter was applied and only RCTs reported in English language were included. This could have significantly affected the inclusion of several studies published in foreign languages. Retrieving such studies requires translation to English that could be challenging and may also influence the methodology of this review. Moreover, we only included fully published studies and there may be unpublished trials that could not be retrieved. The majority of the RCTs reported in this review had small sample size and lacked statistical rigor used to identify sample size. Additionally, most of the RCTs had a short duration thus, the long-term effect of the various pharmacological interventions on the lipid profiles in women with PCOS is not clear.

This systematic review recognises the poor quality of the included RCTs, which is also shown in the summary of evidence of the GRADE score in the supplementary material. Because of the design of some clinical trials (open-label), there was a substantially high level of performance bias. In some studies, the reporting and the selection bias were inadequately evaluated that led to the adjudication of an unclear RoB in 69% of the included RCTs. In addition, only 49% of the RCTs reported information of the method used to blind the participants and the outcome assessor and 45% were judged to have an unclear risk of attrition bias. For the lipid profile outcomes, the grade of evidence was rated as very low, low, or moderate due to the unclear or high risk of performance bias. There was lack of blinding for the participants and the outcome assessors, lack of allocation, unclear risk of attrition bias, unclear risk of selective reporting and considerable heterogeneity.

This study highlights that there is a lack of robust RCTs evaluating various pharmacological agents used in the treatment of PCOS. Moreover, currently available RCTs assessing the effectiveness of these pharmacological interventions are of low or very low quality. Therefore, the present results do not allow a definite conclusion and recommendation for clinical practice. Furthermore, these RCTs are of small sample size that may not have had the power to exclude false negative outcome. Thus, this review acknowledges the need for RCTs with

rigorous design to facilitate a better-informed clinical decisions to draw recommendations and help develop guidelines.

Conclusion

Dyslipidaemia and high level of CRP are associated with a significantly increased risk of cardiovascular disease (CVD). Data pooled in this review showed that metformin, atorvastatin, saxagliptin, rosiglitazone and pioglitazone have significant effects by reducing the mean CRP, TC, TGs, HDL-C and LDL-C. Therefore, these agents could potentially reduce cardiovascular risk associated with PCOS.

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Ethical approval

Not needed as no patients were involved.

Conflict of interest

None to declare.

Availability of data

The datasets generated and analysed for this review are available upon compelling request to the authors.

Authors contributions

M.A; designed the review, completed the databases searches, assessed the quality, extracted, collected, and analysed the data, written, revised, and edited the final manuscript. N.S; assessed the quality, extracted, and collected the data, and revised and edited the final manuscript. H.D; revised and edited the final manuscript. A.S; participated in the critical discussion, revised and edited the final manuscript. L.Ö; developed and performed the systematic search, assessed for predatory journals and revised and edited the final manuscript. R.H.A; contributed to the critical discussion and revised and edited the final manuscript. S.A; participated in the critical discussion and revised the final draft of the manuscript. T.S; acted as mediator for the assessment of the quality of the evidence, supervised the study, participated in the critical discussion, revised, and edited the final manuscript.

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Table 1: The inclusion criteria for the included studies in this systematic review

Inclusion criteria
1. Study design: randomised controlled trials including (randomised open-label trials, double-blind controlled trials, crossover randomised trials, parallel randomised trials).
2. Patients population: adult females aged 18 and over with a diagnosis of PCOS based on a robust diagnostic criterion.
3. Comparators: reported pharmacological interventions compared to placebo or other pharmacological agents.
4. Outcomes: reported outcomes such as CRP, LDL-C, HDL-C, triglycerides, and total cholesterol.
Exclusion criteria
1) Study design: case studies, observational studies and animal studies.
2) Patients population: adolescents females, postmenopausal women, and women without PCOS.
3) Comparators: non-pharmacological interventions, pharmacological interventions versus dietary interventions, pharmacological interventions versus physical activities or surgery.

CRP: C-reactive protein, **PCOS**: polycystic ovary syndrome, **LDL-C**: low-density lipoprotein cholesterol, **HDL-C:** high-density Lipoprotein cholesterol.

Figure 1: PRISMA flow diagram

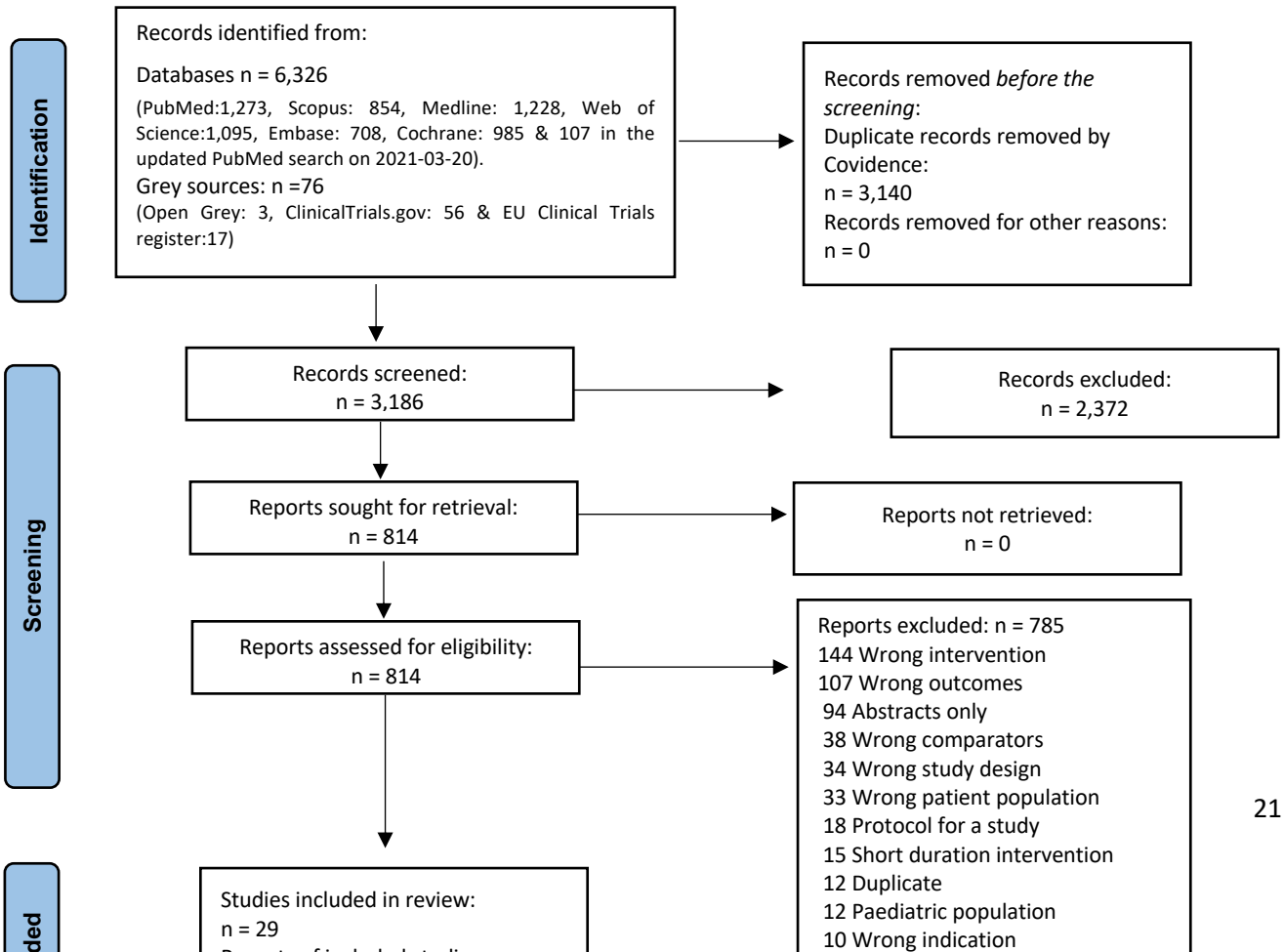

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Table 2: Characteristics of the studies included in the systematic review and meta-analysis

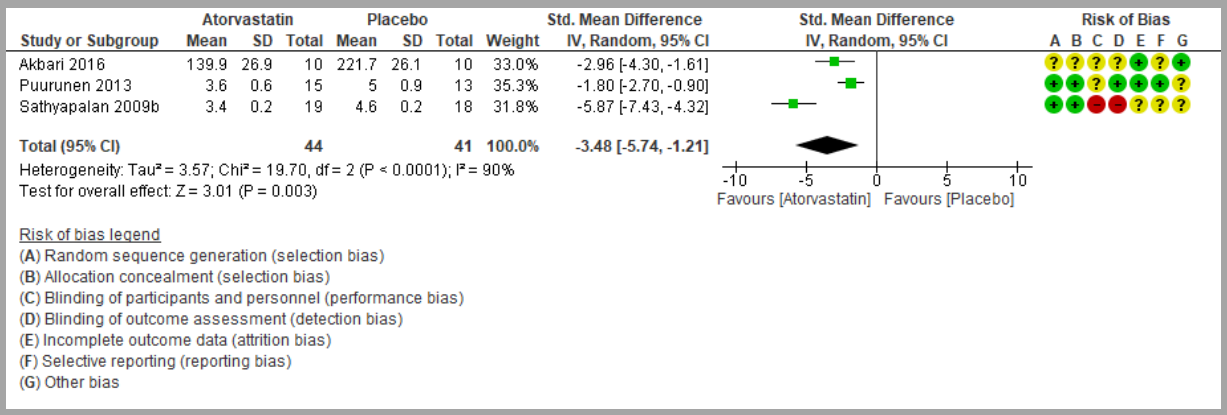
Author	Study design	Country	POCS diagnostic Criteria	Participants characteristics (PCOs)	Interventions	Durations	Biomarkers
Amiri et al[22]	RCT	Iran	Rotterdam	Age:25.6±4.02 BMI: 28.9±5	Metfo, Flu, Metfo+ Flu, Placebo	6 months	TC,LDL,HDL, TG
Akbari et al [51]	RCT	Iran	Rotterdam	Age: 27.7±3.4 BMI:26.6±3.6	Atorv, placeb	6 weeks	HDL, LDL, TG, TC
Brettenthaler et al[23]	RCT	Switzerland	Rotterdam	Age: 30.2± 1.4 BMI: 29.4± 1.7	Piog, placebo	3 months	TC, TG
Elkind-Hirsch et al[24]	RCT	USA	Rotterdam	Age: 28.2 ± 1.1 BMI: 39.9 ±1.5	Exen, Metf,Exen+Metf	24 weeks	CRP, TG, TC,HDL,LDL
Glintborg et al[49]	RCT	USA	N/A	Age: 32 BMI: N/A	Piog, Placebo	16 weeks	TC, TG
Puuruen et al [52]	RCT	Finland	Rotterdam	Age: 29-50 BMI:> 19.9	Atorv, placebo	6 months	CRP, TC, TG, HDL, LDL
Gambineri et al[43]	RCT	Italy	N/A	Age: 27·1 ± 3·6 BMI: 37·6 ± 4·1	Plac, metfo, flut, metf + flut	6 months	TC, TG,LDL, HDL
Heidari et al[25]	RCT	USA	Rotterdam	Age: 32.47.5 BMI: 37.19.1	Metf, placebo	3 months	CRP, TC, TG, LDL, HDL
Jensterle et al[38]	RCT	Slovenia	NIH	Age: 27.6±7.2 BMI: 39.5±6.2	Metf, Lira	12 weeks	TC,TG,LDL,HDL
Jensterle et al[37]	RCT	Slovenia	NIH	Age: 27.6±7.2 BMI: 39.5±6.2	Metf, Lira	12 weeks	TC,TG,LDL,HDL
Jensterle Sever et al[39]	RCT	Slovenia	NIH	Age: 31.3±7.1 BMI: 37.1±4.6	Lira,Metf, Lira+Metf	12 weeks	TC,TG,HDL,LDL
Liu et al[26]	RCT	China	Rotterdam	Age: 27.69 ± 3.80 BMI: 28.29 ± 1.86	Metf, Exena	24 weeks	TC, TG, LDL,HDL
Lord et al[44]	RCT	UK	N/A	Age: 27.76 ±4.89 BMI: 33.74± 6.74	Metf, placebo	3 months	TC, TG, LDL,HDL
Moghetti et al[41]	RCT	Italy	NICHD	Age: 23.9 6 1.2 BMI: 27.1 6 1.5	Metformin, placebo	6 months	TC, TG, LDL
Mohiyiddeen et al[27]	RCT	UK	Rotterdam	Age: 29.0 ±1.0 BMI: 29.7 ±1.0	Metf,Rosig	3 months	TC, TG, LDL,HDL
Mehrabian et al[40]	RCT	Iran	NIH	Age: 29.18±8.28 BMI: 29.83±4.1	Metf, flut, simva	6 months	CRP,TG,HDL
Navali et al[50]	RCT	Iran	N/A	Age:26.43±4.67 BMI:27.71±0.73	Metf, Simva	3 months	TC, TG, LDL,HDL
Ng et al[45]	RCT	China	N/A	Age:30.5 BMI:N/A	Metf, placebo	3 months	TC,TG
Naka et al[47]	RCT	Greece	N/A	Age: 23.3± 4.9 BMI: 28.7± 5.5	Metf,Piogl	6 months	TC, TG, LDL,HDL

Ortega-González et al[48]	RCT	Mexico	N/A	Age: 28.8 ±0.9 BMI: 32.2 ±1.0	Metf, Piogl	6 months	TC, LDL, HDL
Sova et al[31]	RCT	Finland	Rotterdam	Age: : 27.7 ±4.0 BMI: 27.5 ±6.2	Metf, placebo	3 months	CRP
Shahebrahimi et al[29]	RCT	Iran	Rotterdam	Age: 27.5 ± 3.68 BMI: 27.71±4.36	Metf, piog	3 months	LDL,HDL,TG
Sohrevardi et al[30]	RCT	Iran	Rotterdam	Age:N/A BMI: 27.5±3.6	Metf,piog, Metf+Piog	3 months	TC, TG, LDL, HDL
Sathyapalan et al [28]	RCT	UK	Rotterdam	Age: 27.7 ± 1.4 BMI: 33.20 ±1.4	Atorva, placebo	12 weeks	HDL,LDL,TC, TG
Tao et al[32]	RCT	China	Rotterdam	Age: 30 ± 5 BMI: 27.2	Saxag, Metf	24 weeks	LDL,HDL,TG
Trolle et al[46]	RCT	Denmark	N/A	Age: 31 BMI:32	Metf, placebo	6 months	LDL,HDL
Underdal et al[33]	RCT	Denmark	Rotterdam	Age: 29.5 ±3.9 BMI: 28.7± 6.9	Metf, placebo	NA	TC, TG, LDL, HDL
Zheng et al[34]	RCT	China	Rotterdam	Age: 27.70 ± 3.41 BMI: 28.27 ± 4.85	Exena, Metf	12 weeks	HDL,LDL, TG, TC
Ziaee et al[35]	RCT	Iran	Rotterdam	Age: 25.28±4.38 BMI: 26.13 ±3.03	Metf, piog	12 weeks	HDL,LDL,TG,TC

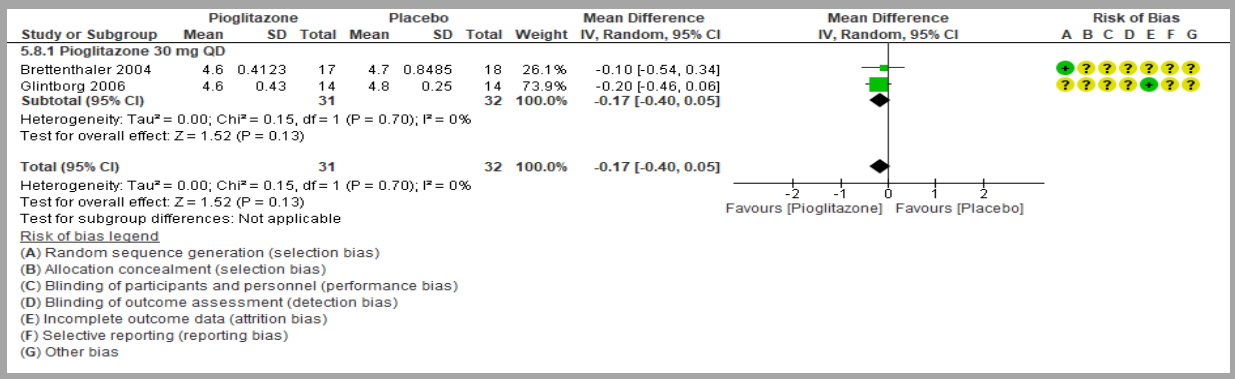
RCT: randomised clinical trial, **N/A**: not available, **HDL**: high density liporotein**, LDL:** Low density lipoprotein, **TG:** triglycerides, **TC**: total cholestero**NIH**: national institute for health, **NICHD**:national inistitute of child health and development. **Metf:**metformin, **Saxa:** saxagliptin,**Piog**: pioglitazone, **Rosig**: rosiglitazone,**Atrova:** atorvastatin, **Simva**:simvastatin, **WHO:** world health organisation,**CRP:**C-reactive protein,**Lira**:liraglutide, **USA:** united state of America.

Figure 2: Forest plot of comparisons on total cholesterol

A) Atorvastatin versus placebo



B) Pioglitazone versus placebo



C) Metformin versus placebo

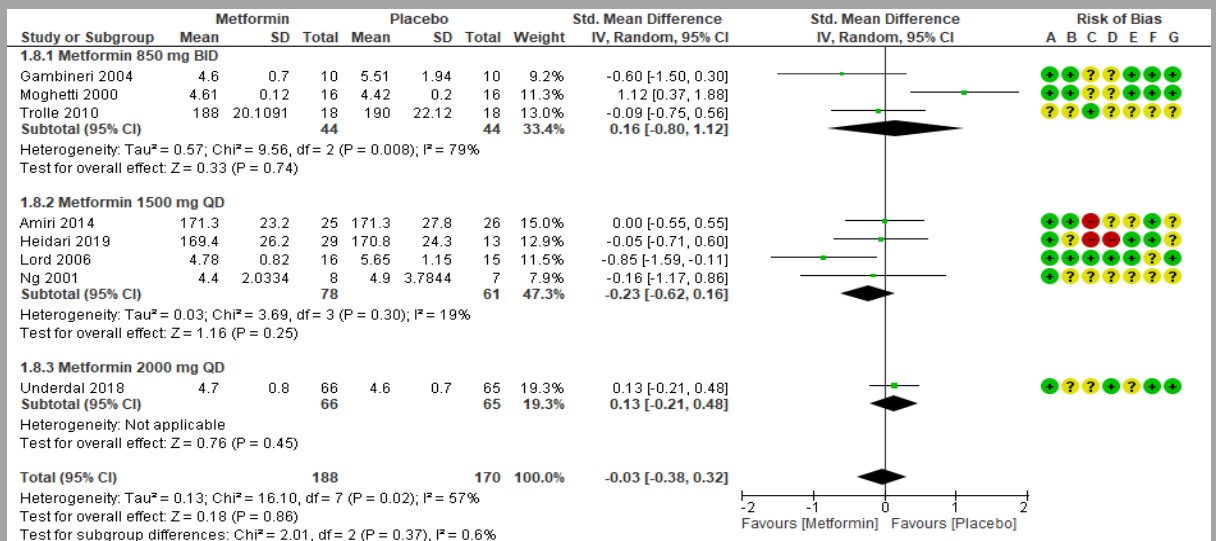
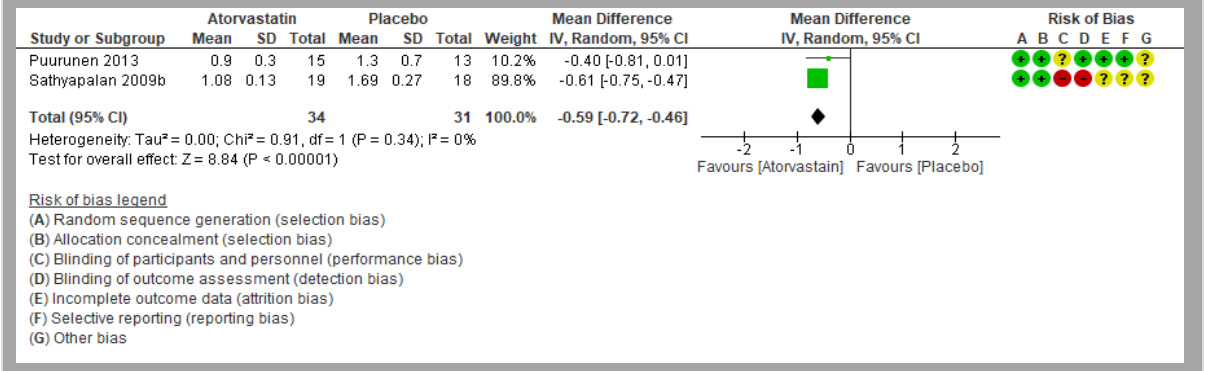
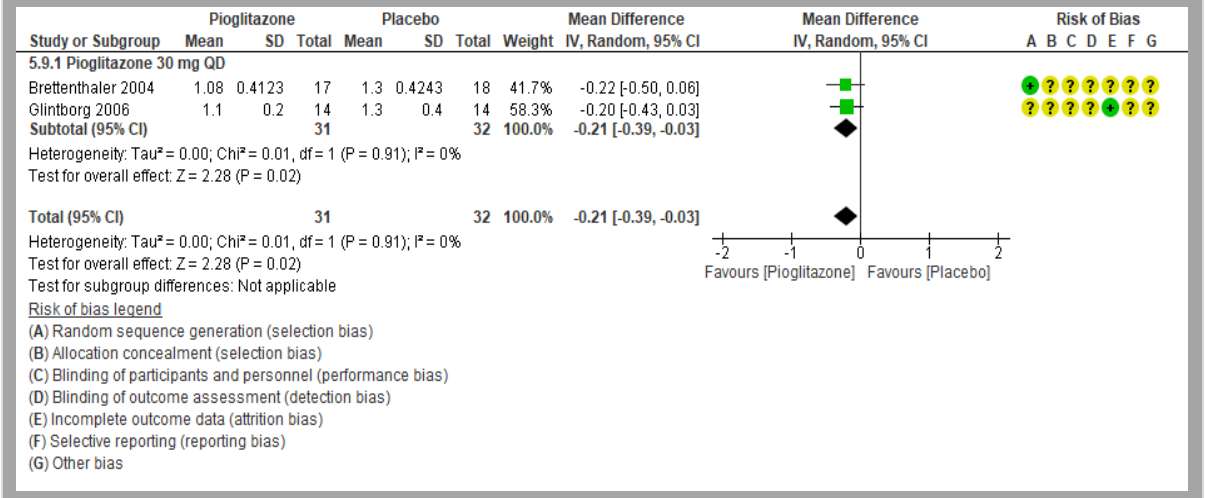


Figure 3: Forest plot of comparisons on triglycerides

A) Atorvastatin versus placebo



B) Pioglitazone versus placebo



C) Metformin versus placebo

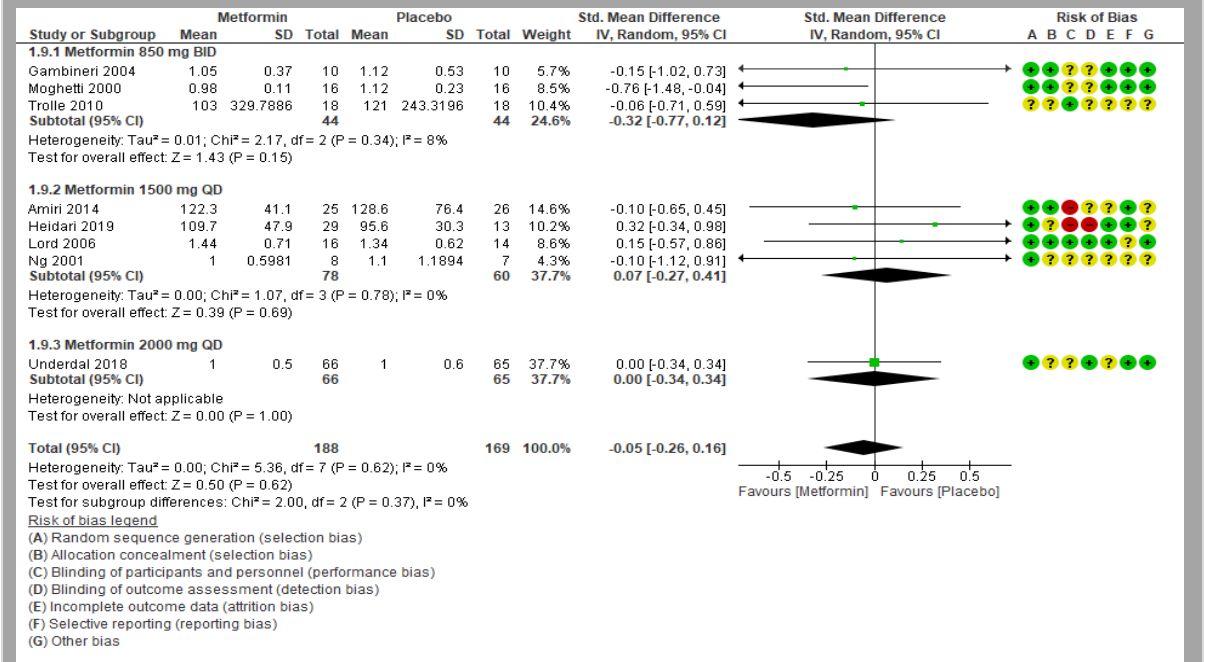


Figure 4: Forest plot of comparisons on HDL-C

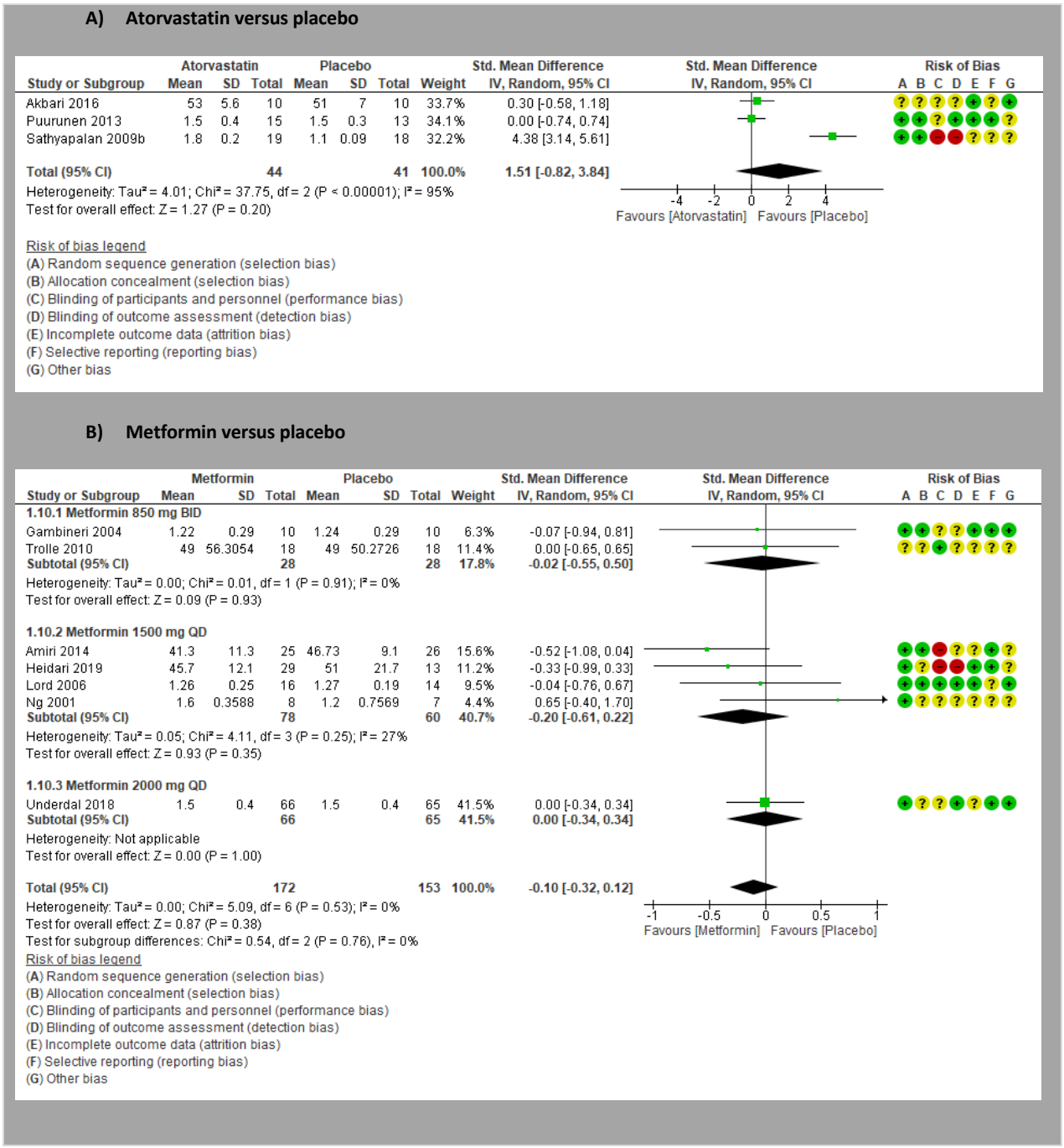
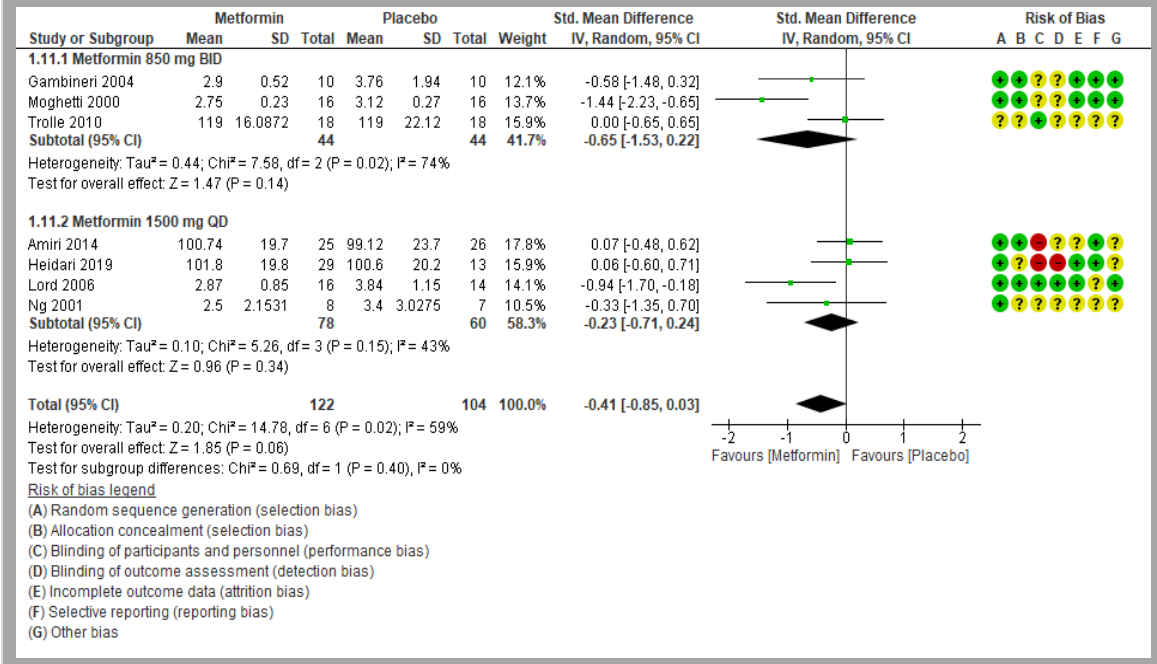


Figure 5: Forest plot of comparisons on LDL-C

A) Metformin versus placebo



B) Atorvastatin versus placebo

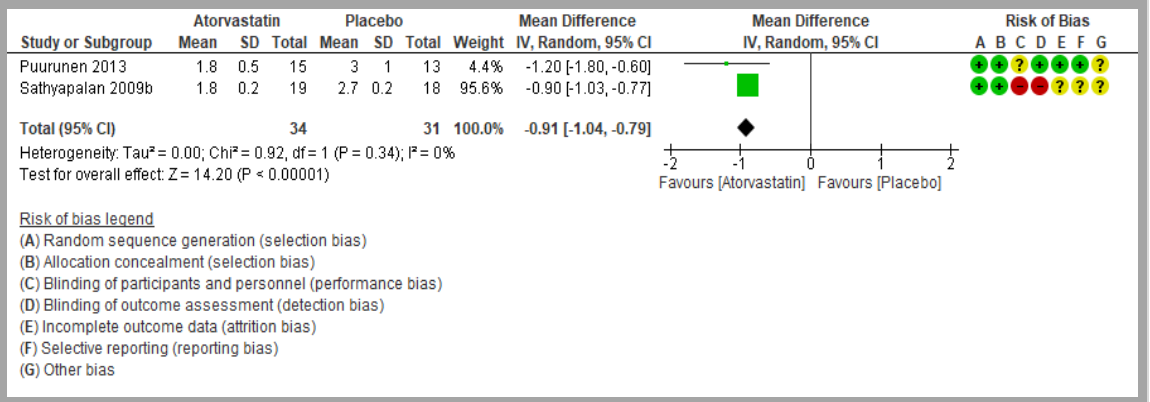
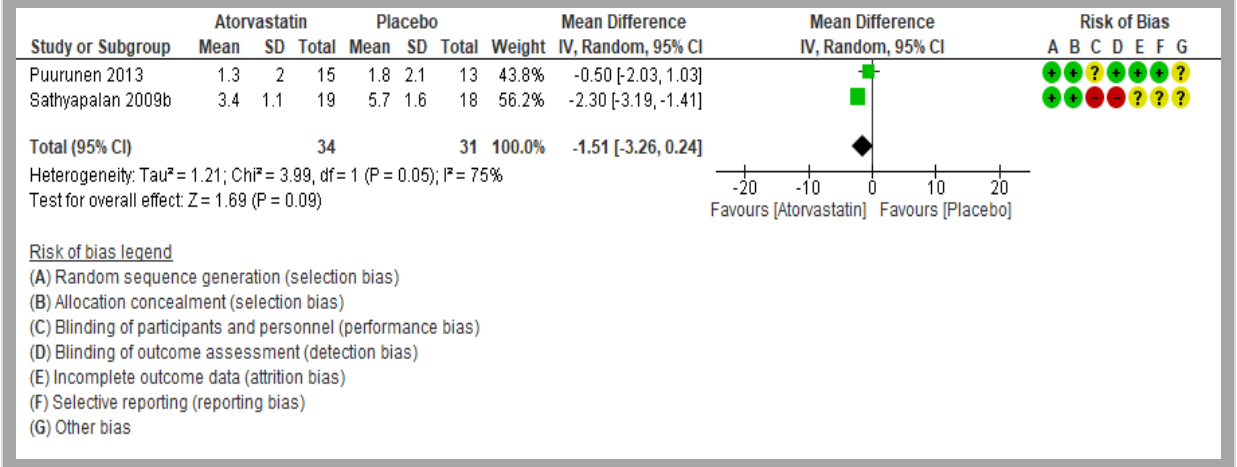


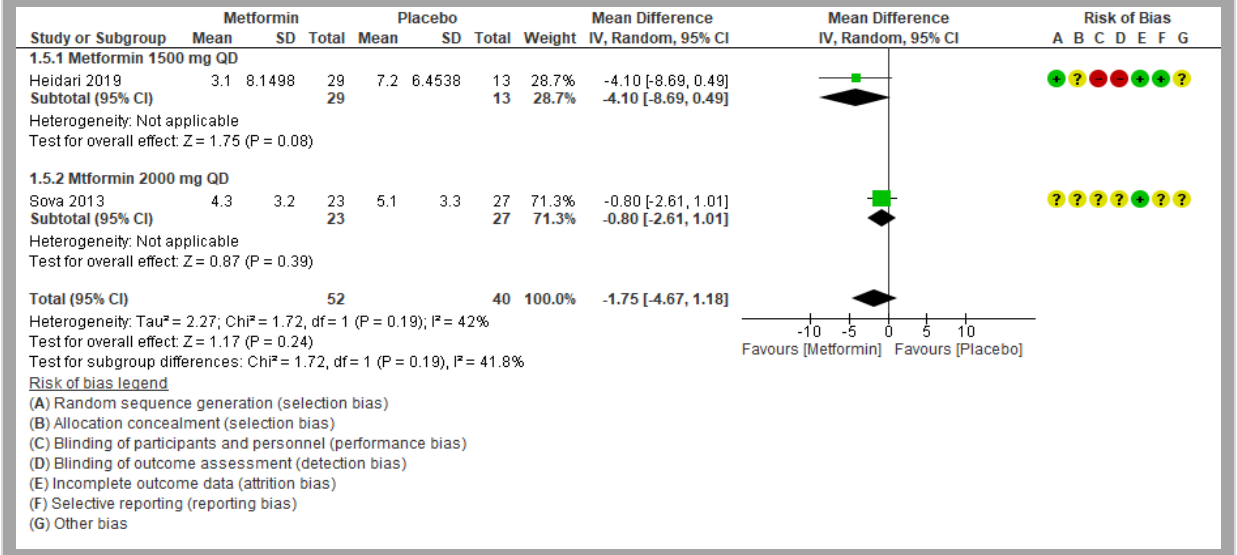
Figure 6 : Forest plot of comparisons on CRP

A) Atorvastatin versus placebo



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

B) Metformin versus placebo



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Table 3: summary pooled effect estimates of various medications on total cholesterol, triglycerides, HDL-C, LDL-C and CRP in women with PCOS

Intervention	Comparison	No of women in the intervention arm	No of women in the control arm	No of RCTs	Pooled effect estimates	95% CI	I^2 (%)	I^2 (*p*-value)	Overall effect (*p*- value*)
Outcome: mean CRP									
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	109	112	2	-0.33	-0.90-0.24	0.0	0.76	0.25
Rosiglitazone 4 mg QD	Metformin 850 mg BID	11	15	1	-1.28	-4.56-2.00	-	-	0.44
Rosiglitazone 4 mg QD	Metformin 1000 mg QD	18	17	1	-0.21	-0.52-0.09	-	-	0.19
Overall: Rosiglitazone versus Metformin		29	32	2	-0.22	-0.53-0.09	0.0	0.52	0.17
Outcome: mean total cholesterol									
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	25	25	2	0.19	-0.27-0.65	0.0	0.67	0.41
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	109	112	2	0.16	-0.06-0.37	0.0	0.38	0.16
Rosiglitazone 4 mg QD	Metformin 850 mg BID	11	15	1	0.81	0.01-1.63	-	-	0.05
Rosiglitazone 4 mg QD	Metformin 1000 mg QD	18	17	1	0.23	0.09-0.37	-	-	0.001
Overall: Rosiglitazone versus Metformin		29	32	2	0.38	-0.12-0.89	49	0.16	0.14
Saxagliptin 5 mg QD	Metformin 2000 mg QD	33	32	2	-0.15	-0.23-0.08	0.0	0.64	<0.0001
Metformin 850 mg BID for six months	Pioglitazone 45 mg QD	33	31	2	-1.44	-13.67-10.79	0.0	0.32	0.82
Metformin 1500 mg QD for three months	Pioglitazone 45 mg QD	77	75	3	-4.02	-15.28-7.24	13	0.32	0.48
Overall: Metformin versus Pioglitazone		110	106	5	-3.34	-11.17-4.49	0.0	0.49	0.40
Outcome: mean triglycerides									
Metformin 1500 mg QD for 3months	Simvastatin 20 mg for three months	100	100	1	-0.28	-15.36-14.80	-	-	0.97
Metformin 1000 mg QD	Simvastatin 20 mg for six months	34	34	1	-12.80	-21.94-3.66	-	-	0.006
Overall: Metformin versus Simvastatin		134	134	2	-8.04	-19.95-3.88	48	0.16	0.19

Saxagliptin 5 mg QD	Metformin 2000 mg QD	32	33	2	-0.01	-0.38-0.37	54	0.14	0.98
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	109	112	2	0.24	-0.21-0.69	77	0.04	0.29
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	25	25	2	0.16	-0.49-0.81	50	0.16	0.62
Metformin 850 mg BID for six months	Pioglitazone 45 mg QD	15	15	1	19.00	-4.12-42.12	-	-	0.11
Metformin 1500 mg QD for three months	Pioglitazone 45 mg QD	77	75	3	2.31	-13.61-18.24	0.0	0.66	0.78
Overall: Metformin versus Pioglitazone		92	89	4	7.68	-5.43-20.80	0.0	0.54	0.25
Outcome: mean HDL-C									
Metformin 1500 mg QD for 3months	Simvastatin 20 mg for three months	100	100	1	-0.80	-4.51-2.91	-	-	0.67
Metformin 1000 mg QD	Simvastatin 20 mg for six months	34	34	1	0.53	-2.56-3.62	-	-	0.74
Overall: Metformin versus Simvastatin		134	134	2	-0.01	-2.39-2.36	0.0	0.58	0.99
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	109	112	2	-0.07	-0.19-0.05	37	0.21	0.24
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	25	25	2	-0.07	-0.22-0.09	0.0	0.55	0.40
Rosiglitazone 4 mg QD	Metformin 850 mg BID	11	15	1	0.01	-0.21-0.23	-	-	0.93
Rosiglitazone 4 mg QD	Metformin 1000 mg QD	18	17	1	0.04	-0.06-0.14	-	-	0.44
Overall: Rosiglitazone versus Metformin		29	32	2	0.03	-0.06-0.13	0.0	0.81	0.46
Metformin 850 mg BID for six months	Pioglitazone 45 mg QD	18	17	1	1.50	-4.35-7.35	-	-	0.62
Metformin 1500 mg QD for three months	Pioglitazone 45 mg QD	76	75	3	-1.16	-5.25-2.93	0.0	0.80	0.58
Overall: Metformin versus Pioglitazone		94	92	4	-0.29	-3.64-3.06	0.0	0.80	0.87
Saxagliptin 5 mg QD	Metformin 2000 mg QD	32	33	2	-0.11	-0.15-0.06	7.0	0.30	< 0.00001
Outcome: mean LDL-C									
Saxagliptin 5 mg QD	Metformin 2000 mg QD	32	33	2	0.02	-0.25-0.29	0.0	0.36	0.88
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	109	112	2	0.09	-0.16-0.34	0.0	0.88	0.48
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	25	25	2	0.59	-0.19-1.38	73	0.05	0.14
Metformin 850 mg BID for six months	Pioglitazone 45 mg QD	33	31	2	0.80	-13.11-14.70	32	0.23	0.91
Metformin 1500 mg QD for three months	Pioglitazone 45 mg QD	77	75	3	-4.25	-15.11-6.60	27	0.25	0.44

Overall: Metformin versus Pioglitazone		110	106	5	-2.59	-10.42-5.24	18	0.30	0.52
Rosiglitazone 4 mg QD	Metformin 850 mg BID	11	15	1	-0.48	-1.19-0.23	-	-	0.18
Rosiglitazone 4 mg QD	Metformin 1000 mg QD	18	17	1	-0.22	-0.36-0.08	-	-	0.003
Overall: Rosiglitazone versus Metformin		29	32	2	-0.23	-0.37-0.09	0.0	0.48	0.001

***RCT**: randomised control trials, **I²:** heterogeneity, *The overall effect was significant at < 0.05, **CI:** confidence interval, **QD**: once a day, **BID:** Twice a day. **LDL:** low density-lipoprotein, **HDL:** high density lipoprotein, **CRP:** C-reactive protein.*