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Effect of atorvastatin on testosterone levels (Review)

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[Intervention Review]

Effect of atorvastatin on testosterone levels

Muhammad Ismail Shawish[1], Bahador Bagheri[2,3], Vijaya M Musini[1], Stephen P Adams[1], James M Wright[1]

[1]Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, Canada. [2]Cancer Research Center, Semnan University of Medical Sciences, Semnan, Iran. [3]Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland

Contact address: Muhammad Ismail Shawish, ishawish@student.ubc.ca.

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ABSTRACT

Background

Statins are one of the most prescribed classes of drugs worldwide. Atorvastatin, the most prescribed statin, is currently used to treat conditions such as hypercholesterolaemia and dyslipidaemia. By reducing the level of cholesterol, which is the precursor of the steroidogenesis pathway, atorvastatin may cause a reduction in levels of testosterone and other androgens. Testosterone and other androgens play important roles in biological functions. A potential reduction in androgen levels, caused by atorvastatin might cause negative effects in most settings. In contrast, in the setting of polycystic ovary syndrome (PCOS), reducing excessive levels of androgens with atorvastatin could be beneficial.

Objectives

Primary objective

To quantify the magnitude of the effect of atorvastatin on total testosterone in both males and females, compared to placebo or no treatment.

Secondary objectives

To quantify the magnitude of the effects of atorvastatin on free testosterone, sex hormone binding globin (SHBG), androstenedione, dehydroepiandrosterone sulphate (DHEAS) concentrations, free androgen index (FAI), and withdrawal due to adverse effects (WDAEs) in both males and females, compared to placebo or no treatment.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for randomized controlled trials (RCTs) up to 9 November 2020: the Cochrane Hypertension Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; Embase; ;two international trials registries, and the websites of the US Food and Drug Administration, the European Patent Office and the Pfizer pharmaceutical corporation. These searches had no language restrictions. We also contacted authors of relevant articles regarding further published and unpublished work.

Selection criteria

RCTs of daily atorvastatin for at least three weeks, compared with placebo or no treatment, and assessing change in testosterone levels in males or females.

Data collection and analysis

Two review authors independently screened the citations, extracted the data and assessed the risk of bias of the included studies. We used the mean difference (MD) with associated 95% confidence intervals (CI) to report the effect size of continuous outcomes,and the risk ratio (RR) to report effect sizes of the sole dichotomous outcome (WDAEs). We used a fixed-effect meta-analytic model to combine effect estimates across studies, and risk ratio to report effect size of the dichotomous outcomes. We used GRADE to assess the certainty of the evidence.

Main results

We included six RCTs involving 265 participants who completed the study and their data was reported. Participants in two of the studies were male with normal lipid profile or mild dyslipidaemia (N = 140); the mean age of participants was 68 years. Participants in four of the studies were female with PCOS (N = 125); the mean age of participants was 32 years. We found no significant difference in testosterone levels in males between atorvastatin and placebo, MD -0.20 nmol/L (95% CI -0.77 to 0.37). In females, atorvastatin may reduce total testosterone by -0.27 nmol/L (95% CI -0.50 to -0.04), FAI by -2.59 nmol/L (95% CI -3.62 to -1.57), androstenedione by -1.37 nmol/L (95% CI -2.26 to -0.49), and DHEAS by -0.63 µmol/l (95% CI -1.12 to -0.15). Furthermore, compared to placebo, atorvastatin increased SHBG concentrations in females by 3.11 nmol/L (95% CI 0.23 to 5.99). We identified no studies in healthy females (i.e. females with normal testosterone levels) or children (under age 18). Importantly, no study reported on free testosterone levels.

Authors' conclusions

We found no significant difference between atorvastatin and placebo on the levels of total testosterone in males. In females with PCOS, atorvastatin lowered the total testosterone, FAI, androstenedione, and DHEAS. The certainty of evidence ranged from low to very low for both comparisons. More RCTs studying the effect of atorvastatin on testosterone are needed.

PLAIN LANGUAGE SUMMARY

What is the effect of atorvastatin on testosterone and other hormone levels in men and women?

Background

Statins are one of the most prescribed classes of drugs, and atorvastatin is the most used drug in that class. People take statins to lower their blood cholesterol levels and reduce their risk of heart disease. However, statins may also lower levels of testosterone and other androgens. These are hormones that have important functions in male and female health and development.

What did we do?

We wanted to measure the effect of atorvastatin on testosterone and other androgens.We searched for all studies in the medical literature that compared the effect of different doses of atorvastatin to placebo or no treatment in males and females, and also reported on their levels of testosterone and other androgens. We looked for studies in which the treatments people received were decided at random. This type of study usually gives the most reliable evidence about the effects of a treatment. Studies could have participants of any age.

After we identified these studies, we compared the results, and summarized the evidence from all the studies. Finally, we rated our confidence in the evidence ("certainty of the evidence"), based on such factors such as study methods and sizes, and how consistent the findings were across studies.

What did we find?

We found six studies, involving a total of 265 participants. Studies were conducted in China, Finland, Iran, Turkey, the UK and the USA.

Evidence from four studies suggests that atorvastatin may have a potentially beneficial effect in females with polycystic ovary syndrome (PCOS), a set of symptoms that may develop in women with higher than normal androgen levels. In women with PCOS, atorvastatin helped to decrease total testosterone and other androgens.

We found two studies in men, where atorvastatin had no significant effect on total testosterone.

What does this mean?

The certainty of the evidence for all outcomes ranged from low to very low. Our statistical estimates for the effects of atorvastatin on testosterone and other androgens in males and females may be very different from the true effects. More studies are needed to answer this important question.

How up-to-date is this evidence?

The evidence from our review is current to November 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Population: Male participants

Intervention: Atorvastatin

Comparison: Placebo or no treatment

Outcomes	Number of participants (RCTs)	Mean difference of atorvastatin compared to placebo (95% CI)	The certainty of evidence (GRADE)
Total testosterone	140 (2)	-0.20 nmol/L (-0.77 to 0.37)	Very low [1, 2, 3]

Acronyms and grades

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RCT: randomized controlled trial

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Unclear risk of selection bias.
2 95% confidence interval around the best effect estimate includes both a reduction and an increase in total testosterone.
3 Evidence was derived from only two studies, which had several limitations.

Summary of findings 2. Summary of findings

Population: Adult female participants with PCOS

Intervention: Atorvastatin

Comparison: Placebo

Outcomes	Number of participants (RCTs)	Mean difference of atorvastatin compared to placebo (95% CI)	The certainty of evidence (GRADE)
Total testosterone	125 (4)	-0.27 nmol/L (-0.50 to -0.04)	Very low [1, 2,3]
FAI	65 (2)	-2.59 (-3.62 to -1.57)	Very low [1, 2, 3]
SHBG	65 (2)	3.11 nmol/L (0.23 to 5.99)	Low [1, 3]
Androstenedione	125 (4)	-1.37 nmol/L (-2.26 to -0.49)	Very low [1, 2, 3]

DHEAS	125 (4)	-0.63 µmol/L (-1.12 to -0.15)	Low [1, 3]

Acronyms and grades

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; DHEAS: dehydroepiandrosterone sulphate; FAI: free androgen index; RCT: randomized controlled trial; SHBG: sex hormone binding globin

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 High risk of bias in source of funding and sponsorship bias in more than one study.
2 Significant heterogeneity.
3 Small sample size.

BACKGROUND

Androgens are a group of sex steroid hormones that are mainly responsible for the development and maintenance of the male sex organs, and secondary male sex traits. Androgens also impact libido and sexual behavior in both males and females. Circulating androgens include testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione (A4), androstenediol (A5), and dihydrotestosterone (DHT). Androgens are mainly produced by the testicles, adrenal cortex, and ovaries (Sriram 2010).

Testosterone, C_{19} H_{28} O_2, is the main male sex hormone. It plays a crucial role in several biological processes, such as regulating the sex drive in both sexes and producing sperm in males. Testosterone is also involved in regulating some other functions in both males and females, e.g. bone mass, muscle mass and strength, fat distribution, and the production of red blood cells (Finkelstein 2013).

Testosterone circulates in the blood in three different forms: as testosterone firmly attached to sex hormone binding globulin (SHBG) (roughly 45% of total testosterone), which is biologically inactive; as free testosterone (approximately 2% to 3% of total testosterone); and as testosterone weakly bound to other proteins, mainly albumin (approximately 50% of total testosterone). Both free testosterone and testosterone attached to albumin are bioavailable for use by tissues (Dunn 1981).

Bioavailable and free testosterone are better measures than total serum testosterone to diagnose abnormal androgen status and their clinical sequelae. However, bioavailable and free testosterone tests are time-consuming, expensive and not always available. Therefore, determining total testosterone level, which is easy and relatively inexpensive to do, is commonly used to diagnose overt male hypogonadism. However, it is an unreliable marker in patients who have total testosterone levels just below the normal range, or in the low normal range. To overcome this issue and provide a more reliable indicator, some researchers use the SHBG and total testosterone, with a formula to calculate an approximate estimate of bioavailable or free testosterone (Stanworth 2008).

The normal ranges of the serum total testosterone are significantly higher in adult men than in adult women, and vary widely depending on various factors that include the laboratory methods used and the patient's age. There is a significant increase in total testosterone in males after puberty and a reduction of approximately 1% in total testosterone per year in males over thirty years old (Brawer 2004; Feldman 2002; Pagana 2015; refer to Table 1).

Research suggests that low serum testosterone in men is associated with health problems, such as reduction in fertility and decreased libido. Low testosterone in both males and females can increase body fat and the incidence of depression. It can also decrease mass and strength of muscles, decrease body hair, decrease the production of red cells leading to anaemia, and decrease bone density (Demers 2010; Traish 2009).

Description of the condition

Statins are 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors, a class of drugs mainly prescribed to lower blood cholesterol. They are widely used in adult patients for secondary and primary prevention of cardiovascular events (Stone 2014). They are also used to lower cholesterol in people of all ages with heterozygous familial hypercholesterolaemia and mixed dyslipidaemia (Schaiff 2008). They are considered to be a highly effective class of drugs in reducing low-density lipoprotein (LDL) cholesterol (Schaiff 2008). Statins are also used to treat women with polycystic ovary syndrome (PCOS) (Sun 2015).

Description of the intervention

Atorvastatin is the most prescribed member of the statin class, which are among the most commonly prescribed medications worldwide (Ioannidis 2014; IQVIA 2017). In Canada, approximately 3 million people aged 20 to 79 (12% of Canada's population) took a statin medication during the period 2007 to 2011; one in four Canadians are potentially eligible for statin treatment (Hennessy 2016). Studies illustrate that long-term statin therapy in secondary prevention significantly reduces all-cause mortality and major adverse cardiovascular events such as myocardial infarction (MI) and stroke. However, it remains controversial whether they reduce mortality in primary prevention patients (Virani 2013; Vrecer 2003).

Atorvastatin is rapidly absorbed after oral administration; reaching peak plasma concentration within one to two hours. Atorvastatin is extensively metabolized by cytochromes P-450 3A4 and P-450 3A5 to two active metabolites ortho- and para-hydroxylated derivatives, which contribute to approximately 70% of the inhibitory activity for HMG-CoA reductase. These two active metabolites also increase the half-life of inhibitory activity for HMG-CoA reductase (about 20 to 30 hours). A Cochrane Review shows that atorvastatin 2.5 mg/day to 80 mg/day reduces total blood LDL-cholesterol by between 27.3% and 52%, respectively (Adams 2015; FDA 2011).

Statins are associated with a number of potential adverse effects. Such adverse effects can be divided into two groups, common adverse effects and serious adverse effects. Common adverse effects include headache, nausea, vomiting, constipation, diarrhoea, rash, insomnia, myalgia, dyspepsia, pain in extremities, upper respiratory infection, arthralgia, elevated creatine kinase (CK), elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), cognitive impairment, and gynaecomastia. Serious adverse effects include muscle symptoms, ranging from muscle pain and weakness to rhabdomyolysis, tendon rupture, acute renal failure, hepatotoxicity, pancreatitis, hypersensitivity reaction, anaphylaxis, photosensitivity, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, thrombocytopaenia, leukopaenia, haemolytic anaemia, diabetes mellitus, and interstitial lung disease (atorvastatin Adverse Reactions - Epocrates Online; Thompson 2016).

The most relevant adverse effect in terms of this review is gynaecomastia. This is listed as a common side effect of statins, which means it occurs in more than 1% of patients. It is a condition clinically defined by an enlargement of male breast tissue, along with other histopathological characteristics including benign proliferation of glandular male breast tissue (Johnson 2009). While the mechanism of action is unclear, statins could lead to gynaecomastia via an increased production of oestrogen, decreased production of androgens, or a combination of both. According to a recent case-control study based on 6147 cases, the use of statins is associated with an increased risk of gynaecomastia

(Skeldon 2018). The occurrence of gynaecomastia among male patients receiving statins most likely reflects an effect of statins to reduce androgen serum levels. This coincides with the hypothesis of our review.

How the intervention might work

The synthesis of steroid hormones occurs within the mitochondria and the endoplasmic reticulum, since the group of required oxidative enzymes exists only within these two intracellular organelles. The transport of free cholesterol from the cytoplasm into the mitochondria is the rate-limiting step. Within the mitochondria, cholesterol is converted to pregnenolone, the immediate precursor, by cytochrome P450 family 11 subfamily A member 1 (CYP11A1). Organs that contain this enzyme, such as the testicles, adrenal cortex, ovaries, and placenta, are the only ones that participate in the synthesis of steroids. The following steps of steroidogenesis are catalyzed by several enzymes that are categorized into two different groups, the cytochrome P450 (CYP) enzymes (oxidative enzymes) and the hydroxysteroid dehydrogenase (HSD) enzymes (Schiffer 2019).

Atorvastatin inhibits the enzyme that converts HMG-CoA into a cholesterol precursor called mevalonic acid in hepatocytes. Atorvastatin molecules bind reversibly to the active site, changing the conformation of the enzyme, which leads to preventing the enzyme from acquiring a functional structure. Inhibition of HMG–CoA reductase leads to a decline in the intracellular cholesterol, resulting in the activation of a protease that cleaves the sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum. SREBPs, in their turn, are translocated in the nucleus and increase the gene expression for LDL receptors in hepatocytes, which leads to a reduction of the circulating LDL and both intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL), precursors for LDL (Stancu 2001).

In terms of its potential effect on testosterone, atorvastatin likely decreases the availability of cholesterol, which is a crucial substrate for testosterone production, leading to a decline in serum testosterone. The reduction of androgen levels can be potentially harmful and an adverse side effect in males and females with normal or below normal testosterone levels. However, women with PCOS (hyperandrogenism) may reap benefits from reduced androgen levels. Distinguishing between these two clinical settings is crucial when the effect of statins on androgen levels is being evaluated.

Why it is important to do this review

Based on the mechanism of action (MOA) of atorvastatin, a decline in the levels of testosterone and other androgens will likely occur in patients taking atorvastatin, as atorvastatin decreases the availability of cholesterol, a crucial precursor for androgen production.

Due to the widely increasing use of atorvastatin and the important role of testosterone in both men and women, concerns have been raised about the effect of atorvastatin on serum testosterone in men and women. A non-Cochrane systematic review attempted to address the effect of statins on testosterone (Schooling 2013). However, this review has a number of limitations. Firstly, it is out of date (the searches range to the end of 2011). It has a limited search strategy, as the review authors searched only MEDLINE and ISI Web of Science, and restricted their search to publications in the English language. Secondly, the review was limited to adults, thus excluding adolescents and children who are potentially particularly vulnerable to reduced serum testosterone levels during their growing years. Thirdly, no protocol was pre-published, and there are errors in the data reported by the review. Finally, the systematic review was potentially biased, as it was funded by one of the manufacturers of rosuvastatin, MedImmune, LLC. At present, there is no Cochrane Review that addresses the effect of atorvastatin on serum testosterone levels.

OBJECTIVES

To quantify the magnitude of the effects of atorvastatin as compared to placebo or no treatment on total testosterone, free testosterone, SHBG, A4, DHEAS concentrations, FAI, and WDAEs.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) with a minimum duration of three weeks, that compared atorvastatin to placebo or no treatment, and measured one or more of the androgenic outcomes.

Types of participants

Participants of both sexes could be of any age, with normal lipid parameters, or any type of hyperlipidaemia or dyslipidaemia. We included participants with various comorbid conditions: diabetes mellitus, hypertension, metabolic syndrome, chronic renal failure, PCOS, or cardiovascular diseases.

Types of interventions

We included atorvastatin doses that ranged from 2.5 mg to 80 mg, administered daily for at least three weeks. We chose a three-week time window in order to allow for a steady-state effect of atorvastatin to occur.

Types of outcome measures

Blood concentrations of different androgens.

Primary outcomes

- The primary outcome of this study was the absolute change in total testosterone concentrations. When the absolute change was reported at different time periods, we chose the absolute change reported at the longest time period.

Secondary outcomes

- Absolute change in free testosterone
- Absolute change in FAI
- Absolute change in DHEAS
- Absolute change in A4
- Absolute change in SHBG

(When the absolute change was reported at different periods for these outcomes, we chose the absolute change at the longest period).

- Patient WDAEs

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist searched the following databases without language, publication year or publication status restrictions:

- the Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 9 November 2020);
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web) (searched 9 November 2020);
- MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 9 November 2020);
- Embase Ovid (from 1974 onwards) (searched 9 November 2020);
- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 9 November 2020);
- World Health Organization International Clinical Trials Registry Platform (www.who.it.trialsearch) (searched 9 November 2020).

The Information Specialist modeled subject strategies for databases on the search strategy designed for MEDLINE. Where appropriate, these strategies were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomized controlled studies (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.c (Higgins 2011). The MEDLINE search strategy was translated into the other databases using the appropriate controlled vocabulary, as applicable. We present search strategies for major databases in Appendix 1.

Searching other resources

The Cochrane Hypertension Information Specialist searched the Hypertension Specialised Register segment (which includes searches of MEDLINE, Embase, and Epistemonikos for systematic reviews) to retrieve existing reviews relevant to this Cochrane Review, so that we could scan their reference lists for additional trials. The Specialised Register also includes searches for controlled trials of CAB Abstracts & Global Health, CINAHL, ProQuest Dissertations & Theses and Web of Science.

We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

Where necessary, we contacted authors of key papers and abstracts to request additional information about their trials, or clarification and further data if trial reports are unclear.

We also searched websites of the following resources, for additional information.

- Pfizer, Inc (Pfizer is the maker of Lipitor which is the commercial name of atorvastatin). (www.pfizer.ca/en/our_products)
- US Food and Drug Administration (www.fda.gov)
- European Patent Office (worldwide.espacenet.com)

Data collection and analysis

Selection of studies

Two review authors independently, in duplicate, screened the titles and abstracts of records that were retrieved in the search results. We applied the eligibility criteria and used the Covidence software (Covidence) to code these records for possible inclusion as ‘yes,’ ‘no’ or ‘maybe’. We excluded articles if the citation appeared completely irrelevant, after reading the title and abstract. We resolved disagreements in the coding by discussion to reach consensus. We obtained the full-text papers for all records coded as ‘yes' and 'maybe' at the title and abstract screening stage. Two review authors independently screened the full-text papers in duplicate to decide which studies met the inclusion criteria. We resolved disagreements by discussion, with adjudication by a third review author (JMW) in the event of non-consensus. We provided the reasons for exclusion and bibliographic details for all articles excluded after full-text review. We identified multiple full-text papers of the same study, which we linked and treated as a single study. We also checked the list of references in the included studies and the articles that cited the included studies in Google Scholar, to identify relevant articles. We created a PRISMA chart diagram to document and report the flow of records and studies through the systematic review process (Liberati 2009).

Data extraction and management

We used an electronic data extraction form based on the Cochrane Public Health template (Data Extraction and Assessment Template), modified to allow extraction of all data required for this review. Two authors independently performed the data extraction, and followed this by a cross-check of the data. We described the characteristics of each included study in the 'Characteristics of included studies' table.

Our data extraction form included details on study design, type of masking, PICO (i.e. the study's population, intervention, comparison, and outcome) elements, primary and secondary outcomes, effect estimates, mean differences (MDs), confidence intervals (CIs), standard deviation (SD) for each group and main differences, details of interventions and comparators, duration of interventions, baseline characteristics of the participants, statistical analysis, the follow-up duration, number of participants lost to follow-up, and funding sources.

We resolved discrepancies by rechecking the data, as well as through discussion and consensus between the two review authors. When we are not able to reach an agreement, a third review author (JMW) acted as arbiter. When necessary, we contacted the authors of the studies to provide clarification on ambiguous information. All extracted data was entered and double-checked in RevMan 5 software (RevMan 2014).

Assessment of risk of bias in included studies

We independently assessed the risk of bias of the included studies using the Cochrane 'Risk of bias' tool (version 1) following Chapter 8 of the *Cochrane Handbook*, for the following domains (Higgins 2011):

- sequence generation (selection bias);
- allocation sequence concealment (selection bias);
- blinding of participants (performance bias);

- blinding of outcome assessors (detection bias);
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias); and
- other potential sources of bias (conflict of interest, funding source)

We produced 'Risk of bias' tables as outlined in the *Cochrane Handbook*, Chapter 8 (Chapter 8). We reported the information obtained in our bias assessment in the 'Risk of bias' tables associated with each included trial.

We included all studies in the meta-analysis, regardless of our assessment of the risk of bias. We performed a sensitivity analysis, excluding studies with a high risk of bias, to explore their impact on the treatment effect estimate. This risk of bias across studies informed our assessment of the certainty of evidence, using the GRADE framework.

Measures of treatment effect

For continuous outcomes, we calculated the MD by using mean values, corresponding SDs, and treatment arm sizes. Moreover, we analyzed the data using 95% CIs. We summarized dichotomous data (from studies reporting WDAEs) as risk ratios (RRs) with 95% CIs. We used an intention-to-treat (ITT) analysis.

Unit of analysis issues

As we included no cross-over trials, we had no unit of analysis issues for cross-over trials. For multi-arm trials, if a study reported more than one intervention arm (with other drugs than atorvastatin), we identified the relevant intervention arm (atorvastatin in any dose) and included that in the review.

Dealing with missing data

We sought missing or unclear data from reports of included studies by contacting the study authors using the contact information provided in the respective articles.

The most common type of value that was not reported was the SD of the change. If a standard error (SE) was given instead of the SD, we used the formula "SD = SE x square root of n" (with 'n' signifying the number of participants) to calculate the SD. We also calculated SD if the 95% CI, P value, or t value were reported in the included studies, according to Chapter 16 of the *Cochrane Handbook* Chapter 16 . If we were not able to obtain the SD from the study authors or calculate from the values mentioned above, we imputed SD using the following hierarchy (listed from highest to lowest):

- SD of the end of treatment value;
- SD of the baseline treatment value; or
- average weighted standard deviation of the change from other trials in the review (Furukawa 2006).

Assessment of heterogeneity

We assessed statistical heterogeneity in results by inspection of a graphical display of the estimated treatment effects from included studies, along with their 95% CIs, and by formal statistical tests of measures of inconsistency (I^2 statistic) (Higgins 2002). If the I^2 statistic value was greater than 50%, we investigated the reasons behind the heterogeneity by looking for clinical and methodological differences among trials.

Assessment of reporting biases

As fewer than 10 studies contributed to any meta-analysis, we did not use a funnel plot to detect the extent of risk of reporting bias, based on the symmetry of the plot, as we had planned to do in the protocol. However, we have discussed the other types of reporting bias, for example multiple publication bias, outcome reporting bias, and language bias (Sterne 2011).

Data synthesis

We used Review Manager 5 (RevMan 2014) to perform data synthesis, and meta-analyzed the results of clinically and statistically homogeneous studies. We analyzed data for each group (males, females and overall) separately. We performed meta-analyses using the Mantel-Haenszel method for dichotomous outcomes (RR) with 95% CIs, using a fixed-effect model, and the inverse variance method for continuous outcomes as MD with 95% CIs, using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned on performing subgroup analysis based on the following.

- According to various doses
- Males versus females
- Age ≥ 60 years versus age < 60 years
- Children (age < 18 years) versus adult (age ≥ 18 years)

It was not possible to conduct a subgroup analysis based on participant age, as we did not have sufficient data.

Sensitivity analysis

We planned the following sensitivity analyses.

- To check if the trials with high risk of bias affected the effect estimate of total testosterone, DHEAS, and A4
- To check the difference between the effect estimates of the outcomes derived by using a fixed-effect model and a random-effects model
- To check the impact of imputed data that we imputed due to missing information on the overall effect size

Summary of findings and assessment of the certainty of the evidence

We used GRADEpro software (GRADEpro GDT 2015) to produce an evidence profile table and used that to generate the 'Summary of Findings' table (Schünemann 2011a; Schünemann 2011b). We considered the following domains in assessing the overall certainty of evidence: limitations in study design and implementation (risk of bias), indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision in results and high probability of publication bias. As outlined in the *Cochrane Handbook* (Schünemann 2011b), we assessed the certainty of the body of evidence for each outcome to be high, moderate, low or very low, and review authors provided comments to support these judgements. RCTs started at a high level of certainty and were downgraded by one level for each domain judged to have some serious concerns (Schünemann 2013).

RESULTS

Description of studies

The summary of the screening process is shown in the PRISMA diagram (Figure 1).

Figure 1. PRISMA diagram for screening studies

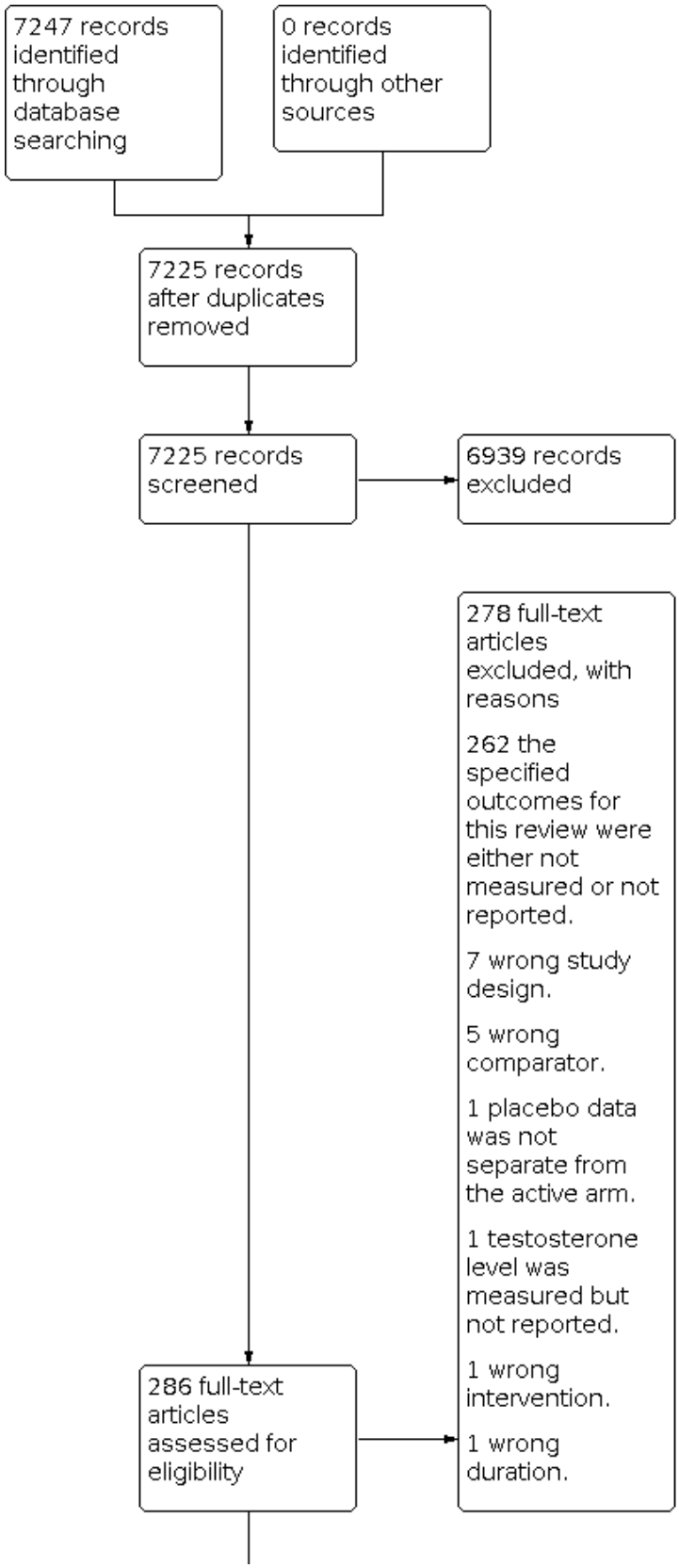
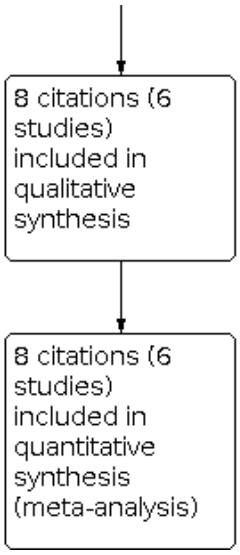


Figure 1. (Continued)



Results of the search

Database searching identified 7247 citations. After duplicates were removed, 7225 records remained. After irrelevant citations were removed, 286 records remained. The remaining 286 records were obtained as full-text articles and assessed for eligibility. Eight citations to six studies (Akbari 2016; Chen 2014; Gokce 2012; Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009) met the inclusion criteria (Figure 1).

Included studies

We have summarized each included study in the 'Characteristics of included studies'. All six studies were published in English. They included 292 participants who were randomized(154 males and 145 females), but only 265 participants(140 males and 125 females) had their data reported. All of them had a parallel-group design. Among the six studies included, one was single-blind, four were double-blind, and one was open-label.

Two of the studies included only male participants (N = 140), with a mean age of 68 years. One study (Gokce 2012) included exclusively healthy male participants while the other study (Chen 2014) included male participants with mild dyslipidaemia and osteopaenia. Four of the studies included female participants (N = 125) and the mean age was 32 years. All participants in the four female studies had PCOS. The dose of atorvastatin in the two male studies was 10 mg. The dose of atorvastatin was 20 mg in two of the female studies, and 40 mg in the remaining two studies.

Excluded studies

We excluded 278 articles after reviewing the full-text articles and recorded the reasons for exclusion. Most articles (262 articles) were excluded because they did not measure and report this review's outcomes of interest. We excluded seven articles because they were not RCTs. In addition, we excluded one study because it measured the testosterone levels but did not report them (see Figure 1 and 'Characteristics of excluded studies').

Risk of bias in included studies

We independently assessed the risk of bias, following the methodology described in Chapter 8 of the *Cochrane Handbook (* Chapter 8).

We assessed the risk of bias based on seven 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);
- other biases (conflict of interest, industry sponsorship).

We assessed the risk of detection bias and reporting bias in WDAEs separately from their assessment in the other outcomes. We also assessed the risk of attrition bias separately for each of the biomedical outcomes. We classified each domain as being at a low, high or uncertain risk of bias.

In the case of disagreement between review authors, a third review author (JMW) helped to discuss and resolve the disagreement.

The expected direction of risk of bias would be to exaggerate the anti-androgen effect of atorvastatin as a potential treatment in women with PCOS, and to underestimate the reduction in androgens when it is was studied and measured as a potential adverse effect of atorvastatin treatment in the general patient population (Figure 2; Figure 3).

Figure 2. Risk of bias summary of the included studies

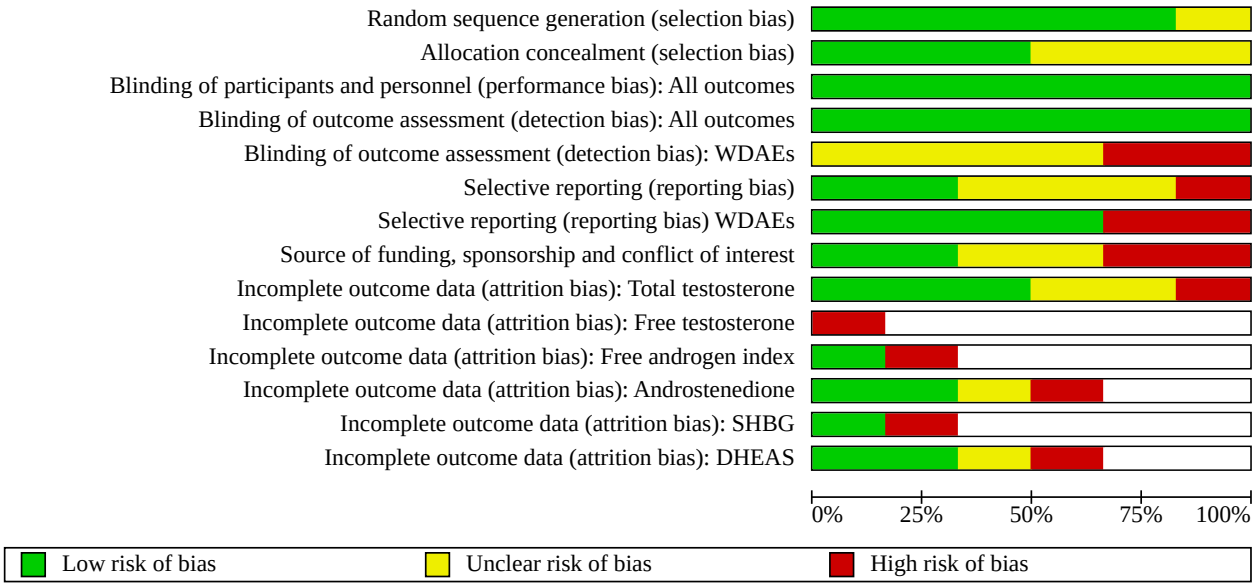
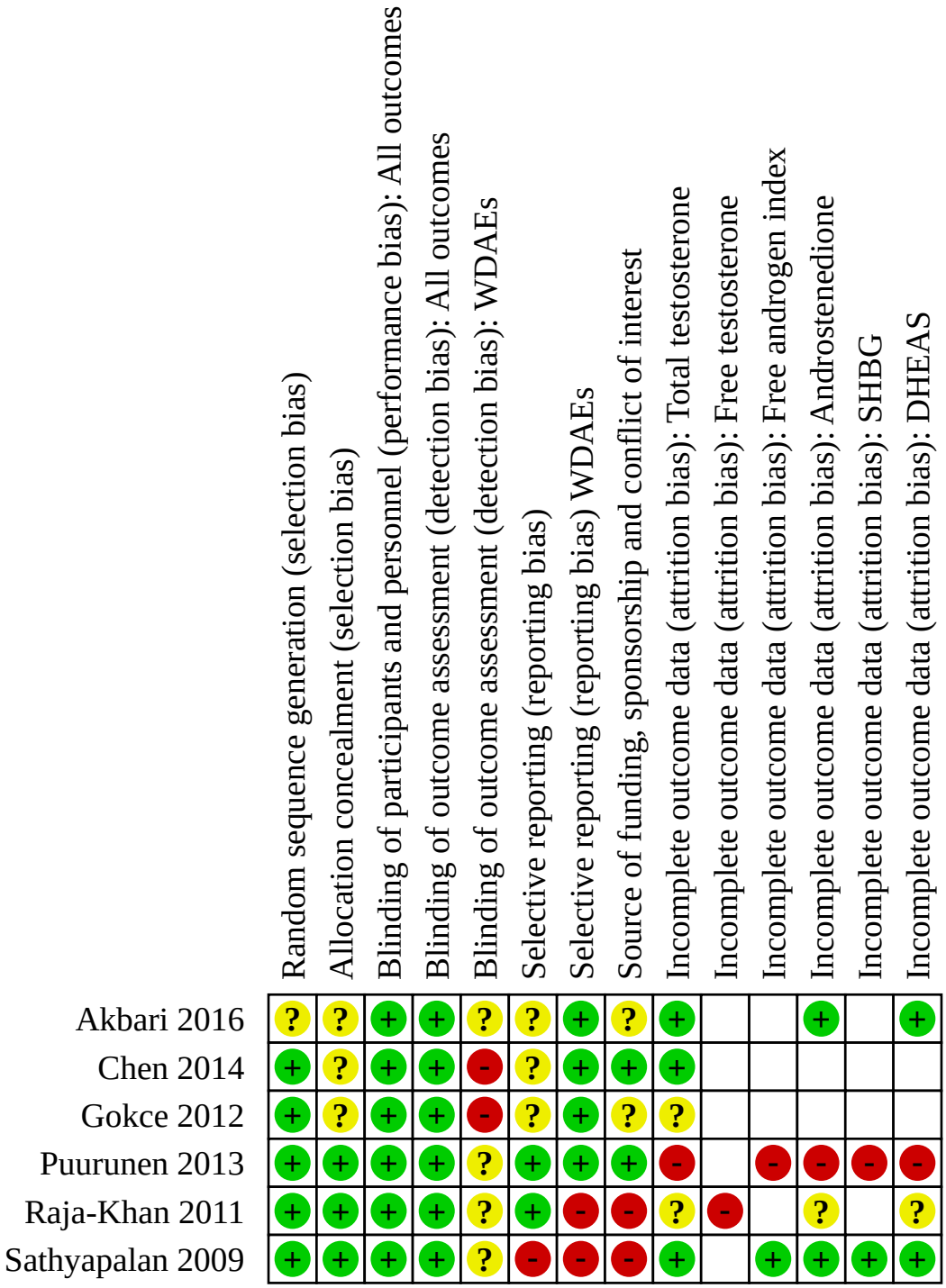


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

We assessed selection bias based on two categories: random sequence generation and allocation concealment.

For random sequence generation, five of the six included studies were classified as having a low risk of bias since they used and described a true randomization method. One study (Akbari 2016) was classified as having an uncertain risk of bias, since the method of randomisation was not described.

For allocation concealment, three included studies (Akbari 2016; Chen 2014; Gokce 2012) were classified as having an uncertain risk of bias because the method of allocation concealment was not reported. The remaining three studies were classified as having a low risk of bias due to the application of appropriate methods, such as central allocation (pharmacy-controlled randomization and sequentially numbered drug containers) (Puurunen 2013) or allocation by external personnel who were not involved in the trial (Raja-Khan 2011; Sathyapalan 2009).

Blinding

All six studies were classified as being at low risk of performance and detection bias, as we consider that the individuals measuring laboratory outcomes were not aware of the treatment allocation.

For WDAEs, a lack of blinding could have had an effect. Four studies (Akbari 2016; Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009) were classified as being at uncertain risk of bias, since the blinding was not described. Two studies (Chen 2014; Gokce 2012) were classified as having high risk of bias, since they were open label and single-blind, respectively.

Incomplete outcome data

We assessed attrition bias based on six outcomes: total testosterone, free testosterone, free androgen index, A4, SHBG, and DHEAS. For total testosterone, three studies (Akbari 2016; Chen 2014; Sathyapalan 2009) were classified as having low risk of bias given that all participants were included in the final analysis, or missing data were balanced across intervention and control groups, with a similar reason for missing data across groups. Two studies (Gokce 2012; Raja-Khan 2011) were classified as being at uncertain risk of bias, since 10% of participants did not complete the trial, although the study authors included all participant data in the analysis. One study (Puurunen 2013) was classified as high risk of bias, since 21.1% of participants were not included in the analysis for the atorvastatin group, and 31.6% of participants were not included in the analysis for the placebo group. For A4 and DHEAS, only four studies measured these outcomes. Two studies (Akbari 2016; Sathyapalan 2009) were classified as having a low risk of bias. Puurunen 2013 was classified as high risk of bias, and Raja-Khan 2011 was assessed to be at uncertain risk of bias. For free testosterone, only one study reported this outcome (Raja-Khan 2011) and was classified as high risk of bias, since only baseline data was reported. For SHBG and FAI, only two studies measured the outcome: Puurunen 2013 was classified as high risk of bias and Sathyapalan 2009 was classified as low risk of bias.

Selective reporting

We assessed this separately for WDAEs and for all other outcomes. For WDAEs, four studies were classified as having low risk of bias (Akbari 2016; Chen 2014; Gokce 2012; Puurunen 2013) because they recorded and reported the WDAEs in the result section. Two studies (Raja-Khan 2011; Sathyapalan 2009) were classified as having unclear risk of bias since the WDAEs were not reported separately from withdrawals due to other reasons.

For all other outcomes, three studies (Akbari 2016; Chen 2014; Gokce 2012) were classified as having uncertain risk of bias since no protocol was published and there was insufficient information to evaluate if it was at low or high risk of bias. Two studies (Puurunen 2013; Raja-Khan 2011) were classified as low risk of bias since all of each study's prespecified outcomes were reported. One study (Sathyapalan 2009) was classified as having high risk of bias since one reported primary outcome (HS-CRP) was not prespecified in its trial registration.

Other potential sources of bias

In this domain, the other potential sources of bias assessed included industry sponsorship. Two studies (Chen 2014, Puurunen 2013) were classified as having low risk of bias because they were funded by government grants. Two studies (Akbari 2016; Gokce 2012) were classified as being at uncertain risk of bias since the funding source was not reported. Two studies (Raja-Khan 2011; Sathyapalan 2009) were classified as high risk of bias because they were funded partially or fully by the Pfizer pharmaceutical company.

Publication bias

We did not pool data from a sufficient number of studies to construct funnel plots for assessing publication bias. However, all studies were published in English. Only six studies from more than 268 placebo-controlled RCTs identified in our search results reported total testosterone levels, and only two studies reported this outcome in males. There are no studies in healthy females or children (under age 18). This suggests that there are likely RCTs measuring and demonstrating an effect of atorvastatin in reducing testosterone and other androgen levels that were not published, because the results of such RCTs might adversely impact the marketing of atorvastatin.

Effects of interventions

See: **Summary of findings 1** Summary of findings; **Summary of findings 2** Summary of findings

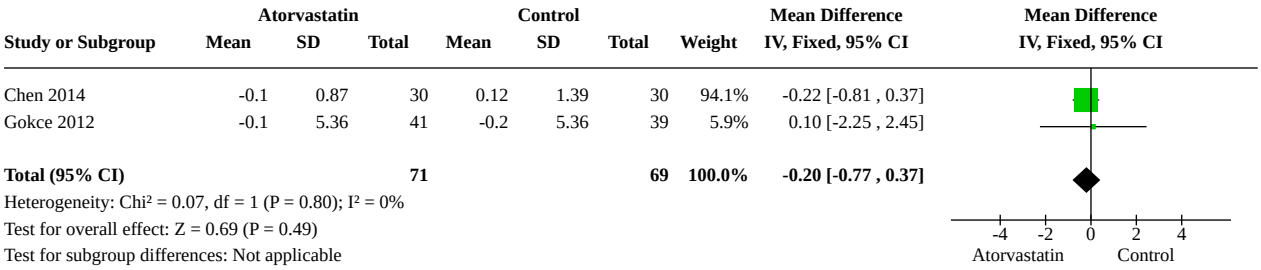
While in the general patient population, the reduction of testosterone levels caused by the administration of lipid-reducing interventions including atorvastatin is considered an adverse side effect, this reduction is potentially beneficial in trials in which atorvastatin is administrated as a treatment for PCOS. Because the risk of bias is in the opposite direction in these two clinical settings, we presented and pooled these two clinical settings separately.

1. The potential adverse effect of atorvastatin on androgens

Effect of atorvastatin on total testosterone levels (males)

Based on two studies (Chen 2014; Gokce 2012), in 140 male participants, the mean change in total testosterone, using a fixed-effect model, was -0.20 nmol/L (95% CI -0.77 to 0.37; P = 0.49). There was no heterogeneity (I^2 = 0%) (Figure 4) .

Figure 4. Forest plot of comparison: Atorvastatin versus control (fixed-effect model), outcome: Total testosterone in males.



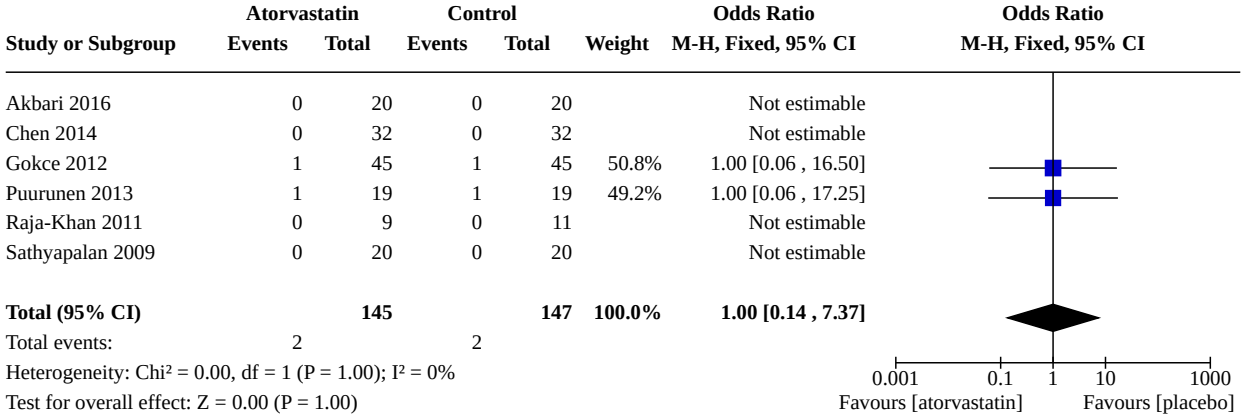
Effect of atorvastatin on free testosterone levels (males)

None of the included studies reported data for this outcome.

Effect of atorvastatin on WDAEs in males and females

Based on six studies (Akbari 2016; Chen 2014; Gokce 2012; Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009) in 292 participants, the RR for WDAEs using the fixed-effect model was 1.00 (95% CI 0.14 to 7.37; P = 1.00). There was no heterogeneity (I^2 = 0%) (Figure 5).

Figure 5. Forest plot of comparison: 5 Atorvastatin versus control (fixed-effect model), outcome: 5.7 Withdrawal due to adverse effects (WDAEs).

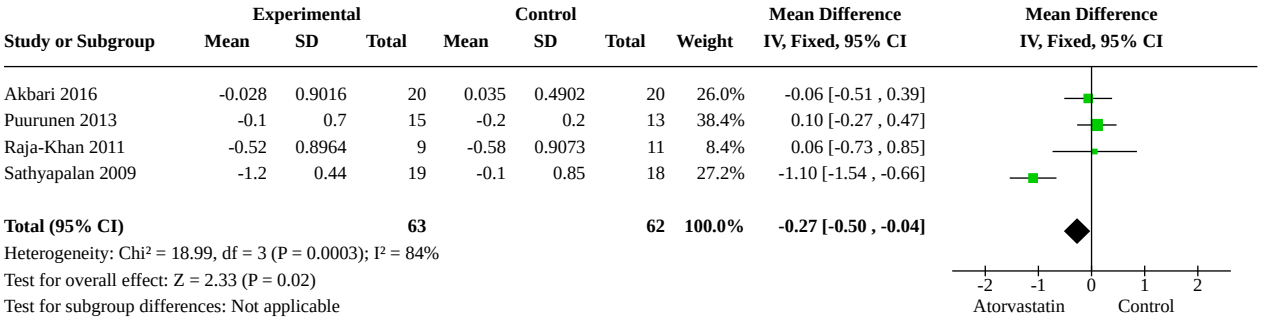


2. The possible beneficial effects of atorvastatin for the treatment of PCOS

Effect of atorvastatin on total testosterone levels

Based on four studies (Akbari 2016; Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009) in 125 participants, atorvastatin decreased total testosterone levels. The mean decrease, using a fixed-effect model, was -0.27 nmol/L (95% CI -0.50 to -0.04; P = 0.02). There was substantial heterogeneity (I^2 = 84%) (Figure 6).

Figure 6.



Effect of atorvastatin on free testosterone levels

None of the included studies reported data for this outcome. Only one study (Raja-Khan 2011) reported free testosterone levels before the treatment, but did not report it after the treatment.

Effect of atorvastatin on FAI

Only two studies in females (Puurunen 2013; Sathyapalan 2009) reported FAI in 65 participants. Atorvastatin decreased FAI. The mean decrease, using a fixed-effect model, was -2.59 (95% CI -3.62 to -1.57; P < 0.00001). There was substantial heterogeneity (I^2 = 94%) (Analysis 1.7).

Effect of atorvastatin on SHBG

Only two studies in females (Puurunen 2013; Sathyapalan 2009) reported SHBG in 65 participants. Atorvastatin increased SHBG. The mean increase, using a fixed-effect model, was 3.11 nmol/L (95% CI 0.23 to 5.99; P < 0.03). There was no heterogeneity (I^2 = 0%) (Analysis 1.3).

Effect of atorvastatin on A4

The four studies in females (Akbari 2016; Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009) reported A4 levels in 125 participants. Atorvastatin decreased A4. The mean decrease, using a fixed-effect model, was -1.37 nmol/L (95% CI -2.26 to -0.49; P = 0.002). There was substantial heterogeneity (I^2 = 68%) (Analysis 1.4).

Effect of atorvastatin on DHEAS

Four studies in females (Akbari 2016; Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009) reported DHEAS in 125 participants. Atorvastatin decreased DHEAS. The mean decrease, using a fixed-effect model, was -0.63 µmol/L (95% CI -1.12 to -0.15 P = 0.01). There was no significant heterogeneity (I^2 = 9%) (Analysis 1.5).

3. Subgroup analysis and exploring heterogeneity

We planned to conduct several subgroup analyses according to dosage and age. Due to the small number of studies, we were not able to conduct subgroup analyses since it is recommended that there should be at least 10 studies in each of the subgroups.

4.Sensitivity analysis

As planned, we conducted a sensitivity analysis to compare the results using the random-effects model and the fixed-effect model. While the reduction in total testosterone, FAI, and androstenedione was statistically significant when the fixed-effect model was used, the reduction in all outcomes mentioned above was not significant when the random-effects model was applied (Analysis 2.1; Analysis 2.2; Analysis 2.3). We planned to conduct sensitivity analysis on the studies based on their level of risk of bias. Most of the included studies had a similar risk of bias across all the domains, except for industry sponsorship bias and incomplete data for total testosterone. Due to the inadequate number of studies, we were not able to conduct a sensitivity analysis on the included studies based on industry sponsorship.

DISCUSSION

This review summarizes the effects of atorvastatin on total testosterone, A4, DHEAS, FAI, and SHBG serum levels in males and females. The primary focus of the review was to document the effect of atorvastatin on these outcomes as a potential adverse effect. However, in conducting the review we identified RCTs meeting the inclusion criteria in which patients with PCOS were given atorvastatin with the goal of reducing androgens, as a potential treatment.

For trials studying the possible adverse effect of atorvastatin to decrease androgens, there is a potential bias towards not showing this effect or not reporting RCTs that found this adverse effect. The knowledge that atorvastatin decreased testosterone could result in a negative impact on sales of atorvastatin.

Summary of main results

1. Summary of the results of the possible adverse effect of atorvastatin on androgens

Effect of atorvastatin on total testosterone

In this review, we only found two trials investigating the effects of atorvastatin on androgen levels among males and no studies reporting the effect of atorvastatin on androgens in normal females. This was a surprising and shocking finding, as we anticipated a much larger number of studies looking at the effects of atorvastatin on androgen levels, given the widespread use of atorvastatin. The dearth of studies, the small sample size and the fact that other androgen levels were not reported resulted in the pooled effect of atorvastatin in males showing a statistically non-significant reduction of total testosterone levels. In addition, the two studies we found used a relatively low dose of atorvastatin, 10 mg/day, when we know that atorvastatin daily doses of 80 mg/day are commonly used. We highly suspect that the companies marketing atorvastatin have successfully suppressed the conduct

and/or publication of trials showing the reduction of testosterone and other androgens.

Additionally, it is important to mention that atorvastatin is given as a treatment for children and adolescents with familial hypercholesterolaemia. In this population, where reduction of androgens is more likely to be problematic, we again found no RCTs reporting the effects of atorvastatin on testosterone or other androgens.

Effect of atorvastatin on free testosterone and other androgens

Although free testosterone is a better indicator of the androgen status than total testosterone, no study reported free testosterone levels.

2. Summary of the results of the possible beneficial effects of atorvastatin for the treatment of PCOS

Effect of atorvastatin on total testosterone

For the possible beneficial reduction of total testosterone levels among females with PCOS, the direction of the potential risk of bias is towards a reduction, as the trials are designed to demonstrate that atorvastatin can be used to treat women with PCOS. In this review, we found that atorvastatin decreased total testosterone levels in females by -0.27 nmol/l. This finding was based on four studies in females with PCOS.

Effects of atorvastatin on SHBG and FAI

Atorvastatin increased SHBG by 3.11 nmol/l and decreased FAI by 2.59 nmol/L. These results were based on only two studies in females with PCOS. The increase in SHBG levels suggests that more testosterone is bound and that there is less bioavailable free testosterone for tissues. The decrease in FAI corresponds with an increase in SHBG and a decline in total testosterone.

Effect of atorvastatin on DHEAS and androstenedione

Atorvastatin decreased DHEAS concentration in females by 0.63 µmol/L, and androstenedione by 1.37 nmol/L. These results were based on four studies in females with PCOS. These results can be explained by the steroidogenesis pathway; the reduction in DHEAS levels would have led to a reduction in both A4 and testosterone levels. It is important to appreciate that the decline in A4 concentration may be an overestimate, since heterogeneity in the meta-analysis was substantial and the reduction comes mostly from the Raja-Khan 2011 study, which was sponsored by the pharmaceutical industry.

Effect of Atorvastatin on WDAEs

In the six trials that reported the impact of atorvastatin on WDAEs, drug therapy had no significant effect on WDAEs compared to placebo or no treatment. However, these were small and short-term trials and do not represent a good opportunity to determine whether atorvastatin leads to adverse effects.

Overall completeness and applicability of evidence

Surprisingly, there is very little available published data to evaluate the effect of atorvastatin on testosterone and other androgens. Given that we have presented evidence that atorvastatin decreases testosterone and other androgens in women with PCOS, we suspect that atorvastatin also reduces testosterone in other settings. There are likely trials meeting our inclusion criteria, showing this effect of atorvastatin, that have not been published. It is very likely that atorvastatin reduces testosterone as a result of its mechanism of action to reduce cholesterol levels. Further strong evidence that this is occurring is the fact that gynaecomastia is being recognized as an adverse effect of atorvastatin. The two studies in males represented a range in terms of age and health conditions, with a mean age of 68 years. It is possible that atorvastatin does decrease androgen levels more significantly in a younger population .

The participant populations were older males with normal libido (Gokce 2012) and elder men with mild dyslipidaemia (Chen 2014). The overall evidence generated in this review is insufficient to answer the question in the populations studied, and cannot be extrapolated to men and women of all ages, or to adults with sexual dysfunction.

Regarding the studies in females, the participant population was women with PCOS, predominantly in premenopausal age (younger than age 40). Unfortunately, we do not have any trials studying the effect of atorvastatin on females at any age without PCOS. It is, however, likely that atorvastatin does decrease androgen levels in women without PCOS, and that this could have adverse consequences.

There was substantial heterogeneity in the meta-analysis of the effect of atorvastatin on testosterone in females with PCOS, due to the presence of one study (Sathyapalan 2009). This study was funded by the Pfizer pharmaceutical company. The mean reduction of total testosterone was greater in this study compared to other studies. Thus, we suspect that this reduction may be an overestimate.

There was substantial heterogeneity in the meta-analysis of the effect of atorvastatin on androstenedione in females, due to the presence of one study (Raja-Khan 2011). This study was funded by the pharmaceutical industry. The mean reduction of total testosterone was greater in this study, compared to other studies. The unbalanced baseline between the comparison groups in Puurunen 2013 may explain the substantial heterogeneity between the two studies in the FAI meta-analysis.

Quality of the evidence

We graded the overall certainty of evidence using the GRADE approach, with the GRADEpro GDT software (GRADEpro GDT 2015), and formulated 'Summary of findings' tables, as outlined in the protocol.

We constructed two 'Summary of findings' tables to show the certainty of evidence and a summary of the effects on the outcomes of interest in females (total testosterone, A4, DHEAS, FAI, SHBG, and WDAEs), and total testosterone in males.

In this review, the certainty of evidence ranged from low to very low, which suggests that the estimated effect of atorvastatin may be substantially different from the true effect. Regarding the effect of atorvastatin on total testosterone levels in males, the certainty of evidence was downgraded to very low due to the small size of the studies, wide confidence intervals, and the high risk of bias. Regarding the effect of atorvastatin on total testosterone, A4, and FAI in females, the certainty of evidence was downgraded to very low due to the small size of the studies, significant inconsistency, and the high risk of bias in some domains.

The certainty of evidence for DHEAS and SHBG in studies in females was downgraded to low due to the small sample size and the high risk of bias in some of the studies.

See Summary of findings 1 and Summary of findings 2.

Potential biases in the review process

We employed a robust methodology to assess biases and used comprehensive search strategies to minimize potential for bias by the authors in the selection process of included studies. A few amendments have been implemented on the protocol which were explicitly mentioned and justified.

We have identified several limitations within this review, which are related to the studies that were included. We highly suspect that there are more studies which meet the inclusion criteria and were not published (publication bias), despite our efforts to search the grey literature. Our review's included studies and its data are only applicable to specific population groups, and therefore should not be generalized. The overall sample size of the studies was not sufficiently large to answer our research question. Finally, the reporting of outcomes in some of the included studies tended to be poor in nature. The reporting of the SD of the change in levels was the main problem. In one of the studies in males (Gokce 2012), the authors did not report the SD of the change or the SD of the means, either before or after the intervention. Thus, we imputed the SD of the change from other studies, using the guidance of Furukawa (Furukawa 2006).

In the studies in females, the SD of change was missing, and we had to calculate it from the reported P values. In some studies (Akbari 2016; Puurunen 2013) we imputed the SD of change using the SD of final values. Accordingly, the results should be interpreted with caution. Another major problem related to data reporting was the units of measurements. In one of the included studies (Gokce 2012), the units were reported incorrectly (the testosterone unit was reported as ng/ml instead of ng/dl). Additionally, units were essentially missing, and the author did not report reasons for not including units (Akbari 2016). Furthermore, withdrawal due to adverse effects was not explicitly reported in some of the studies.

Agreements and disagreements with other studies or reviews

One published review (Schooling 2013) examined the effect of atorvastatin on total testosterone. As discussed earlier in this review, Schooling 2013 pooled the effect of all statin agents on testosterone, by assuming that they all had similar effects. We limited the focus of this review only to atorvastatin. Schooling 2013 concluded that statins reduce testosterone in both males and females. However, there are a number of limitations to the Schooling 2013 review, which we have listed in the background.

Another published review (Yang 2019) examined the effect of atorvastatin on DHEAS. Yang pooled the effect of all statin agents on DHEAS and conducted a subgroup that analyzed the effects of atorvastatin and simvastatin separately. According to Yang 2019, atorvastatin significantly reduced DHEAS, compared to simvastatin. The conclusion of Yang 2019, which was based on three of the studies that were included in this review (Puurunen 2013; Raja-Khan 2011; Sathyapalan 2009), aligns with our review's conclusion.

Statin-induced gynaecomastia was reported by several studies and case reports as a potential adverse effect among male patients (Jeong 2019; Roberto 2012; Skeldon 2018). Although our review did not find significant reduction in androgens among male patients taking statins, this could be due to publication bias and the limitations of studies included.

This review did not detect a significant difference in WDAEs between atorvastatin and placebo, since only two studies reported WDAEs. A previous review (Adams 2015) with 43 short-term RCTs reporting WDAEs, also showed no effect of atorvastatin on WDAEs.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides the most up-to-date clinical evidence on the effects of atorvastatin on testosterone and other androgens in males and females.

The studies in females were limited by trialists to women with polycystic ovary syndrome (PCOS). In adult females with PCOS, very low certainty of evidence shows that atorvastatin (20 mg to 40 mg daily) reduced the following androgens: total testosterone by a mean of -0.27 nmol/L, free androgen index (FAI) by -2.59, androstenedione by -1.37 nmol/L, and dehydroepiandrosterone sulphate (DHEAS) by -0.63 µmol /L. Atorvastatin increased sex hormone binding globin (SHBG) by a mean 3.11 nmol/L. The indicated change in the level of androgens illustrates that through lowering cholesterol levels, atorvastatin can lower all the downstream androgens in the steroidogenic pathway. We have judged this evidence to be of low to very low certainty, and it is unknown whether a reduction of androgens by atorvastatin in women with PCOS would have any beneficial clinical effects.

The studies in males were limited by trialists to men with normal libido. In this specific population, very low-certainty evidence suggests that using 10 mg of atorvastatin did not have a significant effect on total testosterone levels. It is impossible to know, with the limited data available, whether atorvastatin reduces androgens, but given the mechanism of action, the fact that atorvastatin reduces androgens in women with PCOS and that it can be associated with gynaecomastia, we have a high degree of suspicion that atorvastatin does reduce androgens in most if not all settings. Therefore, healthcare providers should be aware of the potential reduction in androgens by atorvastatin, and inform patients of this potential adverse effect.

Implications for research

This review provides better understanding of the available evidence on the effects of atorvastatin on androgens and sheds light on the absence of high-quality evidence in certain patient populations. Based on our findings, we recommend the following:

1. More randomized controlled trials (RCTs) are needed to evaluate the effects of atorvastatin on androgens in females with PCOS.
2. More RCTs are needed to evaluate the effects of atorvastatin on androgens in males, using higher doses of atorvastatin.
3. The review did not find any eligible RCTs that reported the effects of atorvastatin on children, healthy females, or males with abnormal libido. Future RCTs in these populations are needed.

4. The procedures of randomization and blinding must be described in detail within published reports.
5. Trials should report the standard deviation (SD) of the change, and the unit of measurement used.
6. Reporting of withdrawal due to adverse effects should be mandatory for all trials.
7. Free testosterone should be measured and reported, as it provides a more reliable measure of androgen status.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akbari 2016

Study characteristics	
Methods	Study design: Randomized placebo controlled trial Masking: Double-blind Number of arms: 2
Participants	**Inclusion criteria:** women with a diagnosis of PCOD based upon existence of 2 of the 3 criteria specified by Rotterdam, BMI > 25.2, LDL > 100, not pregnant, no other reasons for obesity and metabolic and hormone and glands and metabolism issues, no use of metformin and other medicines that create sensitivity to insulin and no use of OCP over the last three months and no consumption of medicines that reduce androgen, not sensitive to atorvastatin, and participants are 18 to 35 years old **Exclusion criteria:** pregnancy, using metformin or any other medicines that cause sensitivity to insulin and OCP over the last 3 months before the research and androgen reducer (using progesterone for withdrawal or keeping mensuration was ok), LDL < 100, BMI < 25, any hormonal or metabolic disorders not related to PCOS, any sensitivity to atorvastatin exhibited by the rise of liver enzymes more than three times the normal level and severe muscle cramps **Baseline Characteristics** Placebo • *n*: 20 • sex: female • BMI: 26.3 • Age:27.7 • *Total cholesterol*: 224.5 mg/dL (5.81 mmol/L) • *LDL cholesterol*: 138.3 mg/dl (3.58 mmol/L) • *HDL cholesterol*: 50.2 mg/dL (1.30 mmol/L) • *Triglycerides*: 182.4 mg/dL (2.06 mmol/L) • Total testosterone: 0.69 nmol/L (19.90 ng/dL) • Androstenedione: 2.3 • DHEAS: 232.6 • Left ovary size: 13.1 • Right ovary size: 13.6

Akbari 2016 *(Continued)*

	40 mg atorvastatin • *n*: 20 • sex: female • BMI: 26.7 • Age:30.9 • *Total cholesterol*: 223.4 mg/dL (5.78 mmol/L) • *LDL cholesterol*: 146.1 mg/dL (3.78 mmol/L) • *HDL cholesterol*: 50.0 mg/dL (1.29 mmol/L) • *Triglycerides*: 134.9 mg/dL (1.52 mmol/L) • Total testosterone: 0.72 nmol/L (20.77 ng/dL) • Androstenedione: 2.5 • DHEAS: 225.3 • Left ovary size: 14.9 • Right ovary size: 15.1
Interventions	**Intervention characteristics** 40 mg/day for 6 weeks Placebo for 6 weeks
Outcomes	Total testosterone, DHEAS and androstenedione
Statistical analysis and reporting	Sequential nonrandom sampling method was used in both groups. The resulting information was analyzed using SPSS 16. As for qualitative variables, indicators such as frequency, mode, mean, and average were calculated. The frequency of qualitative variables was also measured. Independent t test was used to study qualitative variables, while repeated measures test was used to calculate the changes observed in two groups before and after intervention. Forward linear regression was used to study the confounding effect.
Number of participants lost to follow-up	None
Source of funding	not reported
Notes	Location: clinic of Firouzgar Hospital, Tehran, Iran Ethical approval: The ethics committee of Iran University of Medical Sciences studied the ethical aspects of this research and approved it under the code 93/D/105/4431. The ethical principles specified in the Treaty of Helsinki were observed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Used block randomization, but the process for selecting the blocks was not specified "People qualified for the research were randomly divided into randomised blocks containing 4 people in each one."
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Objective outcomes like serum total testosterone, DHEAS and androstenedione are not likely to be influences by lack of blinding

Akbari 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Androgen parameters were measured in a laboratory and the outcome measurements were not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): WDAEs	Unclear risk	Blinding method was not described
Selective reporting (reporting bias)	Unclear risk	No protocol was found, and there is insufficient information to judge if it is low or high risk of bias
Selective reporting (reporting bias) WDAEs	Low risk	WDAE outcome reported
Source of funding, sponsorship and conflict of interest	Unclear risk	Source of funding not reported
Incomplete outcome data (attrition bias): Total testosterone	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias): Androstenedione	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias): DHEAS	Low risk	All participants were included in the efficacy analysis

Chen 2014

Study characteristics	
Methods	Study design: Randomized controlled trial Masking: Open label Number of arms: 2
Participants	**Inclusion criteria:** subjects diagnosed with mild dyslipidaemia and osteopenia before recruitment; and subjects not treated routinely with lipid-lowering drugs in the last 3 months before recruitment **Exclusion criteria:** history of medications for diseases affecting bone metabolism; therapy for osteoporosis with diphosphonate and calcitriol within the last 6 months; other medications including diuretics, testosterones, thyroid hormones, glucocorticoids, or immunosuppressants within the last 1 year; relevant diseases: malignant tumours, severe hepatic or renal dysfunction, hyperthyroidism, and hyperparathyroidism. **Baseline characteristics** Lifestyle guidance • *n*: 32 • sex:male • age: 79.3 • BMI: 23.2 • *Total cholesterol*: 158.5 mg/dL (4.1 mmol/L)

Chen 2014 *(Continued)*

- *LDL cholesterol*: 138.3 mg/dL (3.6 mmol/L)
- *HDL cholesterol*: 50.2 mg/dL (1.2 mmol/L)
- *Triglycerides*: 182.4 mg/dL (1.9 mmol/L)
- Total testosterone: 295.63 ng/dL (10.25 nmol/L)

10 mg/day atorvastatin and lifestyle guidance

- *n*: 32
- sex: male
- age: 80.8
- BMI: 23.1
- *Total cholesterol*: 154.7 mg/dL (4.0 mmol/L)
- *LDL cholesterol*: 143.1 mg/dL (3.7 mmol/L)
- *HDL cholesterol*: 46.4 mg/dL (1.2 mmol/L)
- *Triglycerides*: 168.3 mg/dL (1.9 mmol/L)
- Total testosterone: 306.59 ng/dL (10.63 nmol/L)

Interventions	10 mg/day atorvastatin and lifestyle guidance for 12 months lifestyle guidance for 12 months
Outcomes	Total testosterone (6-12 months)
Statistical analysis and reporting	Statistical analyses were conducted using SPSS package for Windows, version 17.0. All data were expressed as means SEM. Comparison of baseline characteristics between atorvastatin and control groups was based on independent-sample t-test for continuous variables and chi-square test for categorical variables. In follow-up, comparison of parameters between groups was performed at 6 and 12 months using independent-sample t-test or ANOVA for repeated measurements with treatment group as the independent variables and changing of parameters from baseline as the dependent variables as a function of time. In addition, Mauchly's test of sphericity was analyzed to evaluate the assumption of ANOVA for repeated measurements to adjust the degrees of freedom, according to Greenhouse–Geisser correction coefficient e, if necessary. Moreover, comparison of parameters within groups at different time points of follow-up was performed using one-way ANOVA followed by least significant differences test (LSD test). After obtaining the statistical significance of primary and secondary endpoints, Pearson correlation analysis of changed parameters was undertaken. All analyses were two-tailed and P value of <0.05 was considered significant.
Number of participants lost to follow-up	One subject went abroad to visit relatives and three participants were re-treated due to other reasons
Source of funding	grants from National Nature Science Foundation of China (81370360)
Notes	Location: Ren-Ji Hospital, Shanghai Jiao-Tong University Medical School, China Ethical approval: Ethics Committee of Renji Hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Conducted with complete randomization using SPSS package for Windows, version 17.0
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described

Chen 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Objective outcome like serum total testosterone is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Testosterone was measured in a laboratory and the outcome measurement was not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): WDAEs	High risk	No blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding
Selective reporting (reporting bias)	Unclear risk	No protocol was found and there is insufficient information to judge if it is low or high risk of bias
Selective reporting (reporting bias) WDAEs	Low risk	WDAE outcome reported
Source of funding, sponsorship and conflict of interest	Low risk	Government grants from China
Incomplete outcome data (attrition bias): Total testosterone	Low risk	(2/32)*100 = 6.25% were not included in the testosterone measurement for the control group (2/32)*100 = 6.25% were not included in the testosterone measurement for the atorvastatin group missing outcome data balanced in numbers across intervention and control groups with similar reason for missing data across groups

Gokce 2012

Study characteristics	
Methods	Study design: Randomized controlled trial Masking: single-blind Number of arms: 2
Participants	**Inclusion criteria:** 30–70-year-old male patients, normal libido, IIEF< 17, no previous use of PDE5 Is and normal serum testosterone levels 300 ng/dL **Exclusion criteria: h**istory of any pelvic surgery, having any kind of medication for ED, having any neurological or mental problem, liver or hepatic insufficiency, use of nitrates, and use of antiandrogens **Baseline characteristics** Atorvastatin 10 mg/day • *n*:45 were randomized and 41 were measured • sex: male • age: 57.1 • *Total cholesterol*: 195.1 mg/dL (5.04 mmol/L) • *LDL cholesterol*: 127.3 mg/dL (3.29 mmol/L)

Gokce 2012 *(Continued)*

	• *HDL cholesterol*: 42.2 mg/dL (1.09 mmol/L) • *Triglycerides*: 155.6 mg/dL (1.76 mmol/L) • Total testosterone: 323.4 ng/dL (11.21 nmol/L) No treatment • *n*:45 were randomized and 39 were measured • sex: male • age: 55.8 • *Total cholesterol*: 189.4 mg/dL (4.90 mmol/L) • *LDL cholesterol*: 128.4 mg/dL (3.32 mmol/L) • *HDL cholesterol*: 40.9 mg/dL (1.06 mmol/L) • *Triglycerides*: 149.0 mg/dL (1.68 mmol/L) • Total testosterone: 330.7 ng/dL (11.47 nmol/L)
Interventions	10 mg/day atorvastatin for 3 months no treatment for 3 months
Outcomes	Total testosterone (3 months)
Statistical analysis and reporting	Sample size estimation was performed by a conventional statistical program by taking into account an effect size of 50% improvement in symptoms, andminimum number of patients needed to reject the null hypothesis was 120. For randomisation, NCSS program was used, and patients were blinded for the treatment. The statistical analysis was performed by SPSS ver. 15.0. (SPSS Inc.,Chicago, Illinois). Data are expressed as numbers and percentages for discrete variables and as means ± SD for continuous variables. The chi-square analysis or Fisher's exact test was used to assess the significance of differences between dichotomous variables. Continuous variables were compared by Student's t-test or Mann–Whitney U-test.
Number of participants lost to follow-up	Atorvastatin group: one lost to follow up and three discontinued; Of the three that discontinued; one was due to nausea and two was due to lack of efficacy No treatment group: two lost to follow up and four discontinued; Of the four that discontinued; one was due to headache and three was due to lack of efficacy
Source of funding	not reported
Notes	Location: Department of Urology, Ankara University School of Medicine, Adnan Saygun Caddesi, Altındağ˘, Ankara, Turkey Department of Cardiology, Ankara University School of Medicine, Adnan Saygun Caddesi, Altındağ˘, Ankara, Turkey

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization, NCSS program was used
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described
Blinding of participants and personnel (performance bias)	Low risk	Objective outcome like serum total testosterone is not likely to be influenced by lack of blinding

Gokce 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Testosterone was measured in a laboratory and the outcome measurement was not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): WDAEs	High risk	No blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding
Selective reporting (reporting bias)	Unclear risk	No protocol was found and there is insufficient information to judge if it is low or high risk of bias
Selective reporting (reporting bias) WDAEs	Low risk	WDAE outcome reported
Source of funding, sponsorship and conflict of interest	Unclear risk	No source of funding reported
Incomplete outcome data (attrition bias): Total testosterone	Unclear risk	(4/45)*100 = 8.9% were not included in the testosterone measurement for the atorvastatin group (6/45)*100 = 13.3% were not included in the testosterone measurement for the control group

Puurunen 2013

Study characteristics	
Methods	Study design: randomized, double blind, placebo controlled trial Masking: double-blind Number of arms: 2
Participants	**Inclusion criteria:** Caucasian women with PCOS diagnosis, not menopausal, and reliable non hormonal contraception. The diagnoses of PCOS had been assigned to all subjects during their earlier visits to the Department of Obstetrics and Gynecology, the women generally being between the ages of 20 and 30 years, and the researchers confirmed the criteria before the present study. **Exclusion criteria:** T2DM, medication affecting glucose tolerance, lipid metabolism, or steroid synthesis in the preceding 3 months, menopause, regular smoking, abuse of alcohol, previous ovarian drilling, oophorectomy, or hysterectomy, and contraindications regarding the use of atorvastatin. **Baseline characteristics** Placebo • *n*: 19 • sex: female • age: 38.5 • BMI: 26.7 • Total testosterone: 25.96 ng/dL (0.9 nmol/L) • SHBG: 466.45 µg/dL (49.1 nmol/L) • FAI: 2.2 • DHEAS: 143.7 µg/dL (3.9 µmol/L)

Puurunen 2013 *(Continued)*

	• Androstenedione: 252.03 ng/dL (8.8 nmol/L) 20 mg/day atorvastatin • *n*: 19 • sex: female • age: 40.5 • BMI: 30.4 • Total testosterone: 40.38 ng/dL (1.4 nmol/L) • SHBG:386.65 µg/dL (40.7 nmol/L) • FAI: 4.2 • DHEAS: 143.7 µg/dL (3.9 µmol/L) • Androstenedione: 320.77 ng/dL (11.2 nmol/L)
Interventions	Placebo for 6 months Atorvastatin 20 mg/day for 6 months
Outcomes	Total testosterone, SHBG, FAI, DHEAS, Androstenedione
Statistical analysis and reporting	"Androgen secretion and glucose metabolism served as primary outcome measures. Secondary outcome measures were CRP concentrations and lipid profile. Sample size (power analysis) was calculated on the basis of the decrease in serum testosterone levels (baseline, [mean SD], 2.96 0.82 nmol/L; at 12 weeks, 1.76 0.70 nmol/L) during 12 weeks simvastatin treatment in women with PCOS in a study carried out by Duleba et al (13). The analysis revealed that each study group needed to have 15 subjects to have 95% power. A dropout rate of 20% was expected; thus, we needed to recruit 36 subjects. All variables with skewed distribution went through logarithmic transformation before statistical analysis. All statistical analyses were conducted using SPSS software (version 15.0 for Windows; SPSS Inc). The limit of statistical significance was set at P.05. To analyze changes in the levels of serum glucose, insulin, hormones, lipids, andCRPand glucose tolerance indexes within the same study group at 0, 3, and 6 months of treatment, repeated-measures ANOVA was performed for normally distributed variables and Friedman's test was used for variables with a skewed distribution. Where ANOVA was significant or if the parameters related to glucose metabolism had only 2 time points, the paired-samples t test was used for normally distributed variables and Wilcoxon's nonparametric test was used for variables with a skewed distribution. The independent-samples t test or the Mann-Whitney U test was used to analyze differences between the study groups. The effect of baseline testosterone was controlled in repeated-measures ANOVA using baseline testosterone as a covariate."
Number of participants lost to follow-up	10 6 in the placebo group and 4 in the atorvastatin group
Source of funding	The Academy of Finland, the Sigrid Jusélius Foundation, the Finnish Medical Foundation, the National Clinical Graduate School, the Research Foundation of Obstetrics and Gynecology, Oulu University Scholarship Foundation, the North Ostrobothnia Regional fund of the Finnish Cultural Foundation, the Tyyni Tani Foundation of the University of Oulu, and the Finnish-Norwegian Medical Foundation.
Notes	Location: University of Oulu and Oulu University Hospital, Finland Ethical approval: Ethics Committee of Oulu University Hospital and the Finnish Medicines Agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was conducted using a computer-generated randomisation list in blocks of 6"

Puurunen 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation (pharmacy-controlled randomisation and sequentially number drug containers) "carried out at the Oulu University Hospital Pharmacy by personnel not involved in the study". "They also repacked the medication in closed envelopes, which were sequentially numbered".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Objective outcome like serum androgens are not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Androgens were measured in a laboratory and the outcome measurements were not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): WDAEs	Unclear risk	Blinding method was not described
Selective reporting (reporting bias)	Low risk	Study protocol is available (NCT01072097) and all the study's prespecified outcomes were reported
Selective reporting (reporting bias) WDAEs	Low risk	WDAEs were reported
Source of funding, sponsorship and conflict of interest	Low risk	Government grants "This work was supported by the Academy of Finland, the Sigrid Jusélius Foundation, the Finnish Medical Foundation, the National Clinical Graduate School, the Research Foundation of Obstetrics and Gynecology, Oulu University Scholarship Foundation, the North Ostrobothnia Regional fund of the Finnish Cultural Foundation, the Tyyni Tani Foundation of the University of Oulu, and the Finnish-Norwegian Medical Foundation".
Incomplete outcome data (attrition bias): Total testosterone	High risk	(19-15)*100/19 = 21.1% were not included in the analysis for the atorvastatin group (19-13)*100/19 = 31.6% were not included in the analysis for the placebo group
Incomplete outcome data (attrition bias): Free androgen index	High risk	(19-15)*100/19 = 21.1% were not included in the analysis for the atorvastatin group (19-13)*100/19 = 31.6% were not included in the analysis for the placebo group
Incomplete outcome data (attrition bias): Androstenedione	High risk	(19-15)*100/19 = 21.1% were not included in the analysis for the atorvastatin group (19-13)*100/19 = 31.6% were not included in the analysis for the placebo group
Incomplete outcome data (attrition bias): SHBG	High risk	(19-15)*100/19 = 21.1% were not included in the analysis for the atorvastatin group (19-13)*100/19 = 31.6% were not included in the analysis for the placebo group
Incomplete outcome data (attrition bias): DHEAS	High risk	(19-15)*100/19 = 21.1% were not included in the analysis for the atorvastatin group

Puurunen 2013 *(Continued)*

(19-13)*100/19 = 31.6% were not included in the analysis for the placebo group

Raja-Khan 2011

Study characteristics	
Methods	Study design: randomized, double-blind, placebo controlled Masking: double-blind Number of arms: 2
Participants	**Inclusion criteria:** Women with PCOS and LDL-cholesterol > 100 mg/dL were eligible to participate in the study. **Exclusion criteria:** not reported **Baseline characteristics** Placebo • *n*: 11 • sex: female • age: 29.4 • BMI: 36.0 • *Total cholesterol*: 202.8 mg/dL (5.24 mmol/L) • *LDL cholesterol*: 131.3 mg/dL (3.40 mmol/L) • *HDL cholesterol*: 46.5 mg/dL (1.20 mmol/L) • *Triglycerides*: 125.5 mg/dL (1.42 mmol/L) • Total testosterone: 92.3 ng/dL (3.20 nmol/L) • Free testosterone: 20.2 ng/dL (0.70 nmol/L) • DHEAS: 170.2 µg/dL (4.62 µmol/L) • Androstenedione: 380 ng/dL (13.27 nmol/L) 40 mg/day atorvastatin • *n*: 9 • sex: female • age: 33.8 • BMI: 40.1 • *Total cholesterol*: 215.8 mg/dL (5.58 mmol/L) • *LDL cholesterol*: 140.7 mg/dL (3.64 mmol/L) • *HDL cholesterol*: 44.4 mg/dL (1.15 mmol/L) • *Triglycerides*: 153.3 mg/dL (1.73 mmol/L) • Total testosterone: 61.3 ng/dL (2.13 nmol/L) • Free testosterone: 18.1 ng/dL (0.63 nmol/L) • DHEAS: 162.9 µg/dL (4.42 µmol/L) • Androstenedione: 340 ng/dL (11.87 nmol/L)
Interventions	Placebo for 6 weeks Atorvastatin 40 mg/day for 6 weeks
Outcomes	Total testosterone, Free testosterone, Androstenedione and DHEAS

Raja-Khan 2011 *(Continued)*

Statistical analysis and reporting	Linear mixed-effects models, extensions of regression that account for within-subject correlation inherent in pre-post designs, were fit to continuous outcomes to assess the change from baseline to 6weeks within and between treatment groups. All hypotheses tests were two-sided. All analyses were performed by intention-to-treat using SAS software, version 9.1 (SAS Institute Inc., Cary, NC)
Number of participants lost to follow-up	2
Source of funding	National Institutes of Health (NIH) grant number K12HD055882, GCRC grant M01 RR10732 and construction grant C06 RR016499 to Pennsylvania State University and a research grant from Pfizer
Notes	Location: Department of Medicine, Pennsylvania State University College of Medicine, Hershey, Pennsylvania Ethical approval: The institutional review board of Pennsylvania State University approved the study. Written informed consent was obtained from all participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The biostatistician generated a permuted block randomisation scheme"
Allocation concealment (selection bias)	Low risk	"The biostatistician generated a permuted block randomisation scheme for the allocation sequence and provided it to the pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The atorvastatin and placebo were over encapsulated by the pharmacist so that the participants, research coordinator who administered the intervention, and investigators who assessed the outcomes were blinded to group assignment and objective outcome like serum androgens are not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Androgens were measured in a laboratory and the outcome measurements were not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): WDAEs	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Study protocol is available (NCT00529542) and all the study's prespecified outcomes were reported
Selective reporting (reporting bias) WDAEs	High risk	Not reported
Source of funding, sponsorship and conflict of interest	High risk	National Institutes of Health (NIH) grant number K12HD055882, GCRC grant M01 RR10732 and construction grant C06 RR016499 to Pennsylvania State University and a research grant from Pfizer N.R-K. has nothing to disclose. A.R.K. reports ownership of Merck stock. C.S.H. has nothing to disclose. C.M.S. has nothing to disclose. L.M.D. has nothing to disclose. R.S.L. has received speaker honorarium from Merck-Serono and study support from Solvay

Raja-Khan 2011 *(Continued)*

Incomplete outcome data (attrition bias): Total testosterone	Unclear risk	(20-18)*100/20 = 10% did not complete the trial but the authors included all the data of all participants in the analysis
Incomplete outcome data (attrition bias): Free testosterone	High risk	Only baseline free testosterone was reported in each group
Incomplete outcome data (attrition bias): Androstenedione	Unclear risk	(20-18)*100/20 = 10% did not complete the trial but the authors included all the data of all participants in the analysis
Incomplete outcome data (attrition bias): DHEAS	Unclear risk	(20-18)*100/20 = 10% did not complete the trial but the authors included all the data of all participants in the analysis

Sathyapalan 2009

Study characteristics	
Methods	Study design: randomized placebo controlled Masking: double-blind Number of arms: 2
Participants	**Inclusion criteria:** female participants with PCOS and biochemical hyperandrogaenemia Subjects had no concurrent illness, were not on any prescription or over-the-counter medication that was likely to affect insulin sensitivity, lipids, or ovarian function including hormonal contraceptives for the preceding 6 months. None of the patients had statin therapy in the past. Subjects were not planning to conceive and were using barrier contraception. **Exclusion criteria:** Nonclassical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease, and androgen-secreting tumours **Baseline characteristics** Placebo • *n*: 18 • sex: female • age: 28.8 • BMI: 33.94 • *Total cholesterol*: 174.0 mg/dL (4.5 mmol/L) • *LDL cholesterol*: 104.4 mg/dL (2.7 mmol/L) • *HDL cholesterol*: 42.5 mg/dL (1.1 mmol/L) • *Triglycerides*: 123.1 mg/dL (1.39 mmol/L) • Total testosterone: 126.9 ng/dL (4.4 nmol/L) • FAI: 13.9 • SHBG: 303.1 µg/dL (31.9 nmol/L) • DHEAS: 265.5 µg/dL (7.2 µmol/L) • Androstenedione: 160.4 ng/dL (5.6 nmol/L) 40 mg/day atorvastatin • *n*: 19

Sathyapalan 2009 *(Continued)*

- sex: female
- age: 26.6
- BMI: 33.20
- *Total cholesterol*: 215.8 mg/dL (5.58 mmol/L)
- *LDL cholesterol*: 140.8 mg/dL (3.64 mmol/L)
- *HDL cholesterol*: 44.5 mg/dL (1.15 mmol/L)
- *Triglycerides*: 153.2 mg/dL (1.73 mmol/L)
- Total testosterone: 118.3 ng/dL (4.1 nmol/L)
- FAI: 13.4
- SHBG: 295.45 µg/dL (31.1 nmol/L)
- DHEAS: 261.6 µg/dL (7.1 µmol/L)
- Androstenedione: 163.2 ng/dL (5.7 nmol/L)

Interventions	Placebo for 12 weeks Atorvastatin 40 mg/day for 12 weeks
Outcomes	Total testosterone, FAI, SHBG
Statistical analysis and reporting	The sample size was based on the study on the known effect of atorvastatin on hsCRP in patients with impaired fasting glucose with the assumption that a similar effect would occur in those patients with PCOS. Powered specifically for CRP, the minimum difference worth detecting/observed difference was 32.7%, estimated within-group SD was 11.1; therefore, for 90% power and a significance level of 5%, a sample size of 16 per group was calculated. Adjusting for a possible 20% dropout rate meant a total of 40 patients needed to be recruited. Comparisons between both the groups from baseline were carried out using the paired t test for biochemical data and clinical observations. The Wilcoxon signed rank test was applied to biochemical data that violated the assumptions of normality when tested using the Kolmogorov-Smirnov test. The effect of treatment was evaluated by first calculating the percentage change from baseline for all variables studied and then the percentage change for each variable in each patient group, thus negating the differences in the baseline values of the two groups. Between-group comparison of percent changes was performed using independent-samples t test. For all analyses, a two-tailed P 0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows NT, version 14.0 (SPSS Inc., Chicago, IL).
Number of participants lost to follow-up	3 in the atorvastatin group and 2 in the placebo group
Source of funding	Unrestricted grant from Pfizer
Notes	Location: Department of Diabetes and Endocrinology , University of Hull, Hull HU6 7RX, United Kingdom; Department of Clinical Biochemistry , Hull Royal Infirmary, Hull HU3 2JZ, United Kingdom; and Department of Obstetric Ultrasound, Hull and East Yorkshire Women's and Children's Hospital, Hull HU3 2PZ, United Kingdom Ethical approval: All patients gave informed consent. The study was approved by the Hull and East Riding Local Research Ethics committee

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list

Sathyapalan 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	Labelling was done by personnel not involved in the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind objective outcome like serum androgens are not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Androgens were measured in a laboratory and the outcome measurements were not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): WDAEs	Unclear risk	Blinding method was not described
Selective reporting (reporting bias)	High risk	One reported primary outcome (hs-CRP) was not prespecified in the ISRCTN24474824 registry
Selective reporting (reporting bias) WDAEs	High risk	Atorvastatin 1 out of 20 for non-compliance Placebo 2 out of 20 for non-compliance non-compliance **may** be due to WDAEs
Source of funding, sponsorship and conflict of interest	High risk	Unrestricted grant from Pfizer sponsors had no input into study design, its execution, or interpretation of the findings All of the authors have got nothing else to disclose but in 2017 they claimed that the research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector
Incomplete outcome data (attrition bias): Total testosterone	Low risk	Atorvastatin group: (20-19)*100/20 = 5% were not included in the analysis Placebo group: (20-18)*100/20 = 10% were not included in the analysis Both groups: (40-37)*100/40 = 7.5% were not included in the analysis
Incomplete outcome data (attrition bias): Free androgen index	Low risk	Atorvastatin group: (20-19)*100/20 = 5% were not included in the analysis Placebo group: (20-18)*100/20 = 10% were not included in the analysis Both groups: (40-37)*100/40 = 7.5% were not included in the analysis
Incomplete outcome data (attrition bias): Androstenedione	Low risk	Atorvastatin group: (20-19)*100/20 = 5% were not included in the analysis Placebo group: (20-18)*100/20 = 10% were not included in the analysis Both groups: (40-37)*100/40 = 7.5% were not included in the analysis
Incomplete outcome data (attrition bias): SHBG	Low risk	Atorvastatin group: (20-19)*100/20 = 5% were not included in the analysis Placebo group: (20-18)*100/20 = 10% were not included in the analysis Both groups: (40-37)*100/40 = 7.5% were not included in the analysis
Incomplete outcome data (attrition bias): DHEAS	Low risk	Atorvastatin group: (20-19)*100/20 = 5% were not included in the analysis Placebo group: (20-18)*100/20 = 10% were not included in the analysis

Sathyapalan 2009 *(Continued)*

Both groups: (40-37)*100/40 = 7.5% were not included in the analysis

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Almroth 2009	Outcomes specified for this review were not reported or measured
Amarenco 1999	Outcomes specified for this review were not reported or measured
Amarenco 2006	Outcomes specified for this review were not reported or measured
Amarenco 2007a	Outcomes specified for this review were not reported or measured
Amarenco 2007b	Outcomes specified for this review were not reported or measured
Amarenco 2009a	Outcomes specified for this review were not reported or measured
Amarenco 2009b	Outcomes specified for this review were not reported or measured
Amarenco 2009c	Outcomes specified for this review were not reported or measured
Amarenco 2010	Outcomes specified for this review were not reported or measured
Amarenco 2014	Outcomes specified for this review were not reported or measured
Amudha 2008	Outcomes specified for this review were not reported or measured
Anonymous 1998	Outcomes specified for this review were not reported or measured
Bakker-Arkema 1996	Outcomes specified for this review were not reported or measured
Baspinar 2016	Wrong study design; Not randomized
Berthold 2004	Outcomes specified for this review were not reported or measured
Bleda 2012	Outcomes specified for this review were not reported or measured
Bloomfield 2009	Outcomes specified for this review were not reported or measured
Braamskamp 2015	Wrong study design (non-randomized)
Cai 2014	Wrong study design (systematic review)
Chan 2002a	Outcomes specified for this review were not reported or measured
Chan 2002b	Outcomes specified for this review were not reported or measured
Chan 2002c	Outcomes specified for this review were not reported or measured
Chan 2006	Outcomes specified for this review were not reported or measured
Chapman 2011	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Clough 2009	Outcomes specified for this review were not reported or measured
Cohn 2009	Outcomes specified for this review were not reported or measured
Colhoun 2004	Outcomes specified for this review were not reported or measured
Crisostomo 2008	Outcomes specified for this review were not reported or measured
Cubeddu 2006	Outcomes specified for this review were not reported or measured
Cui 2006	Outcomes specified for this review were not reported or measured
Dallinga-Thie 2006a	Outcomes specified for this review were not reported or measured
Dallinga-Thie 2006b	Outcomes specified for this review were not reported or measured
Davidson 2002	Outcomes specified for this review were not reported or measured
Deanfield 2010	Outcomes specified for this review were not reported or measured
Diabetes 2001	Outcomes specified for this review were not reported or measured
Diepeveen 2005	Outcomes specified for this review were not reported or measured
Dogra 2007	Outcomes specified for this review were not reported or measured
Economides 2004	Outcomes specified for this review were not reported or measured
Elkawy 2014	Testosterone level was measured but not reported
EUCTR2004-000139-27-SE	Outcomes specified for this review were not reported or measured
Faludi 2004	Outcomes specified for this review were not reported or measured
Ferrier 2002a	Outcomes specified for this review were not reported or measured
Ferrier 2002b	Outcomes specified for this review were not reported or measured
Fogari 2004	Outcomes specified for this review were not reported or measured
Fogari 2006	Outcomes specified for this review were not reported or measured
Freed 2002	Outcomes specified for this review were not reported or measured
Ge 2008	Outcomes specified for this review were not reported or measured
Gentile 2000	Outcomes specified for this review were not reported or measured
GlaxoSmithKline 2000	Outcomes specified for this review were not reported or measured
Glinkina 2008	Outcomes specified for this review were not reported or measured
Goldstein 2008	Outcomes specified for this review were not reported or measured
Goldstein 2009	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Grimm 2010	Outcomes specified for this review were not reported or measured
Guo 2012	Outcomes specified for this review were not reported or measured
Hernandez 2010	Outcomes specified for this review were not reported or measured
Holman 2009	Outcomes specified for this review were not reported or measured
Holmberg 2005	Outcomes specified for this review were not reported or measured
Horwich 2011	Outcomes specified for this review were not reported or measured
Hunninghake 2001	Outcomes specified for this review were not reported or measured
Huptas 2006	Outcomes specified for this review were not reported or measured
Iavenko 2014	Outcomes specified for this review were not reported or measured
Inukai 2011	Outcomes specified for this review were not reported or measured
IRCT201208299626N1	Wrong comparator
Ishola 2017	Wrong study design (animal study)
Issa 2012	Outcomes specified for this review were not reported or measured
Jayaram 2007	Outcomes specified for this review were not reported or measured
J-CLAS 1997	Outcomes specified for this review were not reported or measured
Joy 2008	Outcomes specified for this review were not reported or measured
JPRN-UMIN000001114	Outcomes specified for this review were not reported or measured
Kadoglou 2011	Outcomes specified for this review were not reported or measured
Kajimoto 2009	Outcomes specified for this review were not reported or measured
Kanadasi 2006	Outcomes specified for this review were not reported or measured
Kappelle 2009	Outcomes specified for this review were not reported or measured
Kappelle 2010	Outcomes specified for this review were not reported or measured
Karam 2008	Outcomes specified for this review were not reported or measured
Kishi 2009	Outcomes specified for this review were not reported or measured
Kitas 2019	Outcomes specified for this review were not reported or measured
Knopp 2006	Outcomes specified for this review were not reported or measured
Koh 2005	Outcomes specified for this review were not reported or measured
Koh 2010	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Kom 2007	Outcomes specified for this review were not reported or measured
Konduracka 2008	Outcomes specified for this review were not reported or measured
Krysiak 2010	Outcomes specified for this review were not reported or measured
Krysiak 2014	Wrong comparator; absence of controls
Krysiak 2016	Wrong study design (non-randomized)
Kubler 2003	Outcomes specified for this review were not reported or measured
Kuznetsova 2010	wrong duration (14 days)
Lamon-Fava 2007	Outcomes specified for this review were not reported or measured
Lavallee 2009	Outcomes specified for this review were not reported or measured
Lawrence 2004	Outcomes specified for this review were not reported or measured
Lewandowski 2008	Outcomes specified for this review were not reported or measured
Li 2006	Outcomes specified for this review were not reported or measured
Li 2010	Outcomes specified for this review were not reported or measured
Lins 2004	Outcomes specified for this review were not reported or measured
Liu 2009	Outcomes specified for this review were not reported or measured
Loughrey 2013	Outcomes specified for this review were not reported or measured
Macchia 2012	Outcomes specified for this review were not reported or measured
Macin 2005	Outcomes specified for this review were not reported or measured
Magen 2004	Outcomes specified for this review were not reported or measured
Maggioni 2018	Outcomes specified for this review were not reported or measured
Mal'gina 2007	Outcomes specified for this review were not reported or measured
Malekzadeh 2010	Outcomes specified for this review were not reported or measured
Manuel 2003	Outcomes specified for this review were not reported or measured
Marais 1997	Outcomes specified for this review were not reported or measured
Marchesi 2000	Outcomes specified for this review were not reported or measured
Martin 2011	Outcomes specified for this review were not reported or measured
Martin-Ventura 2005	Outcomes specified for this review were not reported or measured
McCrindle 2003	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Mehta 2007	Outcomes specified for this review were not reported or measured
Meng 2009	Outcomes specified for this review were not reported or measured
Messerli 2006	Outcomes specified for this review were not reported or measured
Mills 2007	Outcomes specified for this review were not reported or measured
Mishra 2005	Outcomes specified for this review were not reported or measured
Moga 2005	Outcomes specified for this review were not reported or measured
Mohler 2003	Outcomes specified for this review were not reported or measured
Moini 2012	Outcomes specified for this review were not reported or measured
Monteiro 2008	Outcomes specified for this review were not reported or measured
Muscari 2001	Outcomes specified for this review were not reported or measured
Nakamura 1997	Outcomes specified for this review were not reported or measured
Nakamura 2007	Outcomes specified for this review were not reported or measured
Naoumova 1997	Outcomes specified for this review were not reported or measured
Naoumova 1999	Outcomes specified for this review were not reported or measured
Naoumova 2003	Outcomes specified for this review were not reported or measured
Nawawi 2003	Outcomes specified for this review were not reported or measured
Nawrocki 1995	Outcomes specified for this review were not reported or measured
NCT00433823	Wrong comparator; no placebo;
NCT00522158	Wrong comparator; no placebo
NCT00603590	Outcomes specified for this review were not reported or measured
NCT01555632	Wrong setting; Study was withdrawn before participants were enrolled
NCT02497638	Wrong setting; Not started yet
NCT03784703	Outcomes specified for this review were not reported or measured
NCT04101136	Outcomes specified for this review were not reported or measured
Negi 2011	Outcomes specified for this review were not reported or measured
Neil 2010	Outcomes specified for this review were not reported or measured
Neutel 2009	Outcomes specified for this review were not reported or measured
Nicholls 2011	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Nikitina 2009	Outcomes specified for this review were not reported or measured
Nissen 2007	Outcomes specified for this review were not reported or measured
O'Neill 2001	Outcomes specified for this review were not reported or measured
Okazaki 2004	Outcomes specified for this review were not reported or measured
Okopien 2004	Outcomes specified for this review were not reported or measured
Okopien 2005	Outcomes specified for this review were not reported or measured
Olivotti 2002	Outcomes specified for this review were not reported or measured
Olsson 2001	Outcomes specified for this review were not reported or measured
Olsson 2005	Outcomes specified for this review were not reported or measured
Olsson 2007	Outcomes specified for this review were not reported or measured
Ooi 2012	Outcomes specified for this review were not reported or measured
Oranje 2001	Outcomes specified for this review were not reported or measured
Ormiston 2004	Placebo data not reported separate from the active treatment data
Orr 2009	Outcomes specified for this review were not reported or measured
Oshima 2008	Outcomes specified for this review were not reported or measured
Ozkiris 2007	Outcomes specified for this review were not reported or measured
Packard 2007	Outcomes specified for this review were not reported or measured
Paiva 2003	Outcomes specified for this review were not reported or measured
Paiva 2005	Outcomes specified for this review were not reported or measured
Panahi 2011	Outcomes specified for this review were not reported or measured
Paolisso 2000	Outcomes specified for this review were not reported or measured
Papathanasiou 2008	Outcomes specified for this review were not reported or measured
Parini 2008	Outcomes specified for this review were not reported or measured
Parker 2011	Outcomes specified for this review were not reported or measured
Parker 2013	Outcomes specified for this review were not reported or measured
Pedro-Botet 2001	Outcomes specified for this review were not reported or measured
Peng 2018	Outcomes specified for this review were not reported or measured
Petri 2011	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Pfiser 2003	Outcomes specified for this review were not reported or measured
Pfizer 2003a	Outcomes specified for this review were not reported or measured
Pfizer 2003b	Outcomes specified for this review were not reported or measured
Pfizer 2003c	Outcomes specified for this review were not reported or measured
Pfizer 2004a	Outcomes specified for this review were not reported or measured
Pfizer 2004b	Outcomes specified for this review were not reported or measured
Pfizer 2004c	Outcomes specified for this review were not reported or measured
Pfizer 2005	Outcomes specified for this review were not reported or measured
Pfizer 2006a	Outcomes specified for this review were not reported or measured
Pfizer 2006b	Outcomes specified for this review were not reported or measured
Pfizer 2007	Outcomes specified for this review were not reported or measured
Pfizer 2009	Outcomes specified for this review were not reported or measured
Pfizer 2010	Outcomes specified for this review were not reported or measured
Piperi 2004	Outcomes specified for this review were not reported or measured
Plazak 2011	Outcomes specified for this review were not reported or measured
Pons-Rejraji 2014	Wrong comparator; No control
Pontrelli 2002	Outcomes specified for this review were not reported or measured
Preston 2007	Outcomes specified for this review were not reported or measured
Raal 2000	Outcomes specified for this review were not reported or measured
Raal 2003	Wrong study design (3-SEQUENCE CROSSOVER)
Raison 2002	Outcomes specified for this review were not reported or measured
Reiter 2005	Outcomes specified for this review were not reported or measured
Renders 2001	Outcomes specified for this review were not reported or measured
Riahi 2006	Outcomes specified for this review were not reported or measured
Rosenson 2009	Outcomes specified for this review were not reported or measured
Sadik 2010	Outcomes specified for this review were not reported or measured
Samentzas 2015	Wrong study design
Samy 2011	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Sardo 2002	Outcomes specified for this review were not reported or measured
Sardo 2005	Outcomes specified for this review were not reported or measured
Sasmazel 2010	Outcomes specified for this review were not reported or measured
Sathyapalan 2019	Outcomes specified for this review were not reported or measured
Schaefer 2002	Outcomes specified for this review were not reported or measured
Schaefer 2004	Outcomes specified for this review were not reported or measured
Schaefer 2005	Outcomes specified for this review were not reported or measured
Schanberg 2012	Outcomes specified for this review were not reported or measured
Schneider 2004	Outcomes specified for this review were not reported or measured
Schrott 1998	Outcomes specified for this review were not reported or measured
Sdringola 2008	Outcomes specified for this review were not reported or measured
See 2003	Outcomes specified for this review were not reported or measured
Sever 2003	Outcomes specified for this review were not reported or measured
Sever 2005	Outcomes specified for this review were not reported or measured
Sever 2010	Outcomes specified for this review were not reported or measured
Sharma 2001	Outcomes specified for this review were not reported or measured
Sillesen 2007a	Outcomes specified for this review were not reported or measured
Sillesen 2007b	Outcomes specified for this review were not reported or measured
Sillesen 2008	Outcomes specified for this review were not reported or measured
Singh 2008	Outcomes specified for this review were not reported or measured
Sinski 2009	Outcomes specified for this review were not reported or measured
Soedamah-Muthu 2003	Outcomes specified for this review were not reported or measured
Soedamah-Muthu 2015	Outcomes specified for this review were not reported or measured
Sola 2006	Outcomes specified for this review were not reported or measured
Solem 2006	Outcomes specified for this review were not reported or measured
Sparks 2005	Outcomes specified for this review were not reported or measured
Sposito 2003	Outcomes specified for this review were not reported or measured
Stalenhoef 2005	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Stefanadi 2009	Outcomes specified for this review were not reported or measured
Stein 2012	Outcomes specified for this review were not reported or measured
Strey 2005	Outcomes specified for this review were not reported or measured
Strey 2006	Outcomes specified for this review were not reported or measured
Suleiman 2012	Outcomes specified for this review were not reported or measured
Szramka 2007	Outcomes specified for this review were not reported or measured
Tan 2002	Outcomes specified for this review were not reported or measured
Tanaka 2001	Outcomes specified for this review were not reported or measured
Tanaka 2009	Outcomes specified for this review were not reported or measured
Taneva 2006	Outcomes specified for this review were not reported or measured
Tannous 1999	Outcomes specified for this review were not reported or measured
Tanriverdi 2005	Outcomes specified for this review were not reported or measured
Tantikosoom 2005	Outcomes specified for this review were not reported or measured
Tehrani 2010	Outcomes specified for this review were not reported or measured
Teshima 2009	Outcomes specified for this review were not reported or measured
Tousoulis 2005a	Outcomes specified for this review were not reported or measured
Tousoulis 2005b	Outcomes specified for this review were not reported or measured
Tousoulis 2005c	Outcomes specified for this review were not reported or measured
Tousoulis 2006a	Outcomes specified for this review were not reported or measured
Tousoulis 2006b	Outcomes specified for this review were not reported or measured
Tousoulis 2007	Outcomes specified for this review were not reported or measured
Tousoulis 2010	Outcomes specified for this review were not reported or measured
Tousoulis 2011	Outcomes specified for this review were not reported or measured
Tremblay 2011	Outcomes specified for this review were not reported or measured
Tsai 2008	Outcomes specified for this review were not reported or measured
Urso 2005	Outcomes specified for this review were not reported or measured
van de Ree 2003	Outcomes specified for this review were not reported or measured
Van De Ree 2003	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
van der Harst 2005	Outcomes specified for this review were not reported or measured
van Doorn 2006	Outcomes specified for this review were not reported or measured
van Hoek 2009	Outcomes specified for this review were not reported or measured
Van J 2002	Outcomes specified for this review were not reported or measured
Vansant 2001	Outcomes specified for this review were not reported or measured
van Venrooij 2002	Outcomes specified for this review were not reported or measured
van Venrooij 2003	Outcomes specified for this review were not reported or measured
Vernaglione 2004	Outcomes specified for this review were not reported or measured
von Eynatten 2009	Outcomes specified for this review were not reported or measured
Vrtovec 2005	Outcomes specified for this review were not reported or measured
Wang 2001	Outcomes specified for this review were not reported or measured
Wanner 2005	Outcomes specified for this review were not reported or measured
Wassmann 2004	Outcomes specified for this review were not reported or measured
Waters 2000	Outcomes specified for this review were not reported or measured
Watts 2003a	Outcomes specified for this review were not reported or measured
Watts 2003b	Outcomes specified for this review were not reported or measured
Williams 2009	Outcomes specified for this review were not reported or measured
Wissing 2006	Outcomes specified for this review were not reported or measured
Wojnicz 2006	Outcomes specified for this review were not reported or measured
Wu 2007	Outcomes specified for this review were not reported or measured
Xia 2009	Outcomes specified for this review were not reported or measured
Xie 2010	Outcomes specified for this review were not reported or measured
Yamada 2007	Outcomes specified for this review were not reported or measured
Yamada 2009	Outcomes specified for this review were not reported or measured
Yokoyama 2005	Outcomes specified for this review were not reported or measured
Young 2008	Outcomes specified for this review were not reported or measured
Zeng 2012	Outcomes specified for this review were not reported or measured
Zhang 2009a	Outcomes specified for this review were not reported or measured

Study	Reason for exclusion
Zhang 2009b	Outcomes specified for this review were not reported or measured
Zheng 2019	Outcomes specified for this review were not reported or measured

DATA AND ANALYSES

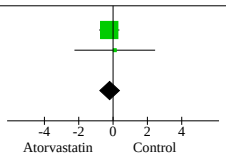
Comparison 1. Atorvastatin versus control (fixed-effect model)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Total testosterone in males	2	140	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.77, 0.37]
1.2 Total testosterone in females	4	125	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.50, -0.04]
1.3 Sex hormone binding globulin (SHBG)	2	65	Mean Difference (IV, Fixed, 95% CI)	3.11 [0.23, 5.99]
1.4 Androstenedione	4	125	Mean Difference (IV, Fixed, 95% CI)	-1.37 [-2.26, -0.49]
1.5 Dehydroepiandrosterone sulfate (DHEAS)	4	125	Mean Difference (IV, Fixed, 95% CI)	-0.63 [-1.12, -0.15]
1.6 Withdrawal due to adverse effects (WDAEs)	6	292	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.37]
1.7 Free androgen index (FAI)	2	65	Mean Difference (IV, Fixed, 95% CI)	-2.59 [-3.62, -1.57]

Analysis 1.1. Comparison 1: Atorvastatin versus control (fixed-effect model), Outcome 1: Total testosterone in males

Study or Subgroup	Atorvastatin Mean	Atorvastatin SD	Atorvastatin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Chen 2014	-0.1	0.87	30	0.12	1.39	30	94.1%	-0.22 [-0.81 , 0.37]
Gokce 2012	-0.1	5.36	41	-0.2	5.36	39	5.9%	0.10 [-2.25 , 2.45]
Total (95% CI)			**71**			**69**	**100.0%**	**-0.20 [-0.77 , 0.37]**

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

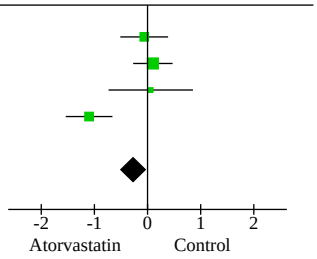


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Blinding of outcome assessment (detection bias): WDAEs
(F) Selective reporting (reporting bias)
(G) Selective reporting (reporting bias) WDAEs
(H) Source of funding, sponsorship and conflict of interest
(I) Incomplete outcome data (attrition bias): Total testosterone
(J) Incomplete outcome data (attrition bias): Free testosterone
(K) Incomplete outcome data (attrition bias): Free androgen index
(L) Incomplete outcome data (attrition bias): Androstenedione
(M) Incomplete outcome data (attrition bias): SHBG
(N) Incomplete outcome data (attrition bias): DHEAS

Analysis 1.2. Comparison 1: Atorvastatin versus control (fixed-effect model), Outcome 2: Total testosterone in females

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Akbari 2016	-0.028	0.9016	20	0.035	0.4902	20	26.0%	-0.06 [-0.51 , 0.39]
Puurunen 2013	-0.1	0.7	15	-0.2	0.2	13	38.4%	0.10 [-0.27 , 0.47]
Raja-Khan 2011	-0.52	0.8964	9	-0.58	0.9073	11	8.4%	0.06 [-0.73 , 0.85]
Sathyapalan 2009	-1.2	0.44	19	-0.1	0.85	18	27.2%	-1.10 [-1.54 , -0.66]
Total (95% CI)			**63**			**62**	**100.0%**	**-0.27 [-0.50 , -0.04]**

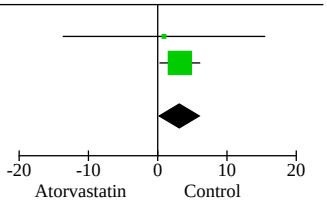
Heterogeneity: Chi² = 18.99, df = 3 (P = 0.0003); I² = 84%
Test for overall effect: Z = 2.33 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Atorvastatin versus control (fixed-effect model), Outcome 3: Sex hormone binding globulin (SHBG)

Study or Subgroup	Atorvastatin Mean	Atorvastatin SD	Atorvastatin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Puurunen 2013	-1.3	19.3	15	-2.2	20	13	3.9%	0.90 [-13.71 , 15.51]
Sathyapalan 2009	4.2	5.23	19	1	3.82	18	96.1%	3.20 [0.26 , 6.14]
Total (95% CI)			**34**			**31**	**100.0%**	**3.11 [0.23 , 5.99]**

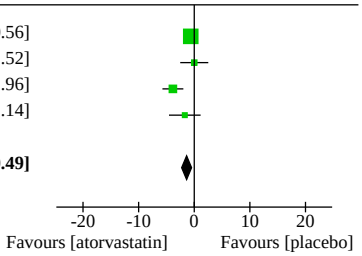
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Atorvastatin versus control (fixed-effect model), Outcome 4: Androstenedione

Study or Subgroup	Atorvastatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Akbari 2016	-0.91	2.51	20	-0.28	1.06	20	55.4%	-0.63 [-1.82 , 0.56]
Puurunen 2013	-1.4	3.8	15	-1.4	3	13	12.4%	0.00 [-2.52 , 2.52]
Raja-Khan 2011	-3.14	1.8686	9	0.7	2.42	11	22.4%	-3.84 [-5.72 , -1.96]
Sathyapalan 2009	-1	1.85	19	0.7	5.88	18	9.8%	-1.70 [-4.54 , 1.14]
Total (95% CI)			**63**			**62**	**100.0%**	**-1.37 [-2.26 , -0.49]**

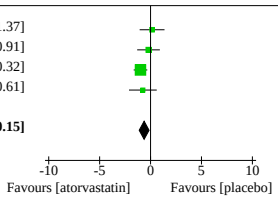
Heterogeneity: Chi² = 9.29, df = 3 (P = 0.03); I² = 68%
Test for overall effect: Z = 3.03 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Atorvastatin versus control (fixed-effect model), Outcome 5: Dehydroepiandrosterone sulfate (DHEAS)

Study or Subgroup	Atorvastatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Akbari 2016	0.23	2.7649	20	0.08	0.3322	20	15.7%	0.15 [-1.07 , 1.37]
Puurunen 2013	-0.6	1.7	15	-0.4	1.3	13	18.9%	-0.20 [-1.31 , 0.91]
Raja-Khan 2011	-0.81	0.7242	9	0.18	0.795	11	52.7%	-0.99 [-1.66 , -0.32]
Sathyapalan 2009	-1.1	1.88	19	-0.345	2.31	18	12.6%	-0.76 [-2.12 , 0.61]
Total (95% CI)			**63**			**62**	**100.0%**	**-0.63 [-1.12 , -0.15]**

Heterogeneity: Chi² = 3.29, df = 3 (P = 0.35); I² = 9%
Test for overall effect: Z = 2.56 (P = 0.01)
Test for subgroup differences: Not applicable

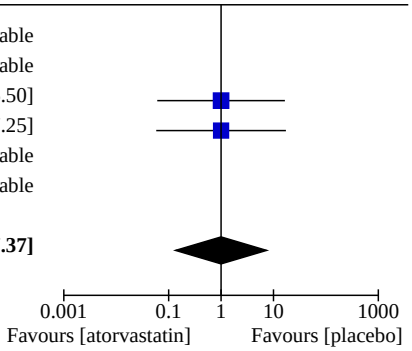


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Blinding of outcome assessment (detection bias): WDAEs
(F) Selective reporting (reporting bias)
(G) Selective reporting (reporting bias) WDAEs
(H) Source of funding, sponsorship and conflict of interest
(I) Incomplete outcome data (attrition bias): Total testosterone
(J) Incomplete outcome data (attrition bias): Free testosterone
(K) Incomplete outcome data (attrition bias): Free androgen index
(L) Incomplete outcome data (attrition bias): Androstenedione
(M) Incomplete outcome data (attrition bias): SHBG
(N) Incomplete outcome data (attrition bias): DHEAS

Analysis 1.6. Comparison 1: Atorvastatin versus control (fixed-effect model), Outcome 6: Withdrawal due to adverse effects (WDAEs)

Study or Subgroup	Atorvastatin Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Akbari 2016	0	20	0	20		Not estimable
Chen 2014	0	32	0	32		Not estimable
Gokce 2012	1	45	1	45	50.8%	1.00 [0.06 , 16.50]
Puurunen 2013	1	19	1	19	49.2%	1.00 [0.06 , 17.25]
Raja-Khan 2011	0	9	0	11		Not estimable
Sathyapalan 2009	0	20	0	20		Not estimable
Total (95% CI)		**145**		**147**	**100.0%**	**1.00 [0.14 , 7.37]**
Total events:	2		2			

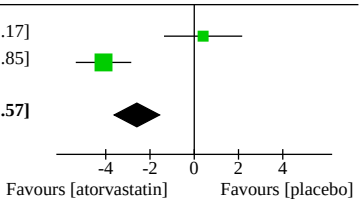
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Atorvastatin versus control (fixed-effect model), Outcome 7: Free androgen index (FAI)

Study or Subgroup	Atorvastatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Puurunen 2013	0.1	3.2	15	-0.3	1.3	13	33.5%	0.40 [-1.37 , 2.17]
Sathyapalan 2009	-4.7	1.74	19	-0.6	2.12	18	66.5%	-4.10 [-5.35 , -2.85]
Total (95% CI)			**34**			**31**	**100.0%**	**-2.59 [-3.62 , -1.57]**

Heterogeneity: Chi² = 16.58, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 4.97 (P < 0.00001)
Test for subgroup differences: Not applicable



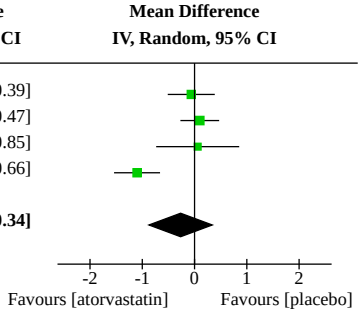
Comparison 2. Atorvastatin vs control (random effects model)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Total testosterone in females	4	125	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.87, 0.34]
2.2 Androstenedione	4	125	Mean Difference (IV, Random, 95% CI)	-1.56 [-3.32, 0.20]
2.3 Free androgen index (FAI)	2	65	Mean Difference (IV, Random, 95% CI)	-1.89 [-6.30, 2.51]

Analysis 2.1. Comparison 2: Atorvastatin vs control (random effects model), Outcome 1: Total testosterone in females

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akbari 2016	-0.028	0.9016	20	0.035	0.4902	20	26.2%	-0.06 [-0.51 , 0.39]
Puurunen 2013	-0.1	0.7	15	-0.2	0.2	13	27.4%	0.10 [-0.27 , 0.47]
Raja-Khan 2011	-0.52	0.8964	9	-0.58	0.9073	11	20.0%	0.06 [-0.73 , 0.85]
Sathyapalan 2009	-1.2	0.44	19	-0.1	0.85	18	26.3%	-1.10 [-1.54 , -0.66]
Total (95% CI)			**63**			**62**	**100.0%**	**-0.27 [-0.87 , 0.34]**

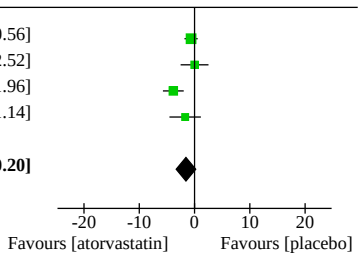
Heterogeneity: Tau² = 0.31; Chi² = 18.99, df = 3 (P = 0.0003); I² = 84%
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Atorvastatin vs control (random effects model), Outcome 2: Androstenedione

Study or Subgroup	Atorvastatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akbari 2016	-0.91	2.51	20	-0.28	1.06	20	32.6%	-0.63 [-1.82 , 0.56]
Puurunen 2013	-1.4	3.8	15	-1.4	3	13	21.5%	0.00 [-2.52 , 2.52]
Raja-Khan 2011	-3.14	1.8686	9	0.7	2.42	11	26.7%	-3.84 [-5.72 , -1.96]
Sathyapalan 2009	-1	1.85	19	0.7	5.88	18	19.2%	-1.70 [-4.54 , 1.14]
Total (95% CI)			**63**			**62**	**100.0%**	**-1.56 [-3.32 , 0.20]**

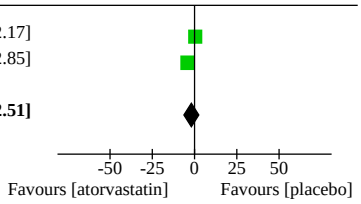
Heterogeneity: Tau² = 2.09; Chi² = 9.29, df = 3 (P = 0.03); I² = 68%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Atorvastatin vs control (random effects model), Outcome 3: Free androgen index (FAI)

Study or Subgroup	Atorvastatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Puurunen 2013	0.1	3.2	15	-0.3	1.3	13	49.0%	0.40 [-1.37 , 2.17]
Sathyapalan 2009	-4.7	1.74	19	-0.6	2.12	18	51.0%	-4.10 [-5.35 , -2.85]
Total (95% CI)			**34**			**31**	**100.0%**	**-1.89 [-6.30 , 2.51]**

Heterogeneity: Tau² = 9.51; Chi² = 16.58, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Total testosterone and free testosterone levels by sex and age

Tests of blood: normal findings		
	Free testosterone pg/mL	
Age/Tanner stage	Male	Female
Postmenopausal		0.6-3.8
7 months-9 years (Tanner stage I)	≤ 3.7	< 2.2
10-13 years (Tanner stage II)	0.3-21	0.4-4.5
14-15 years (Tanner stage III)	1.0-98	1.3-7.5
16-17 years (Tanner stage IV)	35.0-196	1.1-15.5
18-19 years (Tanner stage V)	41.0-239	0.8-9.2
	Free testosterone %	
Adult male	1.6-2.9	

Table 1. Total testosterone and free testosterone levels by sex and age *(Continued)*

Adult female	0.1-0.3

	Total testosterone ng/dL	
	Male	Female
7 months-9 years (Tanner stage I)	< 30	< 30
10-13 years (Tanner stage II)	< 300	< 40
14-15 years (Tanner stage III)	170-540	< 60
16-19 years (Tanner stage IV, V)	250-910	< 70
20 years and over	280-1080	< 70

	Dihydrotestosterone
Adult male	240-650 pg/mL
Adult female	≤ 300 pg/mL

Total testosterone and free testosterone levels by sex and age (Pagana 2015).

APPENDICES

Appendix 1. Search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to November 06, 2020>
Search Date: 9 November 2020
---
1 atorvastatin/ (6631)
2 (atorvastatin$ or atorlip or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or lipitor or liprimar or liptonorm or lowlipen or sortis or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).tw,kf. (8996)
3 or/1-2 (10041)
4 randomized controlled trial.pt. (516561)
5 controlled clinical trial.pt. (93916)
6 randomized.ab. (497951)
7 placebo.ab. (212325)
8 drug therapy.fs. (2249299)
9 randomly.ab. (344379)
10 trial.ab. (526367)
11 groups.ab. (2112842)
12 or/4-11 (4832805)
13 animals/ not (humans/ and animals/) (4720430)
14 12 not 13 (4197674)
15 3 and 14 (5419)
16 15 and (2013 12$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$).dt. (1788)

Database: Cochrane Hypertension Specialised Register via Cochrane Register of Studies (CRS-Web)
Search Date: 9 November 2020

#1 MESH DESCRIPTOR atorvastatin AND INREGISTER
#2 (atorvastatin* OR atorlip OR atovarol OR cardyl OR glustar OR lipibec OR lipitor OR liprimar OR liptonorm OR lowlipen OR sortis OR storvas OR tahor OR torvast OR totalip OR xarator OR zarator) AND INREGISTER
#3 #1 OR #2
#4 RCT:DE AND INSEGMENT
#5 Review:ODE AND INSEGMENT
#6 #4 OR #5
#7 #3 AND #6

Database: Cochrane Central Register of Controlled Trials (Issue 10, 2020) via Cochrane Register of Studies (CRS-Web)
Search Date: 9 November 2020

#1 MESH DESCRIPTOR atorvastatin AND CENTRAL:TARGET
#2 (atorvastatin* OR atorlip OR atovarol OR cardyl OR glustar OR lipibec OR lipitor OR liprimar OR liptonorm OR lowlipen OR sortis OR storvas OR tahor OR torvast OR totalip OR xarator OR zarator) AND CENTRAL:TARGET
#3 (#1 OR #2) AND CENTRAL:TARGET

Database: Embase <1974 to 2020 November 06>
Search Date: 9 November 2020
---
1 atorvastatin/ (37934)
2 (atorvastatin$ or atorlip or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or lipitor or liprimar or liptonorm or lowlipen or sortis or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).mp. (39004)
3 or/1-2 (39004)
4 randomized controlled trial/ (631824)
5 crossover procedure/ (65266)
6 double-blind procedure/ (178669)
7 (randomi?ed or randomly).tw. (1291636)
8 (crossover$ or cross-over$).tw. (109824)
9 placebo.ab. (306862)
10 (doubl$ adj blind$).tw. (215272)
11 assign$.ab. (402529)
12 allocat$.ab. (156801)
13 or/4-12 (1870641)
14 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (6531514)
15 13 not 14 (1633335)
16 3 and 15 (6642)
17 16 and (2013 12$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$).dc,dd. (2367)

Database: ClinicalTrials.gov
Search Date: 9 November 2020

Other terms: sex hormone* OR SHBG OR testosterone
Study type: Interventional Studies (Clinical Trials)
Study Results: All Studies
Intervention/treatment: Atorvastatin OR lipitor

HISTORY

Protocol first published: Issue 12, 2018
Review first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

James M Wright (JMW) formulated the idea, developed the basis of the protocol, and contributed to data analysis, interpretation of the final result, and editing of the final draft of the review.

Muhammad Ismail Shawish (MIS) and Bahador Bagheri (BB) drafted the protocol, with help from JMW.

MIS, BB and SPA independently assessed studies for inclusion or exclusion and assessed the risk of bias of all included studies.

MIS extracted data, checked data entry, conducted data analysis, interpreted study results, and drafted the final review.

Vijaya Musini (VM) contributed to data analysis, interpretation of the final result, and editing of the final draft of the review.

All review authors reviewed and approved the final version.

DECLARATIONS OF INTEREST

Muhammad Ismail Shawish: nothing to declare.

Bahador Bagheri: nothing to declare.

Vijaya Musini: nothing to declare.

Stephen Adams: nothing to declare.

James Wright: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Anesthesiology, Pharmacology & Therapeutics, University of BC, Canada

  infrastructure

External sources

- British Columbia Ministry of Health, Canada

  Therapeutics Initiative grant

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

According to the published protocol, we intended to analyze only four secondary outcomes: free testosterone levels, FAI, SHBG and WDAEs. Because of the clinical importance of DHEAS and androstenedione in conditions such as POCS, we decided to add them as secondary outcomes in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Androgens [blood]; Androstenedione [blood]; Atorvastatin [adverse effects] [*pharmacology]; Bias; Dehydroepiandrosterone Sulfate [blood]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [adverse effects] [*pharmacology]; Placebos [pharmacology]; Polycystic Ovary Syndrome [*blood] [drug therapy]; Randomized Controlled Trials as Topic; Sex Factors; Sex Hormone-Binding Globulin [analysis] [drug effects]; Testosterone [*blood]

MeSH check words

Aged; Female; Humans; Male