

Simvastatin for management of polycystic ovary syndrome (PCOS)

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(see Appendix 1 for a list of additional contributors)

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Project | Remedi aims to uncover new therapeutic uses for hundreds of medicines on the Essential Medicines List, seek approval to add them to the EML, and amplify availability of new uses to benefit priority populations.

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1. Summary statement of the proposal for inclusion, change or deletion

We propose a new listing to the EML to add an additional use of a medicine already on the EML, simvastatin. The new indication is for the treatment of Polycystic Ovary Syndrome (PCOS) in women. This request is being sought for the core EML. Generally, simvastatin is known via substantial preclinical and clinical studies for its lipid lowering and cardioprotective effects, through its mechanism of **HMG-CoA reductase inhibition**. Simvastatin has been in widespread use since the 1990s and has been proven to be safe and well tolerated in diverse populations; its use as a treatment for high cholesterol is already represented on the EML. Based on an extension of the same pathway, and blocking pharmacologic mechanism, simvastatin shows promise in treating Polycystic Ovary Syndrome in women. Briefly, cholesterol is mainly synthesized in the liver. HMG-CoA reductase is the rate-limiting enzyme for cholesterol synthesis.. Statins **block HMG-CoA reductase** and in doing so **reduce testosterone levels** and improve parameters related to hyperlipidemia. (See Figure 1, adapted from (1)) Women who have PCOS have *elevated* total testosterone levels. In addition to lowering cholesterol, statin therapy has been observed to decrease testosterone levels in multiple studies in women with PCOS, and can improve outcomes in this condition (2–6). Although statins are already widely known to improve lipid parameters in broad populations, the evidence described in this application for simvastatin use in PCOS are supportive here of its efficacy in women with PCOS given their increased risk of obesity and cardiovascular disease.

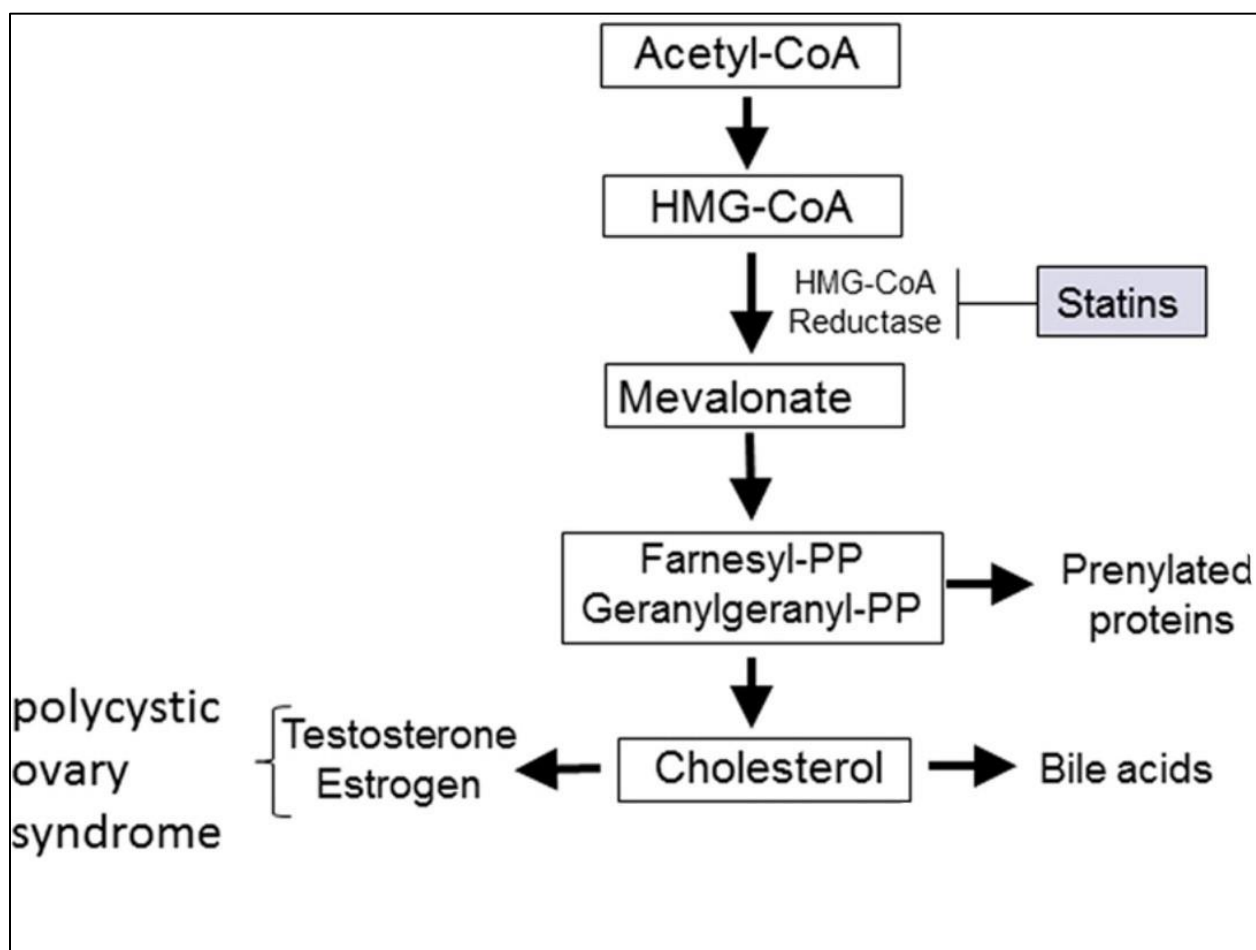


Figure 1: HMG-CoA reductase and therapeutic use of statins in polycystic ovary syndrome.

PCOS is the most common endocrinopathy affecting reproductive-aged women in the world, with an approximate prevalence of 8-13%.(7) There is considerable differentiation in disease presentation by ethnicity and geography.(8) Generally, it presents as a spectrum of heterogeneous disorders of reproduction and metabolism in women with frequent symptoms such as: abnormal menstruation, infertility, obesity, hirsutism, acanthosis nigricans, acne, and ovarian cysts. PCOS is a leading cause of infertility, which is global public health issue.(9) Further, women with PCOS are at a higher risk of poor outcomes, as they are more likely to develop impaired glucose tolerance, Type II diabetes, cardiovascular disease, hypertension, and metabolic syndrome.(7) Globally, there has been a need for better standards in diagnosis and management, which was addressed by the *International Evidence-Based Guideline for The Assessment and Management Of Polycystic Ovary Syndrome*, published in July 2018, expected to support a more consistent disease definition and easier diagnosis and acknowledges that off label use, when evidence-based, is supported for some pharmacologic therapies in PCOS.(10) Thus, a treatment addition to the EML is timely.

Although PCOS is not life-threatening, women with PCOS have a substantially reduced quality of life compared to control groups and population data.(11) Visible signs of excess androgens (such as hirsutism, alopecia, and acne) have prominent effects on physical appearance that can affect neuropsychological status. Obesity also has important psychosocial effect.(12) Women, especially adolescents, with PCOS are at increased risk of depression.(13) Further, women affected by PCOS are at increased risk of adverse health outcomes related to metabolic dysfunction and cardiovascular disease.

Simvastatin has been shown to decrease disease characteristics with adverse impact on health and quality of life in women affected by PCOS, including hyperlipidemia, hirsutism, hormone levels, and BMI. (2–6,14–31) The evidence base supporting benefit and safety of simvastatin in women with PCOS includes systematic reviews, meta-analyses, clinical trials, and observational studies; these studies and their findings are described in detail in Section 9, with additional data extracted within the Literature Summary table.(2–6,14–31) To address an unmet medical need with an existing, safe therapy, we propose a new use for simvastatin in the improvement of outcomes for women with PCOS. Although there is no study of simvastatin supporting fertility in women with PCOS, it has been shown that simvastatin decreases ovarian size and supports LH:FSH (luteinizing hormone to follicle stimulating hormone ratio) balance, which can affect fertility.(3)

Large-scale randomized controlled trials (RCTs) do not predominate in this literature (see **Literature Summary** table); small studies are prevalent in the literature describing use of simvastatin or other statins in management of PCOS, with the largest trial including 400 patients. However, the lack of treatments available for management of the facets of PCOS, combined with the safety profile of simvastatin, and its relative effectiveness and demonstrated safety in real world use across many different settings, suggests that this indication would be a practical, beneficial addition to the EML to promote women's health. The literature indicates that use of simvastatin represents at least a significant incremental gain and potentially a substantial effect on improving outcomes given the large numbers of patients worldwide affected by PCOS, thus leading to a reasonable expectation of reducing morbidity based on the accumulated RCT and observational data. The evidence base is described in further detail in Section 9 below and in the **Literature Summary** table.

New indication summary: Simvastatin should be administered to women with PCOS who have signs of elevated testosterone, to prevent, reduce, or limit disease symptoms such as hirsutism, acne, ovarian volume, and BMI, as well as help to prevent related future cardiovascular and metabolic

morbidity. Beneficial effects on fertility-related outcomes are also outlined in the literature on statin use in PCOS. Relevant trials varied in duration and found positive effects at 3 months, 6 months, or 12 months as dictated by each study's length of intervention. The type of outcomes with positive simvastatin effects varied across studies; directionality of effect typically reflected improvements in measured outcomes. Benefits included a range of laboratory and other clinical measures such as: effects on lipid levels, other metabolic measures (e.g. insulin), testosterone and other hormone levels (e.g. DHEA), systemic inflammatory markers (e.g. CRP), menstrual regularity, ovulation, acne, hirsutism, BMI, waist circumference (see Section 9 and Literature Summary for references and additional detail).

Rationale for recommending simvastatin as an individual medicine for PCOS, rather than statins as a class of agents: We evaluated the literature describing use of statin therapy in PCOS, finding that the bulk of the literature supporting safety and efficacy of this therapeutic path focuses on simvastatin, with relatively smaller evidence base describe atorvastatin use and a very small amount of study describing rosuvastatin use (see Literature Summary table for full details of each of these therapeutic agents and their studies in PCOS). The focus on simvastatin in this current recommendation for the EML is based on its larger evidence base in PCOS as compared with atorvastatin, its similar safety and efficacy to atorvastatin for PCOS, and its current presence on the EML - thus likely leading to its expanded availability on a global scale as compared to atorvastatin, which is not on the EML.

While the cumulative data suggests the possibility of a class effect of statins in PCOS, and there is a class effect on the hyperlipidemia indication already represented on the EML, the evidence base at this point **does not confirm** there is a true class effect for statins in PCOS. In addition, statins have pharmacological variation that might plausibly suggest differential outcomes on PCOS.

2. Relevant WHO technical department and focal point (if applicable).

Maternal, Newborn, Child and Adolescent Health, and Ageing;

Sexual and reproductive health

3. Name of organization(s) consulted and/or supporting the application.

Dr. Robert Wallis, MD; Chief Scientific Officer, AURUM was consulted and reviewed this submission.

Dr. Gordon Bernard, MD; Executive Vice President for Research, Vanderbilt University Medical Center was consulted and reviewed this submission. :

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN: Simvastatin

C10AA01

5. Dose forms(s) and strength(s) proposed for inclusion

Simvastatin: tablet 20 mg

The studies describing use of simvastatin in PCOS employed an orally administered dose of 20 mg per day. This dose is within the range used when simvastatin is used to treat hyperlipidemia (e.g. a starting dose of 10-20 mg/day simvastatin is noted in the package insert for simvastatin, approved by the US Food and Drug Administration(32)).

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

Individual medicine

7. Treatment details (requirements for diagnosis, treatment and monitoring).

Diagnosis: Expert groups commonly recommend use of the Rotterdam criteria for diagnosis of PCOS.(10,33) The Rotterdam criteria require that the patient exhibits two of three of the following characteristics: oligo- and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; and/or polycystic ovaries (by ultrasound).(34) Given resource constraints in some healthcare settings, the first two criteria may be most useful on a global scale.

Treatment and monitoring: Simvastatin is administered in women with PCOS to manage hyperlipidemia and other metabolic effects of this disease, as well as management of other symptoms related to excess testosterone (e.g. acne, hirsutism). Clinical trials have typically employed a dose of 20 mg per day. with trial duration ranging up to 6-12 months. Simvastatin may be administered long-term to maintain positive effects if clinically evaluated to be reasonable in a given patient. Women who are pregnant or attempting to conceive should not use simvastatin due to risk of fetal harm, described further in Section 10 below. Monitoring of lipids and other metabolic parameters (e.g. blood glucose) should be pursued when clinically indicated, as per usual care in this condition; no specific additional requirements needed.

8. Information supporting the public health relevance.

PCOS is the most common endocrinopathy affecting reproductive-aged women in the world, with an approximate prevalence of 8-13%(7); however, due to discrepancies amongst diagnostic criteria and symptom presentation, this prevalence can extend to 20% of reproductive age women.(35) There is considerable differentiation in disease presentation by ethnicity and geography.(8) Prevalence rates are largely similar across the United States, United Kingdom, Spain, Greece, Australia, and Mexico.(36) Caucasian women seem to generally have lower rates of prevalence of PCOS; however, South Asian and Chinese women may see the lowest rates of prevalence, globally.(36) The highest reported prevalence rates are amongst women in the Indian subcontinent based on reported

presentation with polycystic ovaries. (36) Data regarding prevalence in most developing countries is scarce. (23) Prevalence increases with age progression.(37) Associations between socioeconomic status (SES) and PCOS prevalence do vary; however, women with low SES during adulthood, or low SES during childhood yet high personally attained SES during adulthood, are more likely to have PCOS.(38,39)

PCOS is often associated with metabolic syndrome, which results in increased long-term risk of infertility, insulin resistance, hyperinsulinemia, obesity, dyslipidemia, glucose intolerance, hypertension, type 2 diabetes, cardiovascular disease, and certain types (gynecological) of cancer.(37) Estimates of quantitative impact on comorbidities include a risk of metabolic syndrome that is 11 fold greater than age-matched controls; 27% decrease in insulin sensitivity in women with PCOS, independent of BMI, age, or diagnostic criteria; up to 30% prevalence of impaired glucose tolerance; approximately 70% prevalence of fertility issues; and up to 10% prevalence of type 2 diabetes, with risk further increasing with age; further obesity is also associated with more severe PCOS phenotype, impaired quality of life, and increased risk of depression. (39,40) A systematic review reported 4.18 increased odds of moderate or severe symptoms of depression and 5.62 increased odds of symptoms of anxiety in women with PCOS compared to controls.(40) Others have noted that PCOS is associated with a statistically significant increase in having a clinical diagnosis of depression, anxiety disorder, bipolar disorder, and obsessive compulsive disorder.(35)

9. Review of benefits: summary of evidence of comparative effectiveness.

Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

The studies from the literature for this analysis were identified by a trained information scientist searching the PubMed and Web of Science databases, as well as a broad Google search to identify unindexed and grey literature. The search terms used were: “polycystic ovary syndrome” and “simvastatin”; a complementary search for “polycystic ovary syndrome” and (“atorvastatin” or “rosuvastatin” or “pravastatin” or “fluvastatin” or “statin” or “statins” or “hydroxymethylglutaryl-CoA” or “lovastatin” or “pitavastatin”) was also executed to add in adding to the context regarding potential class effects of statins in this disease. This search was not date limited; studies were assessed without restriction by a publication date threshold to ensure inclusiveness. The reference lists of reviewed articles were also assessed, to identify any studies not found by the initial search and to better clarify preclinical and mechanistic underpinnings of both the disease and the therapy. No studies investigating the use of simvastatin for management of PCOS were excluded from this exploration and evidence from all identified reports was systemically extracted (see **Literature Summary**).

Summary of available data (appraisal of quality, outcome measures, summary of results):

A body of trial literature and systematic reviews, described below in more detail, indicates benefit associated with simvastatin therapy in women affected by PCOS, including positive effects on lipid levels and other measures of disease activity including hormone levels, body mass index (BMI), acne, and hirsutism.

Systematic reviews and meta-analyses: We identified five systematic reviews and meta-analyses that included evaluation of simvastatin for management of PCOS, ranging in publication date from 2011-2020(2–6). There is overlap among these papers, but variation in inclusion criteria (typically including any statin), search approach, analytic techniques, and outcomes of interest, leading to variability in their detailed conclusions regarding utility of simvastatin and other statin agents in this disease. Three of these papers focused on evaluation of statins as a class of therapeutics;(2,3,6) two included comparison of atorvastatin, simvastatin, and rosuvastatin. These analyses found improvement in hormone levels (e.g. testosterone, DHEA) and lipid levels associated with use of statins; none of these papers identified notable adverse effect signals. The two meta-analyses comparing atorvastatin to simvastatin found atorvastatin to be superior in terms of effects on testosterone(4) or DHEA(5); however the small size of the comparative data pool for these analyses may limit their clinical utility. **All five papers concluded that statin therapy is a reasonable option in women affected by PCOS.**

RCTs: Fifteen randomized controlled trials, briefly summarized and cited below, compared the utility of simvastatin-containing regimens to one or two other treatment options. Small trial sizes predominated. Trial data indicate positive effects of simvastatin therapy on lipids, hormone levels, and other measures of disease activity in women with PCOS. The range of comparisons in this literature include:

- Two trials compared **simvastatin to placebo**, one focusing on women with PCOS pursuing in vitro fertilization(17) and one on women with general PCOS(25). The IVF in PCOS trial found positive effects on testosterone and cholesterol, but did not find benefit in terms of IVF success. (17) The PCOS trial found positive effects of simvastatin as compared with placebo on a range of outcomes including hormones (testosterone, DHEA, LH:FSH, FSH), lipids, menstrual regulatory, hirsutism, acne, ovarian volume, body mass index, and waist hip ratio; this trial did not find benefit of simvastatin therapy on fasting glucose, fasting insulin, or HOMA-IR index (insulin resistance measure).(25)
- Three trials compared **simvastatin to metformin** in PCOS.(18,21) One trial focused on PCOS and found superiority of simvastatin in effects on lipids, CRP, and acne; metformin performed better in terms of effects on blood sugar and insulin measures.(18) The second trial focused on women with PCOS pursuing IVF; both regimens were associated with beneficial effects on biochemical parameters, but neither regimen had an effect on IVF outcomes.(21)
- Three trials compared **simvastatin to metformin to simvastatin plus metformin** (i.e. three-arm trials; one trial reported in two papers).(14,25–27) All three trials found superiority in the simvastatin-containing arms compared to metformin alone in terms of effects on lipids, hormone levels (e.g. testosterone), and other measures of disease activity.
- One trial compared **simvastatin to metformin to flutamide plus OCPs** (a three-arm trial),(23) finding that simvastatin was superior to the other two regimens in terms of effects on waist circumference, BMI, and triglyceride levels. Metformin was superior in effects on fasting blood sugar.
- Two trials compared **simvastatin to atorvastatin**.(30,31) Both trials found the statin regimens lead to improvements in lipid levels and other measures of disease activity, while benefits attributed to the individual agents varied to some extent; the data suggests possible greater effects of simvastatin on hormone levels, while atorvastatin may have a greater impact on measures of insulin resistance.

Among trials with combination therapies, for which less information specific to simvastatin can be inferred,

- Two trials evaluated **simvastatin plus metformin to metformin alone**.(28,29) Both trials found superiority of the simvastatin-containing arm related to improvements in hormone levels (e.g. testosterone, LH, FSH) and in lipids.
- Two trials evaluated **simvastatin plus oral contraceptives (OCPs) to OCPs alone**.(15) Both studies found significant benefit in the combined therapy group, attributed to the addition of simvastatin, including improvement in hormone levels (testosterone, FSH, LH), lipids, and other measures of disease activity (e.g. hirsutism). An additive effect of simvastatin therapy on measures related to blood glucose or insulin was not identified in either trial.

Observational data: Three observational studies also indicated benefit of simvastatin in managing lipids and other parameters in small groups of women affected by PCOS.(19,20,22) Two of these reports focused on simvastatin only(19,22); one study was a prospective cohort comparing simvastatin to ezetimibe, finding simvastatin to be superior in reducing total and free testosterone.(20)

PheWAS data: We also reviewed a set of data in which a phenome-wide association study (PheWAS) analysis was undertaken. PheWAS can identify diseases that are associated with a specific gene/genetic variant.(41) PheWAS leverages existing data from the Exomechip genotyping platform (~250,000 coding variants across the protein coding region of the genome) and electronic health records for approximately 35,000 patients. Because the logic of PheWAS can be extended to predict phenotypic manifestations of pharmacological targeting (such as with simvastatin) of a given gene product in humans, we use these methods for **drug repurposing**.(42) As a **HMG-CoA reductase inhibitor, simvastatin reduces cholesterol**. The phenotypes associated with this missense single nucleotide polymorphism (SNP) (Ile638Val) in the HMGCR gene are risk causing, so in this regard we can say the SNP is functioning like a **HMG-CoA reductase activator** (the opposite of the drug). Accordingly, the SNP in our data is associated with increased risk of cholesterol disorders in females and males. The same SNP was also associated with oophorectomy, and ovarian cysts in women, which is supportive of our proposal to treat PCOS with the inhibitor simvastatin, as ovarian cysts are the hallmark feature of PCOS. The SNP has not been formally studied but the location and nature of this variant may be associated with impact on the protein: “Despite the conservative change of residues, *I638V could impact on the stability and folding of the HMGCR enzyme*. Many substitutions considered as chemically conservative are not tolerated, because certain amino acids’ properties are highly context-dependent and influenced by the local environment. In this case, the conservative substitution of the hydrophobic pair isoleucine-valine at the interface may be influenced by local interferences or by protein tertiary structure. Environment changes produced for the I638V nsSNP may produce alterations in the protein-protein interface and disruption in the contacts between the protein chains during the tetramer formation. As the I638 variant only known coding in HMGCR is located in a buried and conserved site in the protein interface, we suggest that the 638V allele could affect the protein-protein subunits interaction and this variant could be considered responsible for significant signal disruption in protein structure and, as a consequence, in altered function.”(43)

Relevant phenotypes from the PheWAS analysis are illustrated in **Table 1** below, correlating with potential activity of this SNP in increasing risk of diseases affecting the ovary.

Table 1: PheWAS results, HMGCR variation and ovarian disease

Note: The inferred SNP effect on protein is HMGCR activation, suggesting need for counteraction with an inhibitor (i.e. statin)

SNP (Gene)	Phecode	Phenotype description	Cases (n)	Controls (n)	Odds ratio	P value	AFF_11 *	AFF_12**
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rs5908 (HMGCR)	258.1	Postablative ovarian failure	39	11943	4.7700 0	0.0001169	0	7
rs5908 (HMGCR)	220	Benign neoplasm of ovary	87	10217	2.9510 0	0.00105	1	8
rs5908 (HMGCR)	277.51	Lipoprotein disorders	23	24862	3.3400 0	0.0455	0	3

Key: HMGCR HMG-CoA reductase gene; SNP single nucleotide polymorphism; *AFF_11 homozygous carriers of the SNP of interest; **AFF_12 heterozygous carriers of the SNP of interest

Summary of available estimates of comparative effectiveness:

In the studies comparing use of simvastatin to placebo or another intervention (e.g. metformin, ezetimibe), studies reported that simvastatin was superior to placebo or other intervention arms for improving a number of laboratory parameters typically employed to evaluate disease status in PCOS including lipid levels, testosterone levels, and/or measures of insulin sensitivity, with variation in type of beneficial effect varying based on primary outcomes of each trial.(14–18,21,23–31) These laboratory measures correlate with short term and long term outcomes in PCOS, with those such as testosterone correlating with overall disease activity and associated symptoms (e.g. hirsutism, acne, menstrual cycle issues) and others used more broadly in clinical practice for their longer term significance in terms of patient health (e.g. hyperlipidemia, hyperinsulinemia, BMI). The safety profile reported in this use is consistent with published adverse effects of simvastatin use for other indications, consistent in terms of type and incidence of adverse events.

10. Review of harms and toxicity: summary of evidence of safety.

Estimate of total patient exposure to date:

Simvastatin is an oral HMG-CoA reductase inhibitor that has been widely prescribed globally for the treatment of hypercholesterolemia and diabetic cardiomyopathy since its FDA approval in 1991. Simvastatin drugs are available globally as generics and as branded drugs in many countries including the United States, Canada, Australia and across Europe. Based on exposure reported in the literature and given that oral Simvastatin treatments have been in widespread use as an adjunctive therapy for hypercholesterolemia **since the 1990s** it is estimated that millions of patients have been exposed worldwide to date. Atorvastatin has a similar exposure in terms of regulatory approval and global use. (45,46)

Description of the adverse effects/reactions when used in PCOS

Review of the literature describing use of simvastatin or atorvastatin in treatment of women with PCOS indicates a safety profile comparable to that observed in the substantive evidence base on statin use in hyperlipidemia. A detailed extraction of these concordant safety findings from all identified studies on use of simvastatin(14–31) are outlined in the Literature Summary table included below; similar data regarding concordant safety findings with use of atorvastatin in PCOS(47–57) are also included for context, as well as safety findings from the limited evidence base regarding use of rosuvastatin(58,59) in this condition.

Description of the adverse effects/reactions and estimates of their frequency (drawn from the broader simvastatin literature on human use)

- Oral simvastatin has been in widespread use since the early 1990's and has been proven to be safe and well tolerated in diverse populations. (60)
- **Appendix 2** summarizes safety data reported in systematic reviews of large, randomized controlled trials (RCTs) of simvastatin treatment for various indications

- In the simvastatin-related pre-marketing controlled clinical studies and their open extensions (2,423 patients with median duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were gastrointestinal disorders (0.5%), myalgia (0.1%), and arthralgia (0.1%). (32)
- The most commonly reported adverse reactions (incidence $\geq 5\%$) in simvastatin controlled clinical trials were upper respiratory infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%)(32)
- Oral simvastatin is rarely associated with more severe side effects like Immune-Mediated Necrotizing Myopathy (IMNM) and myopathy. Several risks factors associated with myopathy have been identified and are described below(32):
 - The risk of myopathy is increased by elevated plasma levels of simvastatin and simvastatin acid. Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled 5 hypothyroidism, and renal impairment.
 - Chinese patients may be at increased risk for myopathy.
 - The risk of myopathy, including rhabdomyolysis, is greater in patients on simvastatin 80 mg compared with other statin therapies with similar or greater LDL-C-lowering efficacy and compared with lower doses of simvastatin.
 - Because advanced age (≥ 65 years) is a predisposing factor for myopathy, including rhabdomyolysis, Simvastatin should be prescribed with caution in the elderly

Contraindications listed for various marketed simvastatin drugs

Simvastatin is contraindicated in patients with hypersensitivity to any components of the medication, patients with active liver disease, and nursing mothers. (18) There is limited evidence that simvastatin affects placental explants in vitro and there have been sporadic reports of congenital anomalies with statin use. (15,16) The use of simvastatin in women who are pregnant or may become pregnant is contraindicated for this application to remain in line with current prescribing information until further research is conducted.

Warnings and precautions for various marketed simvastatin drugs (32,61–63)

- Avoid simvastatin if taking CYP3A4 inhibitors, as drug interactions that are associated with increased risk of myopathy/rhabdomyolysis may occur
- Avoid co-administration with large quantities of grapefruit products as this may also increase the risk for adverse effects such as myalgia
- Simvastatin use should be limited or avoided in the following populations(61):
 - Patients with thyroid problems
 - Those who regularly drink three or more alcoholic drinks daily
 - Patients taking any other cholesterol lowering medication such as fibrates (gemfibrozil, fenofibrate), niacin or ezetimibe
 - People who have a family history of muscular disorders or have had any past problems with the muscles (pain, tenderness), after using an HMG-CoA reductase inhibitor (“statin”) such as atorvastatin (Lipitor*), fluvastatin (Lescol*), lovastatin (MEVACOR®), pravastatin (Pravachol*), or rosuvastatin (Crestor*), or have developed an allergy or intolerance to them
 - Patients with kidney or liver problems
 - Patients with diabetes as slightly increased blood sugar can occur when you take ACT SIMVASTATIN
 - Patients who have undergone surgery or other tissue injury

Adverse effects identified through post-marketing experience (note: the effects listed below are voluntarily reported from a population of uncertain size, therefore it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure): alopecia, skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails), dizziness, muscle cramps, myalgia, pancreatitis, paresthesia, peripheral neuropathy, vomiting, anemia, erectile dysfunction, interstitial lung disease, rhabdomyolysis, hepatitis/jaundice, fatal and non-fatal hepatic failure, and depression.

- There have been rare post marketing reports of cognitive impairment (e.g., memory loss or impairment, forgetfulness, amnesia, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).(64)
- A recent disproportionality analysis using VigiBase® (the World Health Organization international database of suspected ADR) revealed a possible drug safety signal linking myasthenia gravis (MG) with statins. The signal is weak, and experts agree the potential risk is offset by the cardiovascular benefits of statins. To our knowledge, no warning has been added to the label of marketed or generic Simvastatin drugs. (65)
- Rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, have been associated with statin use, including simvastatin. These reports were identified by the FDA adverse events reporting system (FAERS) and are now included as a warning on the product insert. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. (32,66)

Summary of available data

Summary of safety information from package inserts for example simvastatin therapies is presented below (**Table 2**; adverse events for various simvastatin oral formulations). Data available suggests that simvastatin is a safe and well-tolerated drug in both adolescent (ages 10-17) and adult populations. Simvastatin has not been well-studied in children under the age of 10. (61)

Note: atorvastatin adverse effects and risks have been wide reported to be similar to simvastatin's safety profile(60,67).

The most common side effects associated with simvastatin from controlled trials are typically mild and can include(32):

- upper respiratory infections (9.0%)
- headache (7.4%)
- abdominal pain (7.3%)
- constipation (6.6%),
- nausea (5.4%)

More severe side effects are rare but can include:(32)

- **Skeletal muscle effects** (e.g., myopathy and rhabdomyolysis): risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥ 65), female gender, uncontrolled hypothyroidism, and renal impairment. A pharmacogenomic risk variant in SLC01B1 has also been identified.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported.

- **Immune-Mediated Necrotizing Myopathy (IMNM):** there have been rare reports of IMNM, an autoimmune myopathy, associated with statin use. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents.
- **Liver enzyme abnormalities:** Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.
- An apparent **hypersensitivity syndrome** has been reported with use of FloLipid which has included some of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.(62)

Safety data from the literature

- **Numerous randomized control trials (RCTs)** have reported safety data from testing statins (including simvastatin) in a variety of indications including hypercholesterolemia (68), pulmonary hypertension (69), coronary heart disease (70), acute coronary syndrome (71), serum cholesterol reduction and stroke (60) and cardiac events avoidance (72). Additional RCTs reported safety data from studies testing specifically simvastatin in various conditions including dyslipidemia (73), dementia (74), kidney disease (75), and others (60) (71) (see **Appendix 2**).
- A large systematic review(74) included one randomized, controlled trial that tested 40 mg daily Simvastatin versus placebo for reducing the occurrence of dementia or Alzheimer's in a total of 20,536 participants aged 40 to 82 years. The trial did not show any reduction in occurrence of Alzheimer's or dementia in people treated with statins (including simvastatin) compared to placebo. Adverse events were low in both groups with no significant differences between statin group and placebo control. Rates of treatment discontinuation due to non-fatal adverse events were less than 5% in both studies and there was no difference between statin and placebo groups in the risk of withdrawal due to adverse events.
- Another meta-analysis of randomized controlled trials (RCTs) surveyed studies in which statins were given for at least 6 months and kidney outcomes were measured. From this survey, a total of 25,361 patients (across 10 randomized controlled trials) were treated with simvastatin (a variety of usual care doses were included) or placebo. In these studies, statin treatment (including simvastatin) did not produce an apparent beneficial effect for kidney failure events however statin therapy significantly reduced the risk for cardiovascular events in patients with chronic kidney disease. Additionally, no major treatment-related adverse events were reported and no trial reported a significant increase in adverse events among patients treated with Simvastatin.(75)
- Another systematic review including a total of 24,907 patients (across 18 RCTs) evaluated the cost-effectiveness of high-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day) versus simvastatin 40 mg/day in individuals with acute coronary syndrome (ACS). The major side effects reported

- included myalgia (variable from 0.7% to 32.9%), myositis (from 0.6% to 1.5%) and myopathy (from 0.6% to 0.9%). Rhabdomyolysis was reported in 1 trial (0.3%).(71)
- As atorvastatin has also been shown to have similar benefit and safety, use of this agent may be considered as a reasonable substitution for simvastatin when the latter agent is not available.

Table 2: Adverse event summary for various simvastatin formulations

Drug (route)	Population	Indication	Adverse event (and frequency, if reported)	Reference
Simvastatin, trade name: Zocor (oral tablet)	Adults and *adolescents (10-17 years), geriatric	<ul style="list-style-type: none"> - Reductions in Risk of CHD Mortality and Cardiovascular Events - Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia - Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH) 	<ul style="list-style-type: none"> - The most commonly reported adverse reactions (incidence $\geq 5\%$) in simvastatin controlled clinical trials were: upper respiratory infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%) - More rare side effects included gastrointestinal disorders (0.5%), myalgia (0.1%), arthralgia (0.1%). 	U.S package insert (32)
Simvastatin, trade name FloLipid (oral suspension)	Adults and *adolescents (10-17 years), geriatric	<ul style="list-style-type: none"> - Reductions in Risk of CHD Mortality and Cardiovascular Events - Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia - Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH) 	<ul style="list-style-type: none"> - The most commonly reported adverse reactions (incidence $\geq 5\%$) in simvastatin controlled clinical trials were upper respiratory infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6), and nausea (5.4%) - More rare side effects included gastrointestinal disorders (0.5%), myalgia (0.1%), arthralgia (0.1%) - Persistent liver dysfunction (1%) 	U.S package insert (62)

Simvastatin (disintegrating tablets)	Adults and *adolescents (10-17 years), geriatric	<ul style="list-style-type: none"> - Reductions in Risk of CHD Mortality and Cardiovascular Events - Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia - Treat patients with Fredrickson type III and IV hyperlipidemia) - Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia 	<ul style="list-style-type: none"> - The safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo. The most common adverse experiences observed in both groups was: abdominal pain (0.9%), diarrhea (0.5%), nausea (0.4%), myalgia (1.2%), eczema (0.8%) - The incidence of myopathy/rhabdomyolysis was <1% 	U.S Package insert (63)
Act Simvastatin (oral tablets)	Adults and *adolescents (10-17 years), geriatric	<ul style="list-style-type: none"> - To treat certain forms of hypercholesterolemia (including but not limited to primary hypercholesterolemia or combined hyperlipidemia, homozygous familial hypercholesterolemia) - To reduce the risk of heart disease and death in patients with atherosclerotic cardiovascular disease - 	<ul style="list-style-type: none"> - The following side effects may occur and generally do not require medical attention: gastrointestinal effects (constipation, diarrhea, gas, upset stomach, nausea), headache, skin rash, poor memory/memory loss, confusion, trouble sleeping, depression, erectile dysfunction, persistent cough or shortness of breath. - Side effects such as myalgia (muscle pain), myopathy (muscle disease with aching or weakness), rhabdomyolysis (a muscle wasting disease), associated tenderness and rare cases of muscle breakdown resulting in kidney damage have been reported with statins including ACT Simvastatin but are very rare. 	Canadian package insert (61)

* Doses greater than 40 mg have not been studied in this population

Identification of variation in safety that may relate to health systems and patient factors

- The package insert for several simvastatin drugs (32,61–63) states possible variations in safety for multiple patient groups, including the following:
 - Patients with active liver disease, including unexplained persistent elevations in hepatic transaminase levels, or patients who consume substantial amounts of alcohol
 - Women who are pregnant or may become pregnant, as statins decrease cholesterol synthesis and possibly the synthesis of other cholesterol-derived biologically active substances. This increases risk for fetal harm.
 - Nursing mothers, as a small amount of another statin does pass into breast milk, and there is the potential for serious adverse reactions in nursing infants
 - Patients with severe renal impairment should be started at 5 mg/day and be closely monitored.
 - Some simvastatin drugs marketed in the US (Zocor, FloLipid) have not been studied in certain types of hyperlipidemia including Fredrickson types I and V.
 - Certain patient groups are at increased risk of developing myopathy,;
 - Chinese patients who are co-administered lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products, due to increased risk for myopathy; it is unknown if this increased risk extends to other Asian patients,
 - Risk for myopathy/rhabdomyolysis may also be aggravated by patient use of CYP3A4 inhibitors, gemfibrozil or other fibrates, cyclosporine or danazol, and amiodarone or verapamil
 - The U.S. Food and Drug Administration (FDA) has advised that protease inhibitors and statin (simvastatin, in particular) taken together may raise blood levels of statins and increase risk for myopathy/rhabdomyolysis . (76) This has been supported by quantitative evaluation of simvastatin with multiple HCV- or HIV-protease inhibitors (nelfinavir, ritonavir-boosted saquinavir, or unboosted atazanavir). (77)
 - Patients ≥ 65 years, with uncontrolled hypothyroidism, or severe renal impairment, due to increased risk for myopathy manifested as muscle pain, tenderness, or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy may also take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of statin activity in plasma.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Simvastatin is already on the EML, with a widespread availability in most countries of the world at very low cost. The current application is not a request to add a medication for which pricing would be needed, as there would be no change to the existing pricing data expected from adding this new use of simvastatin. The prevalence of PCOS is notable, with significant effects on immediate outcomes such as quality of life and fertility, as well as longer term impacts on hyperlipidemia, diabetes, and downstream cardiovascular disease. One national cost analysis conducted using US data, for example, noted that the estimated annual national health care cost associated with PCOS was \$1.16 billion, in 2010 dollars, with the greatest contributors being diabetes, obesity, contraceptives, initial

evaluation, and infertility treatment.(78) Another analysis in the UK, focused on costs associated with diabetes in women with PCOS, found that the annual healthcare burden of PCOS based on their conservative estimate approach was at least £237 million.(79) Given the relative low cost of simvastatin therapy and the supportive body of data in terms of safety and efficacy, the likelihood that increased utilization of this regimen in women affected with PCOS would confer significant benefit in terms of health and health-related costs.

12. Summary of regulatory status and market availability of the medicine.

Simvastatin is approved and marketed globally for the indications listed below. Further, Simvastatin is available as a generic from numerous manufacturers including Actavis Pharma, Inc., and Cardinal Health. (U.S), Angita Pharma Inc. and Apotex Corporation (Canada), among many others globally. Given that simvastatin is in widespread use globally as a lipid-lowering drug, it is anticipated that the currently proposed expanded use for this agent would leverage the existing supply chains established in various regions.

Examples of statin approval for use in various countries are as follows:

Regulatory Agency	Indication
US Food and Drug Administration (FDA)	Simvastatin: to reduce adverse cardiovascular events and to treat various forms of hypercholesterolemia including (32,62): <ul style="list-style-type: none"> - Homozygous/heterozygous familial hyperlipidemia - Heterozygous Nonfamilial hypercholesterolemia - Hypertriglyceridemia - Dysbetalipoproteinemia -
European Medicines Agency (EMA)	Simvastatin(80): <ul style="list-style-type: none"> - To treat various forms of hypercholesterolemia - To reduce the risk of heart disease and death in patients with atherosclerotic cardiovascular disease - Homozygous familial hypercholesterolemia (in conjunction with alternative lipid-lowering therapies such as LDL apheresis). - Cardiovascular event prevention in patients with high risk for first cardiovascular event (in conjunction with the correction of other risk factors).
Australian Government, Department of Health, Therapeutic Goods Administration	Simvastatin(81): <ul style="list-style-type: none"> - To control elevated cholesterol, or hypercholesterolemia (only after other methods such as diet and exercise have not improved cholesterol levels) -
Health Canada	ACT SIMVASTATIN(61): <ul style="list-style-type: none"> - To lower cholesterol levels (in conjunction with diet and exercise) - To decrease the risk of heart attack, stroke, or death regardless of whether cholesterol levels are high for people who have coronary heart disease (CHD) or have other arteries in the body that are blocked, or for those who have diabetes and are over the age of 40. - To treat people who have certain inherited cholesterol disorders. -

13. Availability of pharmacopeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia).

Simvastatin is included in several pharmacopeial standards, including the British Pharmacopoeia; the United States Pharmacopoeia; and the European Pharmacopoeia.

LITERATURE SUMMARY: Evidence describing use of statins in PCOS (simvastatin; literature describing use of atorvastatin or rosuvastatin included for context)

First author, year Country	Design	Condition	Sample size	Drug dose, frequency, duration, route of administration; comparator	Findings	Outcome
<i>Systematic reviews and meta-analyses</i> <i>Note: There is overlap in included studies among these reviews and meta-analyses; however, each analysis employs different approaches for evaluating statin outcomes so all papers are included to create a more nuanced picture of this literature.</i>						
Almalki 2020(4) Saudi Arabia	Meta-analysis of 9 RCTs, including 4 that involved a statin	PCOS	613	Different types of statin at any dose; 2 trials included simvastatin and 2 included atorvastatin	In the network meta-analysis, atorvastatin showed greater reduction in testosterone level compared to COC (MD -2.78, 95%CrI -3.60, -1.97), spironolactone plus metformin (MD -2.83, 95%CrI -3.80, -1.87), simvastatin (MD -2.88, 95%CrI -3.85, -1.92), spironolactone (MD -2.90, 95%CrI -3.77, -2.02), simvastatin plus metformin (MD -2.93, 95%CrI -3.79, -2.06), metformin (MD -2.97, 95%CrI -3.69, -2.25), lifestyle modification (MD -3.02, 95%CrI -3.87, -2.18), and placebo (MD -3.04, 95%CrI -3.56, -2.53).	Positive effect
Yang 2019(5) China	Meta-analysis of 10 RCTs	Serum and plasma levels of DHEA in women with PCOS	735	Different types of statin at any dose that continued for at least two weeks. Six studies simvastatin (20 mg/day), one study atorvastatin (40 mg/day), one study rosuvastatin (10 mg/day) <i>Non- statin treated placebo</i>	Atorvastatin significantly reduced DHEA levels (SMD, -0.63; 95% CI, -1.20 - -0.05; p=0.03; I2=38%) but simvastatin did not significantly reduce DHEA levels (SMD: -0.14; 95% CI, -0.49-0.28; p=0.43; I2=77%). Subgroup analysis based on duration of treatment showed no significant difference between 12 weeks of statin treatment (SMD, -0.61; 95% CI, -1.23-0.02; p=0.06; I2=85%) and 24 weeks of statin treatment (SMD, -0.34; 95% CI -0.95-0.28; p=0.29; I2=83%)	Positive effect
Cassidy-Vu 2016(3)	Systematic review of 12 trials	PCOS	NA	Trials involved simvastatin or atorvastatin (11 trials); one study evaluated rosuvastatin. Most trials were 12 weeks duration; a	10 of 12 trials showed reduction in testosterone levels or other hormones (DHEA-S and androstenedione); some trials showed improvement in LH/FSH ratio ; all	Positive effect

				low to moderate dose of statin was typically used	<p>trials demonstrated positive effects on lipid profiles.</p> <p>No synthesis of overall results by statin type within this review.</p>	
Gao 2012(6)	Meta-analysis of 4 RCTs	"Therapeutic effects" of statins on PCOS, testosterone level as primary outcome	254	<p>atorvastatin 40 mg, QD vs placebo 6 weeks;</p> <p>simvastatin 20 mg, QD vs metformin 850 mg, BID vs sim + met 20mg, QD + 850 mg, BID 12 weeks;</p> <p>simvastatin 20 mg, QD vs placebo 12 weeks;</p> <p>atorvastatin 20 mg, QD vs placebo 12 weeks</p>	<p>Significant reduction of serum total testosterone when comparing statin with placebo (Std MD= - 3.03, 95%CI - 5.85 ~ - 0.22, P=0.03) or statin + metformin with metformin (Std MD=- 1.07, 95%CI: - 2.06 ~ - 0.07, P=0.04). Statin was more effective than placebo in reducing LDL (WMD=- 0.87, 95%CI - 1.18 ~ - 0.55, P<0.0001), TC (WMD=- 1.23 95%CI - 1.35 ~ - 1.11, P<0.00001), TG (WMD= - 0.50, 95%CI - 0.73 ~ - 0.27, P<0.00001); and statin + metformin was more effective than metformin in lowering LDL (WMD= - 0.84, 95%CI: - 1.33 ~ - 0.354, P=0.0009), TC (WMD= - 1.28, 95%CI: - 1.47 ~ - 1.10, P<0.00001), and TG (WMD= - 0.27, 95%CI: - 0.36 ~ - 0.19, P<0.00001).</p>	Positive effect
Raval 2011(82)	Meta-analysis of 4 RCTs	Efficacy and safety of statin therapy for PCOS. Primary outcomes resumption of menstrual regularity, resumption of spontaneous ovulation.	N= 244 in 4 trials	<p>Simvastatin 20 mg QD+ met 850 mg BID vs sim 20 mg QD vs met 850 mg BID;</p> <p>Simvastatin 20 mg plus OCP vs OCP alone;</p> <p>Atorvastatin 40mg QD vs placebo;</p> <p>Atorvastatin 20 mg vs placebo</p>	<p>This earlier review identified no evidence that statins improve resumption of menstrual regularity or spontaneous ovulation, hirsutism, acne, or BMI.</p> <p>Statins lower testosterone levels (nmol/L) (mean difference (MD) -0.90, 95% CI -1.18 to -0.62, P < 0.00001, 3 RCTs, 105 women), reduced the level of total cholesterol (MD - 1.15, 95% CI -1.48 to -0.82, P < 0.00001, 3 RCTs, 105 women, I2 = 46%), LDL (MD - 0.96, 95% CI -1.24 to -0.68, P < 0.00001, 3 RCTs, 105 women, I2 = 24%), and triglyceride levels (MD -0.43, 95% CI -0.63 to -0.23, P < 0.00001, 3 RCTs, 105 women, I2 = 15%)</p> <p>No serious adverse events reported.</p>	Suggests slight positive effects for some outcomes and unknown effects in other
Simvastatin						

Karakas 2013(14) Poland	RCT	PCOS	62	Simvastatin (20mg/day) OR metformin (850mg 2x/day) OR simvastatin + metformin for 3 months	<p>Simvastatin decreased total cholesterol by 21% (p=0.0004), LDL by 29% (p=0.0001), and CRP by 36%(p=0.0002). Surprisingly, simvastatin also decreased fasting insulin (p=0.01) and increased insulin sensitivity (p=0.03). Metformin alone did not affect any of the metabolic parameters.</p> <p>Simvastatin + metformin significantly reduced total cholesterol (p=0.002), LDL (p=0.0001), CRP (p=0.04), and triglycerides (p=0.03). Although simvastatin, both alone and in combination with metformin, exerted significant effects on several metabolic variables, serum FABP4 and RBP4 did not change (both thought to be involved in metabolic syndrome).</p> <p>No mention of adverse effects.</p>	Positive effect
Duleba 2006(15) Poland	RCT	PCOS	48	Simvastatin (20mg/day) + oral contraceptive pill OR oral contraceptive pill only for 12 weeks	<p>Compared to baseline, simvastatin + oral contraceptives significantly reduced serum testosterone (41%), DHEAS (26%), LH (43%), LH/FSH ratio (44%), total cholesterol (10%), LDL (24%), and increased HDL (9%) (all p<0.05). Hirsutism score also declined slightly (0.25 points on the Ferriman-Gallway scale, p=0.03).</p> <p>Fasting insulin, fasting glucose, and glucose AUC during OGTT were not significantly altered, but insulin AUC significantly increased in both groups (44% vs 34%).</p> <p>Simvastatin produced significant between-group differences in testosterone (p=0.006), LH (p=0.02), LH/FSH ratio (p=0.02), total cholesterol (p<0.001), and LDL (p<0.001).</p> <p>Both treatments were well tolerated, and none of the subjects experienced significant side effects.</p>	Positive effect

Banaszewska 2007(16) Poland	Randomized crossover trial	PCOS	48	Simvastatin (20mg/day) + oral contraceptive pill for 12 weeks followed by oral contraceptive pills only for an additional 12 weeks, or vice versa	<p>Compared to baseline, simvastatin + oral contraceptives significantly reduced total testosterone (38%), free testosterone (58%), DHEAS (28%), LH (37%), LH/FSH ratio (40%), Hirsutism score (8%), total cholesterol (7.5%), LDL (20%), and increased HDL (14%) (all $p<0.001$). Simvastatin + oral contraceptive also had a significant effect on markers of systemic inflammation and endothelial dysfunction (hs-CRP decreased by 45% ($p=0.002$) and sVCAM decreased by 18% ($p<0.001$).</p> <p>Compared to oral contraceptive alone, there were significant simvastatin-attributable effects on total testosterone ($p=0.004$), free testosterone ($p=0.006$), LH ($p=0.002$), LH/FSH ratio ($p=0.01$), Hirsutism score ($p=0.02$), total cholesterol ($p<0.001$), LDL ($p<0.001$), hs-CRP ($p<0.006$), and sVCAM-1 ($p=0.01$).</p> <p>Fasting glucose and glucose AUC increased in the range of 4-8% after either treatment, without any significant statin-attributable effect. Fasting insulin and insulin AUC also significantly increased after both treatments with no significant statin-attributable effect.</p> <p>None of the subjects experienced significant side effects; in particular, none of the subjects developed symptoms of muscle damage and liver function tests remained normal throughout study.</p>	Positive effect
Rashidi 2011(17) Iran	Double-blind RCT	<p>PCOS patients undergoing IVF (controlled ovarian hyperstimulation via gonadotropin therapy (hCG))</p> <p>Both patient groups underwent pituitary</p>	61	Simvastatin (20 mg/day) OR placebo for 8 weeks	<p>No significant difference in median number or proportion of MII oocytes observed or the pronuclear zygote fertilization rates between groups. The clinical pregnancy rate was somewhat higher for patients in the statin group (28% vs 21% for patients receiving placebo), but not statistically significant ($p=0.25$). No significant difference in the observed incidence of mild</p>	<p>Positive effects on testosterone and cholesterol levels.</p> <p>No effect on oocyte quality</p>

		down-regulation followed by ovulation induction via daily injection of 150 IU recombinant follicle stimulating hormone (FSH) initiated on cycle day 3. Both simvastatin and placebo were discontinued on the day of hCG injection (when serum estradiol levels exceeded 500 pg/mL and at least 2 follicles of sufficient size present)			<p>or moderate ovarian hyperstimulation syndrome between groups.</p> <p>PCOS patients receiving simvastatin experienced significant reductions in total testosterone (25% vs 10% in placebo group, $p=0.0001$), total serum cholesterol (24% vs 1% in placebo group), and LDL cholesterol (15% decrease vs 8% increase in placebo group). Serum HDL levels increased similarly for both groups. Patients in the statin group demonstrated an average serum LH decline of 29% and a 30% reduction of the LH/FSH ratio ("significantly greater than placebo group" but no p value shown).</p> <p>Simvastatin had a significantly beneficial effect ($p=0.0001$) on systemic inflammatory markers (58% decline in hsCRP compared to 28% in placebo group).</p> <p>All patients tolerated study medications well; there were no discontinuations due to adverse effects.</p>	or reproductive outcomes.
Navali 2011(18) Iran	Double-blind RCT	PCOS	400	Simvastatin 20 mg/day OR metformin 500 mg 3x day for 3 months	<p>Simvastatin significantly decreased the percent of abnormal periods ($p=0.04$), acne ($p=0.04$), positive CRP ($p<0.001$), hyperinsulinemia ($p<0.001$), mean serum total cholesterol ($p<0.001$), LDL ($p<0.001$), and DHEAS ($p<0.001$) and significantly increased mean serum HDL ($p<0.001$). Decreases in percent of abnormal OGTT ($p=0.06$) and mean serum insulin ($p=0.06$) were borderline not significant.</p> <p>Improvements in serum total cholesterol ($p<0.001$), LDL ($p<0.001$), CRP ($p<0.001$), and acne status ($p=0.04$) were significantly superior in the simvastatin group compared to the metformin group. In contrast, the mean fasting blood sugar ($p=0.04$) and serum insulin ($p=0.04$) decreased</p>	Positive effect

					<p>significantly more in the metformin group after treatment.</p> <p>No significant side-effects or complications were documented in the patients within the study period.</p>	
Azargoon 2013(19) Iran	"quasi experimental study" (no control group)	Clomiphene-resistant women with PCOS	25	Simvastatin (20mg/day) for 2 months, starting with the first day of menstrual cycle	<p>Ovulation occurred in 5 out of 25 (20%) patients but none of the patients conceived during this study.</p> <p>No significant change in BMI was observed following simvastatin therapy.</p> <p>All patients tolerated the simvastatin and none developed any side effects.</p>	Positive effect
Krysiak 2014(20) Poland	Prospective parallel groups matched by age and weight	PCOS + hypercholesterolemia	28	Simvastatin (40 mg/day) OR ezetimibe (10mg/day) for 90 days	<p>Both ezetimibe and simvastatin significantly reduced plasma levels of total cholesterol by, respectively, 21% ($p<0.001$) and 23% ($p<0.001$) as well as LDL cholesterol by 29% ($p<0.001$) and 34% ($p<0.001$). Neither altered plasma levels of triglycerides or HDL cholesterol. Neither affected glucose homeostasis markers, although ezetimibe showed a tendency to reduce HOMA1-IR (by 16%, $p<0.092$).</p> <p>Simvastatin decreased serum levels of testosterone by 23% ($p<0.001$), free testosterone by 32% ($p<0.001$), androstendione by 20% ($p<0.01$), and DHEA-S by 17% ($p<0.05$). It tended to reduce the LH/FSH ratio (-23%, $p=0.095$). Simvastatin treatment exerted no effect on serum levels of FSH, LH, prolactin, and SHBG. The degree of reduction in plasma lipids, total and free testosterone, androstendione, DHEA-S, and LH/FSH ratio by simvastatin did not differ between insulin-resistant and insulin-sensitive patients.</p> <p>Between group comparisons showed that simvastatin is superior to ezetimibe in reducing total and free testosterone ($p<0.01$).</p>	Positive effect

					No mention of adverse effects.	
Pourmatroud 2015(21) Iran	Double-blind RCT	PCOS candidates for intra-cytoplasmic sperm injection (ICSI) cycle (history of infertility)	40	Simvastatin (20 mg/day) OR metformin (500 mg 3x day) administered for 8 weeks before starting ICSI cycle (both groups on daily low dose oral contraceptive pills for 8 weeks)	<p>Both the simvastatin and metformin groups saw a significant reduction in mean hirsutism score ($p=0.0001$ vs 0.003). Compared to pretreatment, simvastatin significantly reduced testosterone ($p=0.013$), FSH ($p=0.007$), LH($p=0.01$), total cholesterol ($p=0.001$), and LDL ($p=0.004$), and significantly increased HDL ($p=0.001$). No significant change in triglycerides or FBS.</p> <p>Compared to pretreatment, metformin significantly reduced FSH ($p=0.004$), testosterone ($p=0.001$), triglycerides($p=0.005$), and total cholesterol ($p=0.044$, pre vs post treatment comparison). No significant difference between groups in the number of oocytes in phase 2 meiosis, grade A embryos, or pregnancy rates.</p> <p>No mention of adverse effects.</p>	<p>Positive effect on biochemical parameters</p> <p>No effect on ICSI cycle outcomes</p>
Yang 2016(22) China	Prospective parallel groups matched by age	PCOS	42 (21 PCOS + 21 age-matched healthy controls)	Simvastatin (20 mg/day) for 6 months compared to pre-treatment and healthy controls	<p>After statin administration, the PCOS group had significantly lower cholesterol (0.0005), triglyceride ($p=0.0638$), LDL cholesterol ($p<0.001$), and lower HOMA-IR (0.0470). The post-treatment values were similar to (not significantly different from) those of the control group.</p> <p>Markers of endothelial dysfunction (FMD, ABI, plasma ET-1) were also significantly lower after statin treatment ($p<0.001$), similar to those of controls (not significantly different).</p> <p>No severe side effects were reported during the study.</p>	Positive effect
Mehrabian 2016(23) Iran	Single-blind clinical trial	PCOS + metabolic syndrome	102 (34 in each group)	Simvastatin (20mg/day) OR metformin (1000mg/day) OR flutamide + low dose oral	Compared to baseline values, simvastatin significantly reduced waist circumference, triglycerides, fasting blood glucose, CRP, and BMI (all $p<0.001$). No significant	Positive effect

				contraceptives (62.5mg) for 6 months	<p>change in HDL. The differences in waist circumference ($p<0.001$), triglycerides ($p<0.007$), and BMI ($p<0.001$) were significantly larger in the simvastatin group compared to the others.</p> <p>Mean changes in CRP were significantly larger in both the simvastatin and flutamide + OC groups as compared to the metformin group. Mean changes in fasting blood sugar were significantly larger in the metformin group as compared to the others.</p> <p>No mention of adverse effects.</p>	
Seyam 2018(24) Egypt	Double-blind RCT	PCOS	200	Simvastatin (20mg/day) OR metformin (500 mg/day) OR simvastatin + metformin for 12 months	<p>There were significant between-group differences in most of the parameters tested, with both groups receiving simvastatin generally showing a more positive response than the group receiving metformin alone: spontaneous menses per 6 months ($p=0.001$), ovulation (assessed via ultrasound, $p=0.001$), volume of both ovaries ($p=0.001$), BMI ($p=0.01$), waist/hip ratio ($p=0.01$), hirsutism score ($p=0.001$), acne ($p=0.001$), total testosterone ($p=0.001$), free testosterone ($p=0.001$), DHEAS ($p=0.001$), SHBG ($p=0.04$); LH/FSH ratio ($p=0.005$), prolactin ($p=0.04$), total cholesterol ($p=0.005$), LDL ($p=0.005$), HDL ($p=0.04$), triglycerides ($p=0.04$).</p> <p>There were significant between-group differences in fasting glucose ($p=0.001$), fasting insulin ($p=0.001$), and insulin sensitivity index ($p=0.001$) with both groups receiving metformin showing a more positive response than the group receiving simvastatin alone.</p> <p>No mention of adverse effects.</p>	Positive effect
Seyam 2018(44) Egypt	Double-blind RCT	PCOS	200	Simvastatin (20mg/day) OR placebo for 6 months	<p>Simvastatin significantly decreased serum testosterone (28%, $p<0.001$), LH/FSH ratio (43%, $p<0.005$), total cholesterol (26%, $p<0.005$), LDL (39%, $p<0.005$), and</p>	Positive effect

					<p>triglycerides (23%, $p<0.04$), DHEAS (19%, $p<0.01$), FSH (8%, $p<0.05$), and significantly increased HDL (17%, $p<0.04$), as compared to the placebo group. There was no significant difference in fasting glucose, fasting insulin, or HOMO-IR.</p> <p>Simvastatin also significantly improved menstrual regularity ($p<0.001$) and significantly decreased hirsutism (14%, $p<0.001$), acne (75%, $p<0.001$), ovarian volume (18%, $p<0.001$), BMI (16%, $p<0.01$), and waist/hip ratio (19%, $p<0.01$).</p> <p>No mention of adverse effects.</p>	
Banaszewska 2011(27) and Banaszewska 2009(26) Poland	RCT	PCOS	139 randomized (113 at 3 months, 97 at 6 months)	Simvastatin (20 mg daily) compared to metformin (850 mg twice daily) OR simvastatin (20 mg daily) plus metformin (850 mg twice daily) for 6 months	<p>Total testosterone, declined significantly in all three groups (by 13.6–16.3%), and no significant difference between the groups was noted. BMI declined after all treatments by 1.6–2.7% with no statistically significant difference between the treatment groups. In all groups, there was also a significant and comparable improvement of markers of systemic inflammation and endothelial function, as manifested by reduction of hs-CRP (-0.51 ± 0.23 (-34%) and sVCAM -57 ± 20 (-8.3%). Simvastatin treatment was superior to metformin alone, whereas a combination of simvastatin and metformin was not significantly superior to simvastatin alone.</p>	Positive effects for simvastatin alone (without metformin)
Kazerooni 2010(28) Iran	Randomized, double-blind, placebo-controlled trial	T and LH levels	N=84	Metformin (500 mg three times a day) plus simvastatin (20 mg/day, n=42; group 1) or metformin (500 mg three times a day) plus placebo (once a day, n=42; group 2) for 12 weeks	<p>Serum T levels decreased by 25.5% in group 1 and by 16.8% in group 2, difference between groups $P<.001$. Change in DHEAS value declined by 3% ($P=.043$) and 0.2% ($P=.973$), difference between groups $P=.007$.</p> <p>There was a greater decrease of LH (45.5% vs. 6.7%) and a greater decline of the LH/FSH ratio (38.3% decreased vs. 4.4% increased) in the first group. In group 1 there was a greater decrease of total cholesterol (29.5% vs. 4.2%), low-density</p>	Positive effect for metformin with simvastatin

					lipoprotein (LDL; 18.5% vs. 1.5%), and triglycerides (32% vs. 5.3%). High-density lipoprotein (HDL) increased in the first group by 14%, whereas it decreased by 1% in the second group.	
Malik 2018(29) Pakistan	RCT	PCOS	108	metformin group (control, n=54) and metformin plus simvastatin group (intervention, n=54) over 3 months	<p>Comparison of efficacy in both study groups stratified by mean LH/FSH ratio at baseline</p> <p>3 months: 16 (Control) 25 (intervention)</p> <p>6 months: 20(control) 25 (intervention)</p> <p>Desired efficacy was achieved in 86 (79.63%) cases. Among them, 66.7% with metformin alone while 92.6% with combination of metformin and simvastatin.</p>	Positive effect for combined therapy with metformin and simvastatin
<i>Simvastatin vs. atorvastatin</i>						
Kaya 2010(30) Turkey	RCT	PCOS	64	simvastatin 20 mg/day OR atorvastatin 20 mg/day for 3 months	<p><i>Beneficial effects that were greater in the simvastatin group:</i> Serum levels of LH declined by 19.1+/-4.5% (P<0.05) in the atorvastatin group and by 39.3+/-11.9% (P<0.01) in the simvastatin group. FSHFAI decreased by -20+/-9.9% in the atorvastatin group (P<0.05) and by -38.7+/-13.8% in the simvastatin group (P<0.01). MDA levels decreased by 32.6+/-9.6% in the atorvastatin group (P<0.05) and by 30.3+/-10.9% (P<0.01) in the simvastatin group. Total testosterone significantly decreased in both groups and to a greater degree in the simvastatin group (atorvastatin p<0.05; simvastatin p<0.01). Hirsutism score decreased significantly in both groups and to a greater degree in the simvastatin-treated patients.</p> <p><i>Similar beneficial effects between groups:</i> Total cholesterol declined significantly and HDL-C increased significantly in both groups.</p> <p><i>Beneficial effects greater in the atorvastatin group:</i> CRP levels decreased by 63.6+/-</p>	Positive effect, similar for total cholesterol and HDL-C; some outcomes better for simvastatin and some for atorvastatin

					<p>15.9% in the atorvastatin-treated group ($P<0.01$) and by $34.6\pm 10.7\%$ in the simvastatin-treated group ($P<0.05$). Atorvastatin led to a significant reduction in the HOMA index and fasting insulin ($-26.9\pm 9.6\%$, $-26.2\pm 10.8\%$, both $P<0.01$); both outcomes were reduced in the simvastatin group ($8.3\pm 1.9\%$, $3.0\pm 0.8\%$, respectively) but the changes did not reach statistical significance. LDL declined in both groups, but the difference was significantly greater in the atorvastatin group ($p<0.01$).</p> <p>Both treatments were well-tolerated and no adverse effects were reported.</p> <p>Note: all p values correspond with comparisons to baseline.</p>	
Kaya 2009(31) Turkey	RCT	PCOS	52	simvastatin 20 mg/day OR atorvastatin 20 mg/day for 12 weeks	<p>After 12 weeks of treatment, serum homocysteine levels in the atorvastatin group had decreased from 14.3 ± 2.9 to 10.6 ± 1.7 micromol/L; in the simvastatin group, the levels decreased from 13.6 ± 2.1 to 11.1 ± 1.9 micromol/L. In both groups, free testosterone and total testosterone declined statistically significantly (38.3% and 36.5%; and 40.6% and 46.0%, respectively). In the atorvastatin group, vitamin B(12) increased from 362.1 ± 107 to 478.7 ± 267 pg/mL; in the simvastatin group, it increased from 391.3 ± 107 to 466 ± 211 pg/mL, but the change did not reach statistical significance. There was a considerable decline in the homeostatic model assessment index in the atorvastatin group 1 (40.0% to 32.1%).</p> <p>No adverse events were reported.</p>	Positive effect for both agents; HOMA index decline greater in atorvastatin group
Atorvastatin						
Puurunen 2013(47); Luotola 2018(48)	RCT	PCOS	28	20 mg/day atorvastatin for 6 months <i>Non- statin treated placebo</i>	Serum levels of dehydroepiandrosterone sulfate decreased in the atorvastatin group, whereas no change was observed in serum	Positive effect (DHEA, lipids, CRP)

Finland					<p>testosterone levels. Levels of C-reactive protein, total and low-density lipoprotein-cholesterol, and triglycerides decreased significantly during statin therapy. ISI0 min and ISI120 min were significantly lower than in the placebo group after 6 months of atorvastatin treatment. In IVGTTs, insulin sensitivity had a significant difference between the groups at 6 months.</p> <p>Increased testosterone levels and FAI values in women with PCOS were associated with decreased insulin sensitivity index values and increased early insulin secretion.</p>	Potential negative effect on glucose metabolism
Raja-Khan 2011(49) USA	RCT	PCOS and LDL >100 mg/dl	20	40 mg atorvastatin (n=9) or placebo (n=11) once daily for 6 weeks	<p>Compared to baseline levels, atorvastatin significantly reduced systolic (p=0.04) and diastolic (p=0.03) blood pressure, total cholesterol (p<0.001), LDL (p<0.001), triglycerides (p<0.001), hsCRP (p=0.02), DHEAS (p=0.01), and androstenedione (<0.001). However, there were also significant increases in AUC insulin (p=0.03) and peak brachial artery conductance during reactive hyperemia (p=0.05). No significant differences in BMI, HDL, fasting glucose, fasting insulin, FMD, hirsutism score, mean ovarian volume, free or total testosterone.</p> <p>Compared to placebo, the only significant changes caused by atorvastatin were in systolic (p=0.05) and diastolic (p=<0.001) blood pressure, LDL cholesterol (p<0.001), triglycerides (p<0.001), androstenedione (p<0.001), and DHEAS (p=0.02).</p>	<p>Positive effect (lipids, blood pressure, androstenedione)</p> <p>Potential negative effect (AUC insulin)</p>
Sathyapalan 2009,(50) Sathyapalan 2010,(51) Sathyapalan 2010,(52)	RCT	Medication-naïve PCOS with hyperandrogenemia	40	20 mg atorvastatin daily or placebo for 3 months	Atorvastatin associated with significant reduction in total cholesterol (4.6 +/- 0.2 vs. 3.4 +/- 0.2 mmol/liter, P < 0.01), low-density lipoprotein cholesterol (2.9 +/- 0.2 vs. 1.8 +/- 0.2 mmol/liter, P < 0.01), triglycerides (1.34 +/- 0.08 vs. 1.08 +/- 0.13	Positive effect

Sathyapalan 2012,(53) Sathyapalan 2012,(54) Sathyapalan 2017,(55) Sathyapalan 2019(56) UK					mmol/liter, $P < 0.01$), high-sensitivity C-reactive protein (4.9 ± 1.4 vs. 3.4 ± 1.1 mg/liter, $P = 0.04$), free androgen index (13.4 ± 0.6 vs. 8.7 ± 0.4 , $P < 0.01$), testosterone (4.1 ± 0.2 vs. 2.9 ± 0.1 nmol/liter, $P < 0.01$) and insulin resistance as measured by HOMA-IR (3.3 ± 0.4 vs. 2.7 ± 0.4). There was a significant increase in SHBG (31.1 ± 1.0 vs. 35.3 ± 1.2 nmol/liter, $P < 0.01$). There was a positive correlation between the reduction in HOMA-IR in the atorvastatin group with the reduction in triglycerides and the reduction of free androgen index. There was a significant deterioration of HOMA-IR in the placebo group (3.0 ± 0.4 vs. 3.8 ± 0.5).	
Krysiak, 2014(57) Poland	Randomized control trial	PCOS	23	increased dose of atorvastatin (40mg daily, n=11) or atorvastatin (20mg daily) plus ezetimibe (10mg daily) (n=12).	Atorvastatin Mean (SD) total cholesterol [mmol/L] baseline 6.29 (0.55); after 3 months 5.34 (0.52) Atorvastatin/ Ezetimibe Mean (SD) Mean (SD) total cholesterol [mmol/L] 6.35 (0.57); After 3 months 5.46 (0.49) Although both treatments decreased plasma levels of total and LDL-cholesterol levels, only high-dose atorvastatin reduced serum levels of total testosterone, free testosterone and androstendione	Positive effect
Rosuvastatin						
Ghazeeri, 2015(58) Lebanon	prospective, randomized, double-blinded, placebo-controlled study	PCOS	37	All patients received rosuvastatin 10 mg/day for 3 months after starting the study Then for 3 months, patients were randomized to either intervention group rosuvastatin (10 mg/day) plus metformin (850 mg twice daily after meals); or	Baseline Cholesterol 190.9 ± 50.1 (control); 174.0 ± 31.6 (intervention) 3-month (Note: these values represent the decrease in cholesterol observed after all patients had received rosuvastatin for 3 months) 148.1 ± 34.8 (control); 138.8 ± 38.1 (intervention)	Positive effect

				control group rosuvastatin (10 mg/day) plus placebo	6-month 157.0 ± 44.8 (control); 162.1 ± 43.6 (intervention)	
Celik, 2012(59) Italy	RCT	PCOS	38	20 patients had lifestyle changes and metformin (2000 mg/day) therapy (control group) 18 had statin (rosuvastatin 10 mg/day) in addition to this therapy (intervention group).	Baseline total cholesterol 223.9±22.8 (control); 253.8±21.8 (intervention) 3-month 208.4±29.5 (control); 174±18.9 (intervention) As expected hsCRP, triglyceride, total and LDL-cholesterol levels decreased more in the intervention group.	Positive effect

Key: BAC brachial artery conductance ; DHEA dehydroepiandrosterone; FAI free androgen index; HOMA-IR homeostasis model assessment for insulin resistance; LDL low-density lipoprotein; PCOS polycystic ovary syndrome; CRP C-reactive protein; BMI body mass index; FABP4 fatty acid binding protein-4; RBP4 retinol binding protein-4; SHBG sex hormone binding globulin

14. Comprehensive reference list and in-text citations.

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Appendix 2: Summary of adverse events reported in systematic reviews of statin use, non-PCOS indications

Indication	Statins	Number of participants (studies)	Patient characteristics	Major adverse event(s) reported	Frequency
Dyslipidemia (73)	Simvastatin	437 (10 randomized controlled trials)	Adult patients, males and females	Upset Stomach	Reported only in 1 study, 3.2%
				Nausea	From 6.0-6.5%
				ALT Increase	From 1.9-18.8%
				AST Increase	Reported only in 1 study, 6.0%
				Abdominal Distention	From 6.0-17.5%
				CPK Increase	From 1.5-5.0%
				Anorexia	Reported only in 1 study, 6.5%
				Dry Mouth	Reported only in 1 study, 5.0%
Dementia (74)	Simvastatin	20536 (1 randomized controlled trial)	Adult patients, males and females	Rhabdomyolysis	0.0004%
				Myopathy	0.0003%

Hypercholesterolemia (68)	Simvastatin Atorvastatin	81716 (75 randomized controlled trials)	Adult patients, males and females	Muscle Toxicity	From 0.01-9%
				Abnormal CK	From 0-0.63%
				ALT/AST Abnormal	From 0-7.3%
Kidney Disease (75)	Simvastatin Atorvastatin	47638 (20 randomized controlled trials)	Adult patients, males and females	No major treatment-related adverse events were reported.	No trial reported a significant increase in adverse events among patients treated with Simvastatin/Atorvastatin.
Periodontal Treatment (83)	Simvastatin Atorvastatin	714 (14 trials, 11 randomized controlled trials)	Adult patients, males and females	No major treatment-related adverse events were reported.	No trial reported a significant increase in adverse events among patients treated with Simvastatin/Atorvastatin.
Pulmonary Hypertension (69)	Simvastatin Atorvastatin	482 (6 trials in total, 3 randomized double-blind placebo-controlled trials, 1 randomized control trial, 1 randomized, triple-blind, parallel group trial and 1 randomized, double-blind, controlled trial)	Adult patients, males and females	No major treatment-related adverse events were reported.	No obvious discrepancy in adverse events between the placebo and statin groups was reported.
Age-related macular degeneration (84)	Simvastatin	144 (2 randomized controlled trials)	Adult patients, males and females	Reported adverse events include acute hepatitis,	Adverse outcomes reported in 1 study in 44% of patients receiving simvastatin.

				death and muscle aches.	
Coronary Heart Disease (70)	Simvastatin Atorvastatin	124752 (35 randomized controlled trials)	Adult patients, males and females	Trials indicated that statins increased muscle and kidney disease risk in comparison to placebo.	No trial reported a significant increase in adverse events among patients treated with Simvastatin/Atorvastatin specifically.
Multiple Sclerosis (85)	Simvastatin Atorvastatin	458 (4 trials in total, 3 double-blinded randomized controlled trials and 1 open-label randomized controlled trial)	Male and female patients of all age groups.	No major treatment-related adverse events were reported	No trial reported a significant increase in adverse events among patients treated with Simvastatin/Atorvastatin. Statins resulted to be well tolerated.
Acute Coronary Syndrome (71)	Simvastatin Atorvastatin	8504 (8 trials in total, 5 single center randomized controlled trials and 3 multicenter randomized controlled trials)	Adult patients, males and females	Rhabdomyolysis	Reported in 1 trial, 0.001%
				CK>10x ULN (Myopathy)	From 0.003-0.25%
				ALT>3x ULN	From 0.006-0.024%
Serum cholesterol reduction and stroke (60)	Simvastatin	40352 (6 trials in total, 2 randomized double-blind, placebo-	Adult patients, males and females	Rhabdomyolysis	From 0-0.0005%
				Myopathy	From 0.0048-0.005%

	Atorvastatin	controlled trials, 2 randomized controlled trials, 1 randomized double-blind trial and 1 long-term survival study).		Minor Muscle Pain	From 0.032-0.32%
				Elevated CK	Reported in 1 trial, 0.0027%
				Elevated ALT	From 0.0042-0.025% (Single Measure) From 0.00088-0.0063% (Consecutive Measures)
Cardiac Events Avoidance (72)	Simvastatin Atorvastatin	29672 (27 randomized controlled trials).	Adult patients, males and females	Aminotransferase	From 0-2.6%
				Myalgia	From 0.7-32.9%
				Myositis	From 0-1.5%
				Myopathy	From 0-0.9%
				Rhabdomyolysis	From 0-0.3%