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Systematic Review

Role of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor Therapy in treatment of Patients with Polycystic Ovary Syndrome: A systemic Review of Metabolic and Cardiovascular Outcomes

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Abstract:

Polycystic Ovary Syndrome (PCOS) is a common endocrine condition that affects both obese and non-obese women of reproductive age group. Its clinical presentation is dysmenorrhea, hirsutism, acne, metabolic complications, infertility, and polycystic ovaries. The study is aimed to assess the efficacy of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors to lower dyslipidemia in women with PCOS to prevent long term cardio-metabolic complications. PCSK 9 Inhibitors (Alirocumab, Evolocumab, and Inclisiran) bind to LDL receptors in liver and lower LDL-C levels, preventing long term adverse side effects. This review aims at showing that these drugs can be effective when prescribed to women with PCOS early-on to prevent some serious cardiovascular and metabolic complications in the long run. In terms of medical therapy, most physicians prescribe Metformin and Statins as first line agents to control risk factors. But much of the research supported the use of PCSK 9 Inhibitors early in the disease process or as an add-on to statins for controlling the lipid profile. When compared to Statins, the control rates of PCSK 9 Inhibitors were equal or superior and they showed additive effect when given along with other lipid lowering agents. Studies showed these drugs have only minor side effects and have good tolerability profile. They do not have severe side effects as compared to statins or fibrates.

Introduction:

The most prevalent endocrine illness in women of reproductive age is numerous cysts growing on the ovaries, called polycystic ovary syndrome (or PCOS) [1]. And according to data from National Health portal, the estimated pooled prevalence of PCOS in India is around 9-11% and dyslipidemia was present about 90-95% of the time. Women with PCOS experience dysmenorrhea, amenorrhea, menorrhagia, hirsutism, acne, pelvic pain, infertility, and acanthosis nigrans[2]. Anovulation, metabolic syndrome, hyper-androgenism, insulin resistance, and neurohormonal axis imbalance are the main features [3]. Most typical signs of this metabolic, endocrine, and reproductive illness occur when the ovaries are pushed to create an excessive amount of androgenic hormones and polycystic ovaries are formed [4]. Classical condition is when number of follicles produced in the ovaries every month are increased by more than 2-3 times. A woman must have at least two of these three symptoms—multiple ovarian cysts, anovulation/oligo-ovulation, and hyperandrogenism—in order to have PCOS (the syndrome) as opposed to polycystic ovaries (PCO). Illnesses associated with PCOS are metabolic syndrome, type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mental disorders, and endometrial cancer [5]. 1/5 of the woman suffering from PCOS are thin or non-obese and about 4/5 of the woman suffering from PCOS are fat or obese [6]. Either half of PCOS patients acquire type 2 diabetes, or they also have concurrent diabetes. Additionally, women who also have PCOS and are obese or diabetic are at an even higher chance of experiencing worse scenarios. In terms of metabolic and cardiovascular risk, women with PCOS have increased risk due to presence of Hyperadrogenism (HA), Insulin Resistance (IR), Dyslipidemia (DL). Women who have PCOS maybe obese or may have Type 2 Diabetes (T2D) which even further increases their risk compared to non-obese, non-diabetic females. PCOS is primarily treated with medication and lifestyle modifications. Four categories of therapy objectives can be thought of : decreasing insulin resistance and dyslipidemia, regaining fertility, treating hirsutism/acne, and resuming regular menstruation [7]. The conservative course of action is to maintain a healthy weight and manage dyslipidemia by eating right and exercising frequently. Vitamins and antioxidants found in various dietary supplements are beneficial. Oral Contraceptives and Metformin are used as initial treatment drugs. Thiazolidinediones and Spironolactone are added-on agents. To achieve fertility and regularise menstruation, Ovulating Agents are employed. For hirsutism/acne, Anti-Androgen Medications are utilised. Drugs that reduce lipid levels are used to treat dyslipidemia [8]. Ovarian Drilling, a laparoscopic treatment, is a technique that can be used to treat polycystic ovaries even though surgery is not frequently performed. In order to regulate dyslipidemia and prevent harmful cardio-metabolic events, this systematic review will concentrate on the relevance of

a contemporary approach and the effectiveness of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors in PCOS-affected women [9]. This study seeks to identify practical treatment for a widespread ailment while taking into account the drawbacks, dangers, and efficacy of the proposed therapy. A wide and diversified population is impacted by PCOS. Before giving the traditional therapy precedence, an alternative method should be investigated and taken into consideration for all circumstances. The usefulness of PCSK 9 Inhibitors for treating dyslipidemia in PCOS has not yet been directly studied. The objective of this study is to compile the existing information and offer justification for the prescription of PCSK 9 Inhibitors [10]. This study acknowledges that PCSK 9 inhibitors alone are not typically administered as first-line treatments for PCOS. The best lipid-lowering medications were Statins and PCSK 9 inhibitors. Additionally, PCSK9 inhibitors had effects comparable to those of statins and did not have statin-related side effects. Furthermore, this study explores the function of PCSK 9 in the pathogenesis of dyslipidemia in PCOS as well as the need of early PCSK 9 inhibitor introduction to prevent any long-term complications.

Below are two images showing respectively-

Image 1: PCSK9 binds LDL receptors, preventing their separation from the LDL particle upon entering the endosome, which results in LDLR degradation rather than a return to the cell surface. Therefore, increased levels of plasma PCSK9 seen in woman with PCOS, lead to increased levels of local PCSK9 in liver and ovaries leading to increased inflammation, dyslipidaemia, decreased cholesterol clearance, increased levels of LDL, insulin resistance, increased androgen levels and increased plaque formation. PCSK9 inhibitors are antibodies designed to bind to PCSK9 and block its activity, thereby allowing LDL receptors to be recycled and resurfaced after endocytosis. This will lead to more clearance of LDL particles and reduced LDL cholesterol [31].

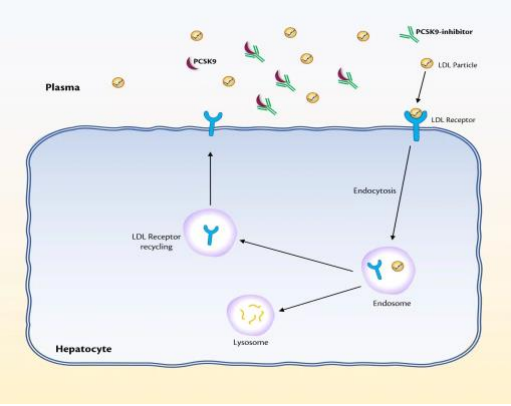
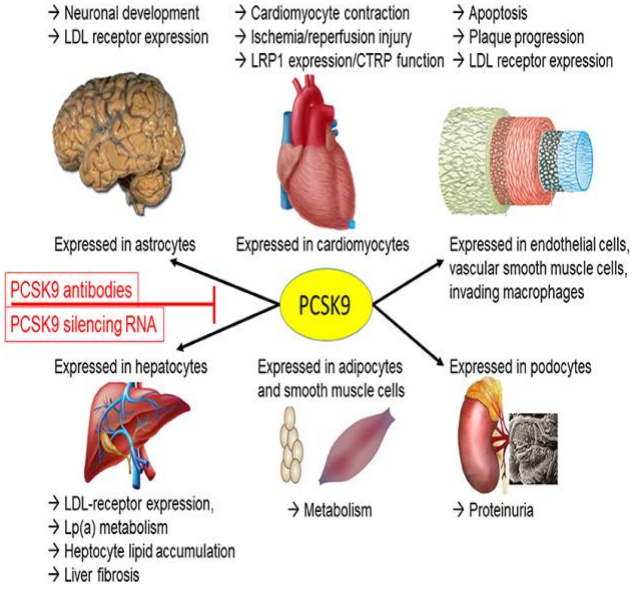


Image 2 : PCSK 9 functions and actions at different sites are mentioned and how drugs against PCSK 9 can bring about their mechanism of action [32].



Methodology:

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility Criteria

The inclusion criteria used in this systematic review included keywords related to four concepts in relation to the topic. Further criteria were added to narrow down the relevant articles. Articles published between 2000 and 2022; only English; randomised control trials (RCT); cohorts; case-control; meta-analysis and systematic reviews were included. Paid literature, unpublished work, intervention studies, conference abstracts and gray literature were excluded. Study selection, quality assessment and data extraction were performed by two independent researchers.

Search Strategy

There were many publications regarding the topic. Hence, a search strategy was developed to include more articles that were relevant to the review. We searched from Year 2000 to October 2022 in PubMed, Google Scholar, Cochrane libraries using controlled terms (e.g. MESH) and general keywords for Polycystic Ovary Syndrome (PCOS), Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors, Dyslipidemia and Cardio-Metabolic Outcomes including cardiovascular disease (CVD), type 2 diabetes (T2D), metabolic syndrome. Systemic Reviews, Meta-Analysis, Randomized Control Trials, Cohort Studies and Case-Control Studies comparing the effects of PCSK 9 Inhibitors in women of ≥18 years of age with PCOS irrespective of congruent obesity and diabetes and decrease in incidences of T2D, HT, fatal or non-fatal CVD and/or lipid concentrations of total cholesterol (TC),

low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were eligible for this systematic review and meta-analysis. Studies were eligible regardless of the degree to which they adjusted for confounders including obesity and diabetes. Result is in table 1 below.

Database	Keywords	Search Strategy	Filters	Results
PubMed	Polycystic Ovary Syndrome, Hyperandrogenemia, Insulin Resistance, Polycystic Ovaries, Dyslipidemia, Metabolic Syndrome, Hyperlipidemia, PCSK 9 Inhibitors, Pro-protein Convertase subtilisin/kexin type 9 Inhibitors	("Polycystic Ovary Syndrome/complications"[Majr:NoExp] OR "Polycystic Ovary Syndrome/drug therapy"[Majr:NoExp] OR "Polycystic Ovary Syndrome/metabolism"[Majr:NoExp] OR "Polycystic Ovary Syndrome/physiopathology"[Majr:NoExp] OR "Polycystic Ovary Syndrome/therapy"[Majr:NoExp]) AND ("Dyslipidemias/complications"[Majr:NoExp] OR "Dyslipidemias/drug therapy"[Majr:NoExp] OR "Dyslipidemias/metabolism"[Majr:NoExp] OR "Dyslipidemias/physiopathology"[Majr:NoExp] OR "Dyslipidemias/prevention and control"[Majr:NoExp] OR "Dyslipidemias/therapy"[Majr:NoExp]) AND ("PCSK9 Inhibitors/chemistry"[Majr:NoExp] OR "PCSK9 Inhibitors/metabolism"[Majr:NoExp] OR "PCSK9 Inhibitors/pharmacokinetics"[Majr:NoExp] OR "PCSK9 Inhibitors/pharmacology"[Majr:NoExp] OR "PCSK9 Inhibitors/physiology"[Majr:NoExp] OR "PCSK9 Inhibitors/therapeutic use"[Majr:NoExp])	Dates: 2000 - 2022 Language: English and free full-text	6820
Google Scholar	Polycystic Ovary Syndrome, Dyslipidemia, PCSK 9 inhibitors, Alirocumab	Polycystic Ovary Syndrome AND Dyslipidemia AND PCSK 9 inhibitors AND Alirocumab	Dates: 2000 - 2022	650 (Searched first 300
Cochrane	Polycystic Ovary Syndrome, Dyslipidemia, PCSK 9 inhibitors, Alirocumab	Polycystic Ovary Syndrome AND Dyslipidemia AND PCSK 9 inhibitors AND Alirocumab	Dates: 2000 - 2022	342

Table 1 :Using keywords from the four concepts of the topic, the MeSH vocabulary system was used. The search's articles were all transferred to an excel sheet. Only the articles containing keywords in the title remained after the articles were initially sorted out based on how relevant their titles were. Articles with irrelevant titles were excluded. Then, the articles were further filtered out based on the abstract, leaving any article featuring PCSK 9 inhibitor treatment, effect on lipid levels and cardio-metabolic outcomes in women with PCOS . Articles with irrelevant abstracts were excluded. The articles were then sorted out based on how relevant their material was. Articles featuring PCSK 9 inhibitors as part of the novel treatment were included. Articles focusing on other PCOS treatment were excluded. Finally, gray research and editorials were removed. This was done to focus on stronger forms of research, including randomized control trials, cohorts, case-control, meta-analysis and systematic reviews.

Methodological Quality Assessment

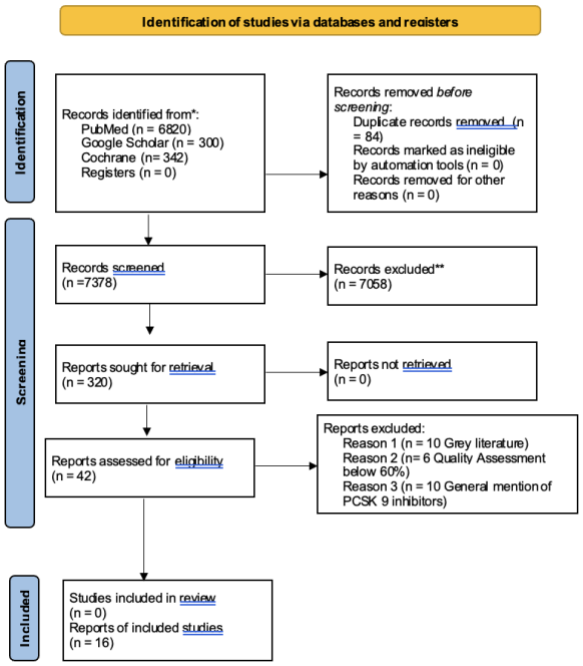
Three types of quality assessment tools were used for various types of research. Newcastle Ottawa Scale was used for non-randomized trials and observational studies. Systematic reviews were assessed by using The Assessment of Multiple Systematic Reviews (AMSTAR). The Scale for the Quality Assessment of Narrative Review Articles (SANRA) was used for other studies. All scores were converted to a percentage, and articles that scored less than 60% were excluded.

Result:

Study Selection

As seen in Figure 1 below, the PRISMA Flow Diagram shows the three databases used (PubMed, Google Scholar, and Cochrane). A total of 7462 articles were extracted and listed in an excel document. All duplicate articles were eliminated after the articles were arranged alphabetically. After removing 84 duplicates, 7378 results were left for screening. Then the articles were screened using the keywords mentioned above, leaving 40 relevant articles. From there, 10 articles were excluded due to their being grey literature and 11 articles were removed due to their being only general mention of PCSK 9 inhibitors. According to the type of study, the appropriate quality assessment tool was utilised. A quality rating was then assigned to each article. Six articles had a score of less than 60%, leaving 13 articles to qualify. Both the first author and the second author were involved in the selection of each article.

Figure 1:



Methodological Quality

AMSTAR 2 guidelines were used for the included two systematic reviews and six meta-analysis. Four narrative reviews were included and assessed using The Scale for the Quality Assessment of Narrative Review Articles (SANRA). One case-control study was included

and assessed using the Newcastle Ottawa Scale. One Non-Randomised Clinical Trial was included and assessed using the Newcastle Ottawa Scale.

Data Synthesis

Statistical pooling was not possible because the publications were heterogeneous so a narrative representation of the results is presented. Table 2 below shows the key points extracted from each article.

Author	Type	Place	Conclusion
Qi Liu et al., 2019 [11]	Review	China	It is now understood that dyslipidemia contributes significantly to the emergence of PCOS. Lipid abnormalities like elevated low-density lipoprotein and triglyceride levels and reduced high-density lipoprotein levels are found in women with PCOS.
Robert A Wild et al., 2011 [12]	Meta-analysis	USA	Women with PCOS have higher LDL-cholesterol and non HDL-cholesterol, regardless of weight. Study recommended that all women with PCOS should be screened for dyslipidemia for effective cardiovascular risk prevention.
V Wekker et al., 2020 [13]	Meta-analysis	Nether-lands	Risk of developing cardio-metabolic disease is higher in women with PCOS. This review quantified this risk, which is important for clinicians to inform patients and to take into account the cardiovascular risk assessment of women with PCOS.
Shiqin Zhu et al., 2019 [14]	Meta-analysis	China	Metabolic abnormalities and possibility of long-term metabolic complications is also present in non-obese women with PCOS.
Luqian Zhao et al., 2017 [15]	Meta-analysis	China	PCOS was a risk factor for the increased risk of Cardiovascular Disease.
Licy L Yanes Cardozo et al., 2017 [16]	Review	USA	Hyperandrogenemia is present in a significant fraction (~80%) of women with PCOS and it increases cardio-metabolic risk factors such as obesity, insulin resistance, and increased blood pressure by stimulating the renin-angiotensin system (RAS), 20-HETE, and leptin systems, which finally leads to cardiovascular diseases.
Olatokunbo Osiboqun et al., 2020 [17]	Review	USA	Insulin resistance is a prevalent factor in PCOS pathogenesis, which raises women's risk for cardiovascular disease (CVD) by causing a number of cardio-metabolic abnormalities (such as dyslipidemia, hypertension, glucose intolerance and metabolic syndrome).
Miguel A Sanchez-Garrido et al., 2020 [18]	Review	Spain	Metabolic abnormalities linked to PCOS occur substantially due to excess androgen.
Rui Yang et al., 2016 [19]	Review	China	Hyperadrogenism plays an important role in metabolic disorders in PCOS patients and biomarkers of serum lipid metabolism were significantly different between patients with and without hyperandrogenism.
Olivier Valkenburg et al., 2008 [20]	Case- Control	Nether-lands	A more pronounced atherogenic lipid profile is linked to PCOS. Obesity and hyperandrogenism also contribute to an adverse lipid profile.
Yue Zhang et al., 2022 [21]	Meta-analysis	China	Blood lipid levels significantly improved when PCSK9 inhibitors were added to regular therapy compared to treatments without them.
Nathalie Bergeron et al., 2015 [22]	Review	USA	A promising therapeutic approach for lowering the risk of cardiovascular disease is PCSK9 inhibition.
Chuanwei Li et al., 2015 [23]	Meta-analysis	China	In patients with hypercholesterolemia, PCSK9 inhibitors significantly reduced low-density lipoprotein cholesterol and other lipid levels while maintaining acceptable safety and tolerability.
Meijiao Wang et al., 2019 [29]	Non-RCT	China	Abnormally high levels of PCSK9 in blood, liver and ovary lead to pathogenesis of PCOS impacting lipid metabolism and ovarian function. Patho-physiological changes of PCOS can be reversed, partly by inhibiting PCSK9.
Anna Bizoń et al., 2021 [30]	Review	Poland	High levels of PCSK 9 and changes in paraoxonase 1 activity are seen in women with PCOS leading to low levels of HDL-C, high levels of LDL-C, insulin resistance and other metabolic complications.

Setting

Two systematic reviews and four narrative reviews were conducted: two were in China in 2016 and 2019; one in Spain in 2020; three in USA in 2015, 2017 and 2020; one in Poland. Six meta-analysis were conducted: four in China in 2015, 2017, 2019, 2019 and 2022; one in USA in 2011; one in Netherlands in 2020. One case-control was conducted in Netherlands in 2008. One Non-Randomised Clinical Trial was conducted in China in 2019.

Outcomes Measured

This review integrates specific outcomes from the selected studies. This includes dyslipidemia seen in PCOS and worse cardio-metabolic outcomes in long term; new effective treatment in form of PCSK 9 Inhibitors. All the outcomes were related to high lipid levels seen in women with PCOS.

Discussion:

This section explores the results and effectiveness of using PCSK 9 Inhibitors as a treatment of choice. This study will assess the effectiveness of PCSK 9 Inhibitors in decreasing lipid profile of women with PCOS and help them with preventing future cardio-metabolic complications and comparing them to the statins as a first line treatment and the complications associated with that treatment option.

Polycystic Ovary Syndrome:

Women with PCOS mainly suffer from dyslipidemia, insulin resistance, and hyperandrogenism, which collectively results into metabolic syndrome like scenario. These conditions act as risk factors for potential future cardio-metabolic complications. This review quantifies this risk, which is important for clinicians to inform patients and to consider in the cardiovascular disease (CVD) risk assessment of women with PCOS. Future clinical trials are needed to assess the ability of cardio-metabolic screening and management in women with PCOS to reduce future CVD morbidity [11-20].

Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors:

Due to its role in maintaining lipoprotein homeostasis, PCSK9 is significant in PCOS. The level of LDL particles can be reduced by PCSK9 Inhibitors. Existing lipid-lowering medications only work on a single target and the majority of them can only successfully modulate one or two lipids at a time. In individuals with a high risk of cardio-metabolic complications, such as women with PCOS, PCSK 9 inhibitor medication led to a favourable and thorough modulation of serum LDL-C, total cholesterol, triglycerides, lipoprotein (a), non-HDL-C, and HDL-C levels. Adding PCSK 9 inhibitors to high-intensity statin therapy can dramatically further reduce the expression of blood LDL-C. Final aim of the therapy is to control lipid levels to prevent cardiovascular events [21-23].

Application Possibilities:

These studies used PCSK 9 inhibitors - alirocumab, evolocumab and inclisiran. Except for side events such flu-like symptoms, upper respiratory tract infections, and naso-pharyngitis, they were generally well tolerated. Therefore, PCSK 9 might be a wise candidate for lipid-lowering medication in the future. Clinical investigations that demonstrate numerous pathways by which PCSK 9 medications enhance cardiovascular prognosis have validated these advantages. Additionally, current research indicates that PCSK 9 Inhibitors may partially reduce inflammation. A meta-analysis revealed that the addition of PCSK 9 inhibitors to statins considerably increases the regression of total atheroma volume. PCSK 9 Inhibitor treatment combined with statins is currently receiving a lot of interest. In conclusion, PCSK 9 inhibitor development in the future appears promising. New molecular mechanisms to modulate PCSK 9's binding to LDL-R, such as PCSK 9 small molecule stem RNA and PCSK 9 vaccine, are to be studied in order for a better understanding of the mechanism of PCSK 9 in LDLR degradation. Reduced LDL-C levels, high tolerance, and a low incidence of adverse events are all benefits of PCSK 9 siRNA inhibitors like inclisiran, which may inspire new strategies for more potent PCSK 9 inhibition [21-23].

Adverse Effects:

Injection site reactions (ISR):

Injection site reactions are known PCSK9 inhibitor adverse effects that might affect up to 5% of individuals. Irritative reactions and allergic reactions are the two pathophysiological types of ISR that can be distinguished based on the mechanism of reaction to the excipient(s) or the drug itself. In irritative reactions, the causative factor causes the innate immune system to become un-specifically activated, which results in a fast response, typically minutes or hours after contact with the irritant. In allergic reactions, the immune system reacts to self-proteins/-peptides that have been altered by foreign substances to make them immunogenic or non-self-antigens (haptenization). The innate and adaptive immune systems are then activated, which can be broken down into two phases: the initial sensitisation phase, which happens after the skin first comes into contact with the chemical, and the elicitation phase, which happens after a second encounter with the causal agent. Some biological medications have been known to cause injection site reactions that can appear up to a week after the injection and during the first 1-2 months of treatment. The average reaction time is three to five days. Clinically, it can be challenging to distinguish between allergic and irritative ISR without additional laboratory testing or histology. The threshold for local immunological reactions is significantly lowered for ISR in the presence of a pro-inflammatory milieu such as concurrent infections. Speculating that the presence of a pro-inflammatory condition during injection may have facilitated immune reaction against the drug (or excipients), resulting in transient ISR. This is because patients initially tolerated drug well and only displayed transient ISR during an acute activation of the immune system (infection, vaccination). An active immune system and ISR can be linked in terms of timing. Local steroids, cooling, oral antihistamines, and systemic steroids may also be used to treat injection site responses as needed. Also, it is demonstrated that using adequate skin sterilisation methods, letting the injectable agent warm up to room temperature, switching up injection sites, and avoiding sensitive skin areas can all lower the incidence of ISR. ISR is one of the most common side effects of PCSK9 inhibitors. As a result, this may address a crucial issue that should raise awareness among doctors caring for patients taking PCSK9 inhibitors by emphasising the need to avoid unnecessarily stoppage of treatment with these potent LDL-lowering medications in the presence of transient, fully reversible ISR. Given the temporary and benign nature of the reactions, such patients should be encouraged to continue their care while being closely monitored and receiving the recommended therapy because tolerance may return after the pro-inflammatory condition has been resolved [24].

Neuro-cognitive effects:

Considering that the brain contains around 25% of the body's cholesterol and that lipid-lowering medications may have an unfavourable influence on brain function, including cognitive adverse effects, this possibility is scientifically possible. Moreover, cholesterol is the main constituent of myelin, a fatty sheath that is crucial for cellular signalling and the integrity of the blood-brain barrier (BBB). Not withstanding these facts, no research have yet shown a link between lower cholesterol levels in the central nervous system and functional impairment. The indications and symptoms of neuropsychiatric ADRs can vary, from minor ADRs like sleep disturbance, strange dreams, vertigo, loss of balance, and tinnitus to more serious ADRs including depression, suicide, seizures, and paralysis. According to published research, ezetimibe and statins are both linked to neuropsychiatric adverse drug reactions (ADRs). The finding that lipid-lowering medications exhibit similar side effects lends credence to the idea that lower levels of brain cell membrane cholesterol may play a significant role in the pathogenesis of these adverse effects. Moreover, the BBB restricts the central nervous system access of PCSK9 inhibitors. The penetration of alirocumab and evolocumab is therefore expected to be around 0.1% if the BBB is intact. Beta-amyloid (Aβ) and tau protein evolution may have been influenced by disruption of lipid and glucose metabolism. Alzheimer's disease and other dementias are caused by the accumulation and presence of the beta-amyloid and tau proteins. N-methyl-d-aspartate (NMDA) receptors are strongly modulated by cholesterol at the endogenous level. They play a role in the central nervous system's excitatory neurotransmission and are cationic channels that are permeable to calcium ions. Due to an excessive calcium influx into the neurons, excessive excitatory neurotransmission may cause neuro-degeneration and possibly dementia. Lipids are essential for maintaining the integrity of cell membranes, altered cholesterol synthesis may have an impact on the growth and operation of neuronal cell membranes [25].

Cost-benefit:

The use of PCSK9 inhibitors as recommended could significantly lower MIs, strokes, and cardiovascular mortality, according to an economic analysis of the drugs from the viewpoint of the Indian health system, they are not cost-effective at current prices, and exceeding frequently recognised cost-effectiveness standards would require price reductions of more than four-fifths even if they prove to be extremely effective in reducing cardio-metabolic mortality. The size of the target population, the length and efficacy of therapy, the price of the drug, and the costs of care affects how much money is spent on healthcare when a new pharmaceutical is introduced. Although PCSK9 inhibitors are intended to be a lifetime therapy for both the huge expanding population with cardiovascular disease as well as the relatively limited number of patients with PCOS, the high cost of PCSK9 inhibitors presents a distinct challenge. So, despite cost reductions from avoided cardiovascular events, the potential increase in health care spending at current or even significantly discounted pricing could be startling. Several studies findings indicate that the key strategy for raising the value of these treatments is still to lower the cost of PCSK9 inhibitors. Even while producing biologic drugs is more expensive than statins payers must weigh the potential trade-off between funding innovative medication therapies like PCSK9 inhibitors and spending money on initiatives that are known to increase access to, physician prescribing of, and patient adherence to statin therapy among people at high cardiovascular risk. Despite evidence of their long-term effectiveness, safety, and cost-efficiency more than one-third of patients with an LDL-C level of at least 70 mg/dL are not currently taking statins as seen by the national representative data. The cost of using even a single injection of PCSK9 inhibitors in these individuals ranges from Rs.15,000 to Rs. 20,000 hence they cannot be compared to statins in a developing nation like India [26].

Information on long-term safety data:

Growing scientific and clinical evidence demonstrates that PCSK9 inhibitors offer a great safety and tolerability profile with a low frequency of adverse events. As a result, these drugs are being utilised more often in modern clinical practise. Particularly, injection site reactions are the most often reported side effects. Unlike statins, PCSK9 inhibitors don't seem to have a negative impact on glycemic management or raise the risk of newly developing diabetes mellitus. PCSK9 inhibitors are a better alternative treatment option for patients with statin intolerance, according to mounting evidence. On the other hand, research has looked at the effects of their long-term administration on neurocognition and on levels of vitamin E and other fat-soluble vitamins. Even though, there are still several facets of PCSK9 inhibitor therapy that need to be investigated. It is unclear how PCSK9 inhibitors affect HIV patients, who are more likely to develop cardiovascular disease and are more likely to experience statin-related side effects from medication interactions with specific antiviral regimens. Also, the safety of using PCSK9 inhibitors during pregnancy has not yet been determined. However, when all of the aforementioned factors are taken into account, it is clear that PCSK9 inhibitors generally represent a safe, well-tolerated, and efficient therapeutic approach with a recognised place in the current therapeutic therapy of hyperlipidemia. As experience with PCSK9 inhibitors grows quickly, more trials are anticipated to provide more insight into their long-term safety and tolerability [27].

Safety in Women Desiring Pregnancy:

Statins are highly successful at lowering LDL-C levels, however they should not be used when pregnant or breastfeeding. Since non-statin medications like ezetimibe, niacin, and fibrates have also been linked to teratogenicity, they are not advised for use during pregnancy. PCSK9 inhibitors have not been evaluated

for safety during pregnancy and they are not currently approved. Bile Acid Sequestrants are not systemically absorbed and are therefore unlikely to pose a risk to the foetus and are currently the only medications that are acceptable during pregnancy. For very high risk pregnant women with substantial atherosclerotic disease, lipoprotein aphaeresis is also permitted and regarded as safe. Before, during, and after pregnancy, a healthy lifestyle with a low-fat, low-cholesterol diet and regular exercise is strongly advised [28].

Limitations

Due to the fact that this study only covered free-text research, the selection of papers for the review was constrained. This review could have been more specific by finding out the actual dose-effect relation of PCSK 9 Inhibitors in PCOS. The main limitation of this study was the limited amount of research regarding the specific use of a PCSK 9 Inhibitor as primary agent to treat dyslipidemia in women with PCOS. Given that PCSK 9 Inhibitors are not conventionally used alone to treat the patient and most studies look at statins as the conservative treatment, it limits this study's accuracy. Secondly, this article only focuses on the dyslipidemic aspect in PCOS, ignoring other independent risk factors like smoking, menopause, stress, family history, and the multi-factorial causation of future cardio-metabolic complications with genetic and environmental factors have also not been studied. Lastly, there is no long-term clinical outcome data for PCSK9 inhibitors. Many non-statin drugs that lower LDL-C have not demonstrated therapeutic benefit in long-term trials, despite the fact that short-term trials suggest lower risks of MI and cardiovascular death. In order to prevent early coronary heart disease, LDL-C lowering therapy may start in young adulthood; however, the model may not have fully accounted for the clinical and financial costs associated with its advantages. However, there are only few studies on the effectiveness or safety of PCSK9 inhibitors in young people, and PCSK9 inhibitors are currently only permitted for use in adults. The underlying hypothesis was that the heightened cardiovascular risk was caused by a combination of other known cardiovascular risk factors and high LDL-C levels.

Conclusion:

This systematic review focused on the feasibility of using Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors as an effective treatment for lowering lipid levels in women with Polycystic Ovary Syndrome. PCSK 9 Inhibitors have an effect on liver and lower LDL-C concentration in the blood thereby can control dyslipidemia seen in women with PCOS. In line with the results presented, the study finds PCSK 9 Inhibitors to have good lipid lowering properties as well as a very low side effects profile. However, when compared to other anti-lipid agents, there is a significant difference in the effect rate at the end of the treatment, with PCSK 9 Inhibitors being superior or equal to Statins. The side effects experienced in the conservative treatment mostly resulted from using statins in management of PCOS for over a long period. Questions that arose during the study revolved around the use of PCSK 9 Inhibitors as a first line treatment. More studies need to be done with using both statins and PCSK 9 inhibitors for controlling lipid profile in women with PCOS along with secondary aim of finding out a perfect balance between their dosage levels to minimise side effects arising from prolong statin use without affecting the effect benefit. To broaden our understanding, more studies are advised in form of clinical trials targeting the use of PCSK 9 Inhibitors versus that of Statins and that of both being used together, implementing direct results in terms of superiority and efficacy.

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