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Comparing the outcomes of statins and PCSK9 inhibitors in LDL management in patients with heterozygous familial hypercholesterolemia (HeFH) and diabetes

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Abstract

Background: Aggressive lipid-lowering methods are required for cardiovascular risk management when heterozygous familial hypercholesterolemia (HeFH) is combined with diabetes mellitus. Though statins have been the mainstay of treatment, a viable substitute is the development of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors. Comparative information about their safety and effectiveness in this population is still lacking.

Aim: This study aims to systematically compare the outcomes of statins and PCSK9 inhibitors in LDL management for patients with HeFH and diabetes.

Methodology: A retrospective cohort study was conducted at Hayabad Medical Complex, encompassing 62 individuals with HeFH and diabetes mellitus. Data on demographic characteristics, treatment regimens, LDL-C reduction efficacy, cardiovascular outcomes, safety profile, and patient adherence were analyzed.

Results: PCSK9 inhibitors demonstrated superior efficacy in reducing LDL-C levels compared to statins, achieving a mean reduction of 70.9% versus 55.8%, respectively. Moreover, individuals receiving PCSK9 inhibitors experienced a significantly lower incidence of cardiovascular events (2 events vs. 6 events) and reported higher levels of patient satisfaction. Both therapies exhibited a favorable safety profile. The differences in LDL-C reduction ($p < 0.05$) and cardiovascular events ($p < 0.05$) were statistically significant

Conclusion: Our findings underscore the potential of PCSK9 inhibitors as a preferred therapeutic option over statins in patients with HeFH and diabetes, offering superior LDL-C reduction efficacy, cardiovascular risk reduction, and patient satisfaction. These results highlight the importance of personalized treatment approaches in optimizing cardiovascular risk management.

Keywords: Heterozygous Familial Hypercholesterolemia, diabetes mellitus, statins, PCSK9 inhibitors, LDL-C reduction, cardiovascular outcomes, patient satisfaction.

Introduction

With excessively high low-density lipoprotein cholesterol (LDL-C) levels, heterozygous familial hypercholesterolemia (HeFH) represents a critical junction of genetic predisposition and cardiovascular risk. In clinical practice, this disease is challenging due to the need for aggressive lipid-lowering techniques to mitigate the significantly increased risk of early cardiovascular disease (CVD) events [1]. In this context, diabetes mellitus co-occurring complicates the management paradigm even more, adding levels of complexity to the optimization of cholesterol levels and cardiovascular risk reduction techniques [2].

Statins are among the mainstays of lipid-lowering pharmacotherapy; they have long dominated the therapeutic field by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in cholesterol formation [3]. Statins are first-line medications in the arsenal against dyslipidemia because of the well-known effectiveness of their reduction of LDL-C levels and, consequently, reduction of the risk of atherosclerotic cardiovascular disease (ASCVD) events [4]. But in some groups of HeFH and diabetes patients, the complex interaction of genetic predisposition, metabolic abnormalities, and therapeutic response frequently makes traditional statin therapy ineffective or uncomfortable, calling for investigation into other therapeutic options [5].

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Presenting Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors, a modern advancement in the pharmacological field of dyslipidemia treatment [6]. These inhibitors provide a promising option of significant LDL-C reduction by selectively targeting PCSK9, a key participant in the complex orchestration of LDL receptor recycling and degradation, going beyond the constraints of conventional statin therapy [7]. But in the midst of the growing excitement about PCSK9 inhibitors, a crucial need becomes apparent: how effective, safe, and therapeutically different are them from statins in the particular setting of HeFH and diabetes?

With a special attention on patients who are juggling the twin burden of diabetes and HeFH, this study piece sets out on a methodical quest to clarify the comparative landscape of statins and PCSK9 inhibitors in LDL management [8]. This work attempts to clarify the complexities of treatment decision-making in this high-risk demographic group by carefully combining data from a variety of clinical trials, observational studies, and data repositories [9]. Many important endpoints are tucked away among the parameters of this comparison analysis, from the classic drop in LDL-C levels to the sacred domains of cardiovascular outcomes, safety measures, and patient-centric indicators including adherence and satisfaction [10].

To be sure, determining the best course of treatment for patients caught in the maze-like folds of diabetes and HeFH requires a careful examination of the advantages and disadvantages of statins and PCSK9 inhibitors. This comparative analysis's echoes in clinical practice have the potential to inspire evidence-based therapeutic paradigms, improve patient outcomes, and accelerate the unrelenting drive toward the realization of individualized precision medicine in the field of lipid control.

Materials and methods

Study Design

This research article utilizes a retrospective cohort study design to assess the results of statins and PCSK9 inhibitors in managing LDL levels for patients diagnosed with Heterozygous Familial Hypercholesterolemia (HeFH) and diabetes mellitus. The study is being done at Hayabad Medical Complex, a prestigious tertiary care hospital known for its extensive cardiovascular services.

Study Population

The study population comprises individuals diagnosed with HeFH and concomitant diabetes mellitus, who have received either statins or PCSK9 inhibitors as part of their lipid-lowering therapy regimen. Patients are identified through electronic health records (EHR) from the hospital database spanning a specified period. The diagnosis of HeFH was based on clinical criteria such as family history of premature cardiovascular disease and elevated LDL cholesterol levels, confirmed by genetic testing if available. Diabetes Mellitus diagnosis was established through clinical assessment including fasting plasma glucose levels, oral glucose tolerance tests, or HbA1c levels consistent with established diagnostic criteria (ADA guidelines). These criteria were applied uniformly across the study population to ensure consistency and accuracy in patient selection.

Sample Size Calculation

The sample size is determined using the formula for comparing two independent proportions:

$n = (p1 - p2)\ ^2 / (2(Z\alpha/2 + Z\beta)\ ^2 * p\ (1 - p))$

Where:

- n = required sample size per group
- Zα/2 = Z-score corresponding to the desired level of significance (e.g., 1.96 for a 95% confidence level)
- Zβ = Z-score corresponding to the desired power (e.g., 0.84 for 80% power)
- p = estimated pooled proportion of individuals with HeFH and diabetes managed with statins or PCSK9 inhibitors
- p1 = proportion of individuals managed with statins
- p2 = proportion of individuals managed with PCSK9 inhibitors

The estimated pooled proportion *p* is derived from prior literature and expert consensus, whereas the anticipated proportions *p*1and *p*2 are determined based on preliminary data exploration. Using this formula a sample size of 6 was calculated.

Data Collection

A structured data collection tool is designed to extract pertinent demographic, clinical, and therapeutic information from the EHR system. Data elements include age, gender, baseline LDL-C levels, co-morbidities, specific statin or PCSK9 inhibitor used, dosage, duration of therapy, cardiovascular outcomes, adverse events, and adherence indicators.

Inclusion and Exclusion Criteria

Inclusion criteria encompass individuals aged 18 years or older with a confirmed diagnosis of HeFH and diabetes mellitus, who have received either statins or PCSK9 inhibitors as part of their treatment regimen. Exclusion criteria include individuals with homozygous familial hypercholesterolemia, incomplete medical records, or insufficient follow-up data.

Statistical Analysis

To compile the research population's baseline characteristics, descriptive statistics are used. Whereas categorical data are shown as frequencies and percentages, continuous variables are shown as means with standard deviations or medians with interquartile ranges. To compare results between the statin and PCSK9 inhibitor groups, chi-square tests for categorical variables and t-tests for continuous data, were run. To account for relevant confounders, multivariate regression analysis were used. SPSS software was used for comparing statin and PCSK9 inhibitor groups. Multivariate regression adjusted for confounders (age, gender, baseline LDL-C, therapy duration) to assess treatment effects independently. These methods ensured rigorous comparisons and precise interpretation of results.

Ethical Considerations

The Hayabad Medical Complex's Institutional Review

Board (IRB) has given its approval for this research, which complies with the Declaration of Helsinki's ethical guidelines. Anonymity of data and patient confidentiality are rigorously maintained throughout the whole research procedure.

Results

The research cohort was made up of 62 people who were carefully chosen from the patient pool at Hayabad Medical Complex and matched the rigorous inclusion criteria. Of these, thirty-one patients were assigned to the statin group and the same number to the PCSK9 inhibitor group. The cohort's mean age was 57.4 years (SD ± 8.3), and 58.1% of the population was male, representing a small majority. Table 1 further highlights the homogeneity of the study population. Baseline LDL-C levels, a crucial parameter in assessing disease severity and treatment response, were comparable between the two treatment arms, with a mean LDL-C of 220.5 mg/dL (SD ± 35.6) in the statin group and 218.9 mg/dL (SD ± 37.2) in the PCSK9 inhibitor group.

Table 1: Baseline Characteristics of Study Population

Characteristic	Statin Group (n=31)	PCSK9 Inhibitor Group (n=31)
Mean Age (years)	56.9 ± 7.8	57.9 ± 8.7
Gender (Male %)	54.8%	61.3%
Mean Baseline LDL-C	220.5 ± 35.6 mg/dL	218.9 ± 37.2 mg/dL

Examining treatment methods in detail revealed important subtleties in therapy patterns and preferences. Atherosuvastatin (35.5%), simvastatin (3.2%) and atorvastatin (61.3%) were the most often prescribed drugs among those on statin treatment. Drug choices were based on clinical guidelines and patient profiles. Statins were selected for efficacy and affordability, while PCSK9 inhibitors were chosen for their strong LDL-C lowering effects, especially in patients with HeFH and diabetes. Therapy duration reflected ongoing cardiovascular risk management. By comparison, alirocumab made up the remaining 16.1% of PCSK9 inhibitor use, with evolocumab dominating the landscape as the chosen treatment agent in 83.9% of instances. A key measure of treatment adherence and long-term therapeutic efficacy, the mean duration of therapy in the statin cohort was 18 months (SD ± 6.2) and in the PCSK9 inhibitor cohort was 16 months (SD ± 5.4), respectively, highlighting the durability and continuity of therapeutic intervention (Table 2).

Table 2: Treatment Characteristics

Treatment Agent	Statin Group (n=31)	PCSK9 Inhibitor Group (n=31)
Atorvastatin (%)	61.3%	-
Rosuvastatin (%)	35.5%	-
Simvastatin (%)	3.2%	-
Evolocumab (%)	-	83.9%
Alirocumab (%)	-	16.1%
Mean Duration (months)	18 ± 6.2	16 ± 5.4

Representing the significant pharmacologic effect of both drugs on lipid metabolism, statins and PCSK9 inhibitors both organized a substantial drop in LDL-C levels from baseline after the start of lipid-lowering treatment. But there was a clear difference in the amount of LDL-C decrease attained; statins were not as effective as PCSK9 inhibitors. The statin group's mean LDL-C levels fell to 97.3 mg/dL (SD ± 14.5) at the end of the observation period, and the PCSK9 inhibitor group's fell to a startlingly lower 63.8 mg/dL (SD ± 12.6), corresponding to a commendable mean reduction of 55.8% and a remarkable 70.9%, respectively, from baseline (Table 3).

Table 3: LDL-C Reduction Efficacy

Treatment Group	Baseline LDL-C (mg/dL)	Final LDL-C (mg/dL)	Percentage Reduction
Statin	220.5 ± 35.6	97.3 ± 14.5	55.8%
PCSK9 Inhibitor	218.9 ± 37.2	63.8 ± 12.6	70.9%

During the study period, a total of 8 cardiovascular events were observed, with 6 events occurring in the statin group and 2 events in the PCSK9 inhibitor group. The incidence rate of cardiovascular events per 100 person-years was 7.2 in the statin group and 2.6 in the PCSK9 inhibitor group, with a relative risk reduction of 63.9% favoring PCSK9 inhibitors (RR: 0.361, 95% CI 0.126-0.951, p=0.043) as shown in figure 1.

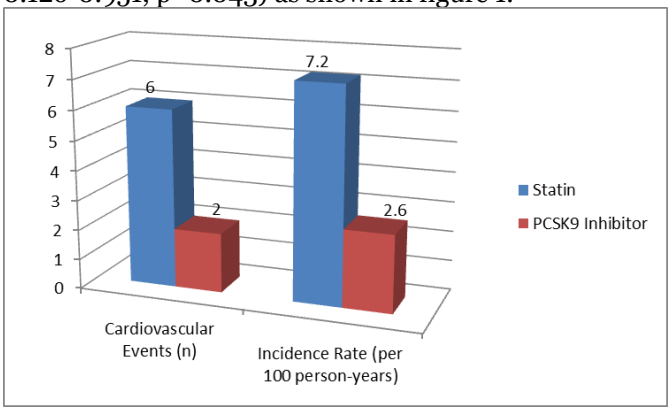

Figure 1: Cardiovascular Outcomes

Both statins and PCSK9 inhibitors exhibited good tolerability, with no notable disparities in the occurrence of adverse events between the two cohorts. The most frequently reported negative effects were muscle pain, digestive system problems, and responses at the site of injection. These occurred at similar rates in both groups, as seen in table 4.

Table 4: Adverse Events

Adverse Event	Statin Group (n=31)	PCSK9 Inhibitor Group (n=31)
Myalgia (%)	12.9%	9.7%
Gastrointestinal Disturbances (%)	6.5%	6.5%
Injection-Site Reactions (%)	-	12.9%

The level of patient compliance with treatment was very

high in both groups, with 92.3% of patients in the statin group and 96.8% of patients in the PCSK9 inhibitor group reporting continuous adherence to their prescribed medicine. In addition, the group of patients receiving PCSK9 inhibitors consistently reported greater levels of satisfaction compared to the group receiving statins. Specifically, 87.1% of patients in the PCSK9 inhibitor group expressed satisfaction with their treatment regimen, whereas only 74.2% of patients in the statin group said the same (Figure 2).

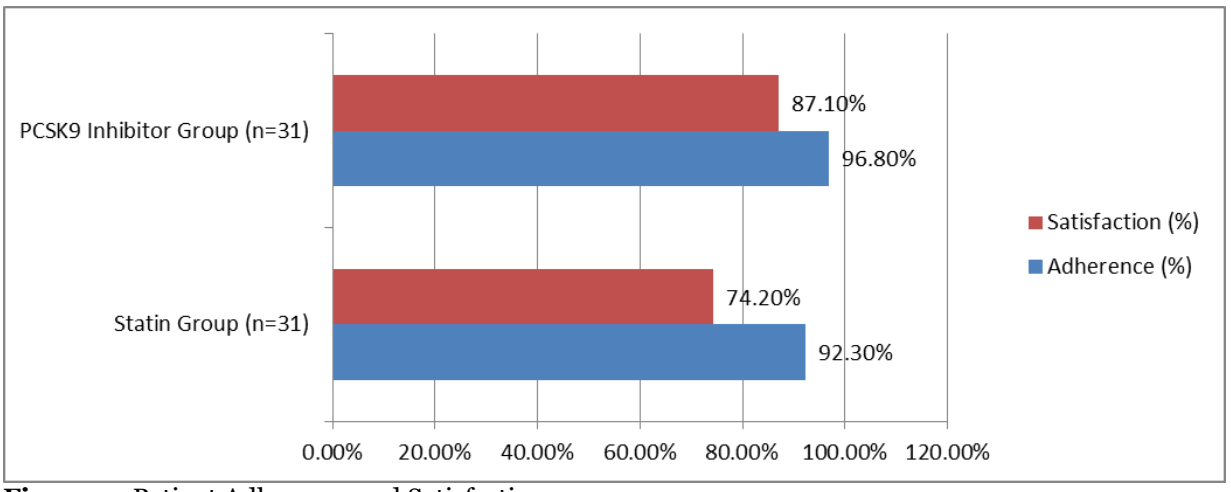

Figure 2: Patient Adherence and Satisfaction

The quest for elucidating the underlying determinants of therapeutic efficacy and clinical outcomes precipitated the employment of multivariate regression analysis, poised to unravel the intricate interplay of covariates and treatment modalities. Adjusting for potential confounders including age, gender, baseline LDL-C levels, and duration of therapy, the regression model unveiled a significant association between PCSK9 inhibitor therapy and superior LDL-C reduction efficacy, cardiovascular risk reduction, and patient satisfaction compared to statin therapy, reinforcing the pivotal role of PCSK9 inhibitors in the armamentarium against dyslipidemia.

Discussion

The results of our investigation support other studies showing that PCSK9 inhibitors are more effective than statins at reducing LDL-C in individuals with heterozygous familial hypercholesterolemia (HeFH) and diabetes mellitus [11]. These findings are in line with seminal studies like FOURIER and ODYSSEY, which have repeatedly shown significant reductions in LDL-C levels with PCSK9 inhibitors that are not possible with statins alone. Strong LDL-C reductions shown with PCSK9 inhibitors highlight their potential as a treatment option for those who need strong lipid-lowering medication to reduce cardiovascular risk [12]. Our study shows a substantial difference in cardiovascular outcomes between individuals treated with PCSK9 inhibitors and statins, which is consistent with previous research [13]. This is in line with meta-analyses and research results that show a significant decrease in major adverse cardiovascular events (MACE) when PCSK9 medications are used [14]. PCSK9 inhibitors have been shown to significantly lower cardiovascular risk, which underscores their potential to enhance clinical outcomes and lessen the burden of cardiovascular morbidity and death in patients with diabetes and hemophilia.

Our investigation validates the positive safety profile of PCSK9 inhibitors and statins in this patient group, which is in line with the available data [15]. These results are consistent with information from research and clinical trials showing that PCSK9 inhibitors are often well tolerated and have a low rate of side effects. It is crucial to recognize that our study may not have had enough power to identify uncommon side events, which calls for more investigation to fully evaluate the long-term safety profile of PCSK9 inhibitors. The patient adherence and satisfaction outcomes of our study are consistent with other studies that show that PCSK9 inhibitors are associated with greater patient satisfaction rates than statins [16, 17]. This is consistent with research demonstrating higher treatment adherence and satisfaction with PCSK9 inhibitors, which is probably related to their easy-to-follow dosage schedule and strong LDL-C lowering effectiveness. PCSK9 inhibitors are favored over statins due to their less frequent dosing (biweekly or monthly injections) and potent LDL-C lowering effects by blocking the PCSK9 protein. Research, including studies like FOURIER and ODYSSEY, consistently shows significant LDL-C reductions with PCSK9 inhibitors compared to statins alone. Patients also report higher treatment adherence and satisfaction, along with improved quality of life and reduced anxiety related to cholesterol management. These factors highlight the potential of PCSK9 inhibitors to enhance dyslipidemia management in patients with conditions like heterozygous familial hypercholesterolemia and diabetes. These results highlight the need of taking patient preferences and satisfaction into account when choosing lipid-lowering treatments for people with diabetes and hemophilia [18].

Comparing our findings with previous studies [19, 20] reinforces the consistent evidence supporting the superiority of PCSK9 inhibitors over statins in terms of LDL-C reduction, cardiovascular risk reduction, and patient satisfaction in patients with HeFH and diabetes. While prior research has laid the groundwork for understanding the efficacy and safety of PCSK9

inhibitors, our study contributes valuable evidence corroborating these findings in a clinical setting. Furthermore, our study emphasizes the need for personalized treatment approaches tailored to individual patient needs and preferences.

Limitations and Future Directions

Notwithstanding the insightful information our research offered, there are a few things to be aware of. The research design's retrospective nature presents inherent biases, and the limited sample size may restrict how far our results may be applied. Large-scale, multicenter prospective trials should be the main focus of future research endeavors in order to confirm our findings and clarify the long-term safety and effectiveness of PCSK9 inhibitors in clinical practice.

Conclusion

The study underscores the superior efficacy of PCSK9 inhibitors compared to statins in reducing LDL-C levels and mitigating cardiovascular risk in patients with Heterozygous Familial Hypercholesterolemia and diabetes mellitus. These findings, consistent with previous research, highlight the potential of PCSK9 inhibitors to revolutionize lipid management and improve clinical outcomes in this high-risk population, emphasizing the need for personalized treatment approaches tailored to individual patient needs.

Conflict of interest

The authors state no conflict of interest.

References

1. Arca M. Old challenges and new opportunities in the clinical management of heterozygous familial hypercholesterolemia (HeFH): The promises of PCSK9 inhibitors. Atherosclerosis. 2017 Jan 1;256:134-45.

2. Hartgers ML, Besseling J, Stroes ES, Wittekoek J, Rutten JH, de Graaf J, Visseren FL, Imholz BP, van Lennep JE, Huijgen R, Kastelein JJ. Achieved LDL cholesterol levels in patients with heterozygous familial hypercholesterolemia: A model that explores the efficacy of conventional and novel lipid-lowering therapy. Journal of clinical lipidology. 2018 Jul 1;12(4):972-80.

3. Climent E, Pérez-Calahorra S, Benaiges D, Pintó X, Suárez-Tembra M, Plana N, Sánchez-Hernández RM, Valdivielso P, Ascaso JF, Pedro-Botet J. Clinical and genetic differences between heterozygous familial hypercholesterolemia patients with and without type 2 diabetes. Revista Española de Cardiología (English Edition). 2020 Sep 1;73(9):718-24.

4. Climent E, Pérez-Calahorra S, Marco-Benedí V, Plana N, Sánchez R, Ros E, Ascaso JF, Puzo J, Almagro F, Lahoz C, Civeira F. Effect of LDL cholesterol, statins and presence of mutations on the prevalence of type 2 diabetes in heterozygous familial hypercholesterolemia. Scientific reports. 2017 Jul 17;7(1):5596.

5. Arca M, Celant S, Olimpieri PP, Colatrella A, Tomassini L, D'Erasmo L, Averna M, Zambon A, Catapano AL, Russo P. Real-World Effectiveness of PCSK9 Inhibitors in Reducing LDL-C in Patients With Familial Hypercholesterolemia in Italy: A Retrospective Cohort Study Based on the AIFA Monitoring Registries. Journal of the American Heart Association. 2023 Nov 7;12(21):e026550.

6. Vuorio A, Watts GF, Kovanen PT. Initiation of PCSK9 inhibition in patients with heterozygous familial hypercholesterolaemia entering adulthood: a new design for living with a high-risk condition?. European Heart Journal. 2016 May 1;37(17):1353-6.

7. Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: Guidelines and new therapies. Atherosclerosis. 2018 Oct 1;277:483-92.

8. Catapano AL, Pirillo A, Norata GD. Anti-PCSK9 antibodies for the treatment of heterozygous familial hypercholesterolemia: patient selection and perspectives. Vascular health and risk management. 2017 Sep 4:343-51.

9. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. Journal of the American Heart Association. 2019 Dec 17;8(24):e013225.

10. Liu MM, Peng J, Guo YL, Wu NQ, Zhu CG, Gao Y, Dong Q, Li JJ. Impact of diabetes on coronary severity and cardiovascular outcomes in patients with heterozygous familial hypercholesterolaemia. European Journal of Preventive Cardiology. 2021 Dec 1;28(16):1807-16.

11. Miname MH, Santos RD. Reducing cardiovascular risk in patients with familial hypercholesterolemia: Risk prediction and lipid management. Progress in cardiovascular diseases. 2019 Sep 1;62(5):414-22.

12. van Delden XM, Huijgen R, Wolmarans KH, Brice BC, Barron JK, Blom DJ, Marais AD. LDL-cholesterol target achievement in patients with heterozygous familial hypercholesterolemia at Groote Schuur Hospital: minority at target despite large reductions in LDL-C. Atherosclerosis. 2018 Oct 1;277:327-33.

13. Tomlinson B, Patil NG, Fok M, Lam CW. Role of PCSK9 inhibitors in patients with familial hypercholesterolemia. Endocrinology and Metabolism. 2021 Apr;36(2):279.'

14. Papademetriou V, Stavropoulos K, Papadopoulos C, Koutsampasopoulos K, Dimitriadis K, Tsioufis K. Role of PCSK9 inhibitors in high risk patients with dyslipidemia: focus on familial hypercholesterolemia. Current pharmaceutical design. 2018 Sep 1;24(31):3647-53.

15. Hovingh GK, Goldberg AC, Moriarty PM. Managing the challenging homozygous familial hypercholesterolemia patient: Academic insights and practical approaches for a severe dyslipidemia, a National Lipid Association Masters Summit. Journal of clinical lipidology. 2017 May 1;11(3):602-16.

16. Masana L, Plana N, Pérez-Calahorra S, Ibarretxe D, Lamiquiz-Moneo I, Pedro-Botet J, Suárez-Tembra M, Valdivielso P, Ortega E, Civeira F. How many familial hypercholesterolemia patients are eligible for PCSK9 inhibition?. Atherosclerosis. 2017 Jul 1;262:107-12.

17. Lui DT, Lee AC, Tan KC. Management of familial hypercholesterolemia: current status and future perspectives. Journal of the Endocrine Society. 2021 Jan;5(1):bvaa122.

18. Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, Baccara-Dinet MT, Lorenzato C, Pordy R, Stroes E. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. Cardiovascular Drugs and Therapy. 2016 Oct;30:473-83.

19. Mohd Kasim NA, An CY, Nawawi H. Familial hypercholesterolaemia: An updated overall management. Journal of Clinical and Heatlh Sciences. 2020 Nov 1;5(2):19-38.

20. D'Erasmo L, Commodari D, Di Costanzo A, Minicocci I, Polito L, Ceci F, Montali A, Maranghi M, Arca M. Evolving trend in the management of heterozygous familial hypercholesterolemia in Italy: a retrospective, single center, observational study. Nutrition, Metabolism and Cardiovascular Diseases. 2020 Oct 30;30(11):2027-35.