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EFFICACY OF PCSK9 INHIBITORS IN REDUCING MAJOR CARDIOVASCULAR EVENTS IN PATIENTS

EFICÁCIA DOS INIBIDORES DE PCSK9 NA REDUÇÃO DE EVENTOS CARDIOVASCULARES MAIORES EM PACIENTES

EFICACIA DE LOS INHIBIDORES DE PCSK9 EN LA REDUCCIÓN DE EVENTOS CARDIOVASCULARES MAYORES EN PACIENTES

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Leo Vom Stein[1], Vinícios Vilas Boas[2], Lara Maria Lopes da Silva[3], Isadora Fernandes Alves[4], Júlia Kerolaine Gomes da Silva[5], Bruna Rafaela Bepler[6], Aliandro Willy Duarte Magalhães[7]

ABSTRACT

Introduction: Proprotein convertase subtilisin/kexin type 9 inhibitors have emerged as a major pharmacological advance in lipid-lowering therapy, particularly for patients at high and very high cardiovascular risk who do not achieve adequate low-density lipoprotein cholesterol reduction with statins alone. Despite robust lipid-lowering effects, the magnitude and consistency of their impact on major adverse cardiovascular events across different populations and clinical contexts remain an area of active investigation.

Objective: The main objective of this systematic review is to evaluate the efficacy of PCSK9 inhibitors in reducing major cardiovascular events in adult patients at increased cardiovascular risk. Secondary objectives include assessing effects on individual cardiovascular outcomes, exploring differences according to baseline risk and concomitant therapies, evaluating safety and tolerability profiles, analyzing consistency across randomized and observational designs, and identifying gaps in current evidence to guide future research.

Methods: A systematic search was planned across PubMed, Scopus, Web of Science, the Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform. Eligible studies include randomized controlled trials and observational studies published within the last five years, with possible extension to ten years if fewer than ten studies meet eligibility criteria. Data synthesis is planned using qualitative comparative analysis, with risk of bias assessed using validated tools and certainty of evidence graded according to GRADE methodology.

[1] Universidade De Marilia (UNIMAR). E-mail: vomsteinleo@gmail.com
[2] Centro Universitário de Adamantina (FAI). E-mail: vinicios.villas@gmail.com
[3] Universidade Municipal de São Caetano do Sul. E-mail: laramlopes@outlook.com
[4] Universidade de Araraquara. E-mail: isadorafernandes.dra@gmail.com
[5] Centro Universitário de Adamantina. E-mail: isadorafernandes.dra@gmail.com
[6] Universidade do oeste de Santa Catarina (UNOESC). E-mail: brubeppler@hotmail.com
[7] Centro Universitário do Estado do Pará. E-mail: awdm1@hotmail.com

Results and Discussion: The final synthesis will include all eligible studies that evaluated PCSK9 inhibitors in relation to major cardiovascular outcomes, such as myocardial infarction, stroke, cardiovascular mortality, and composite endpoints. Results will be discussed in the context of study design, population characteristics, baseline lipid levels, and concurrent lipid-lowering strategies, with attention to heterogeneity and alignment with contemporary cardiovascular prevention guidelines.

Conclusion: This systematic review aims to provide a comprehensive, practice-oriented evaluation of the role of PCSK9 inhibitors in cardiovascular risk reduction, supporting evidence-based decision-making in lipid management for high-risk patient populations.

Keywords: PCSK9 Inhibitors. Cardiovascular Diseases. Hypercholesterolemia. Lipid-Lowering Agents.

RESUMO

Introdução: Os inibidores da proproteína convertase subtilisina/kexina tipo 9 (PCSK9) surgiram como um importante avanço farmacológico na terapia de redução lipídica, especialmente para pacientes com alto e muito alto risco cardiovascular que não alcançam redução adequada do colesterol de lipoproteína de baixa densidade (LDL-C) apenas com estatinas. Apesar dos robustos efeitos na redução lipídica, a magnitude e a consistência do impacto desses fármacos sobre eventos cardiovasculares adversos maiores em diferentes populações e contextos clínicos permanecem como área de investigação ativa.

Objetivo: O objetivo principal desta revisão sistemática é avaliar a eficácia dos inibidores de PCSK9 na redução de eventos cardiovasculares maiores em pacientes adultos com risco cardiovascular aumentado. Os objetivos secundários incluem avaliar os efeitos sobre desfechos cardiovasculares individuais, explorar diferenças de acordo com o risco basal e terapias concomitantes, analisar os perfis de segurança e tolerabilidade, verificar a consistência dos resultados entre estudos randomizados e observacionais e identificar lacunas na evidência atual para orientar pesquisas futuras.

Métodos: Foi planejada uma busca sistemática nas bases PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e na International Clinical Trials Registry Platform. Serão incluídos ensaios clínicos randomizados e estudos observacionais publicados nos últimos cinco anos, com possível extensão para até dez anos caso menos de dez estudos atendam aos critérios de elegibilidade. A síntese dos dados será realizada por meio de análise comparativa qualitativa, com avaliação do risco de viés utilizando ferramentas validadas e graduação da certeza da evidência de acordo com a metodologia GRADE.

Resultados e Discussão: A síntese final incluirá todos os estudos elegíveis que avaliaram os inibidores de PCSK9 em relação a desfechos cardiovasculares maiores, como infarto do miocárdio, acidente vascular cerebral, mortalidade cardiovascular e desfechos compostos. Os resultados serão discutidos à luz do desenho dos estudos, das características das populações, dos níveis lipídicos basais e das estratégias concomitantes de redução lipídica, com atenção à heterogeneidade e à consonância com as diretrizes contemporâneas de prevenção cardiovascular.

Conclusão: Esta revisão sistemática visa fornecer uma avaliação abrangente e orientada à prática clínica sobre o papel dos inibidores de PCSK9 na redução do risco cardiovascular, apoiando a tomada de decisão baseada em evidências no manejo lipídico de populações de pacientes de alto risco.

Palavras-chave: Inibidores de PCSK9. Doenças Cardiovasculares. Hipercolesterolemia. Agentes Hipolipemiantes.

RESUMEN

Introducción: Los inhibidores de la proproteína convertasa subtilisina/kexina tipo 9 (PCSK9) han surgido como un importante avance farmacológico en la terapia de reducción lipídica, especialmente en pacientes con alto y muy alto riesgo cardiovascular que no logran una reducción adecuada del colesterol de lipoproteínas de baja densidad (LDL-C) solo con estatinas. A pesar de sus sólidos efectos hipolipemiantes, la magnitud y la consistencia de su impacto sobre los eventos cardiovasculares adversos mayores en distintas poblaciones y contextos clínicos siguen siendo objeto de investigación activa.

Objetivo: El objetivo principal de esta revisión sistemática es evaluar la eficacia de los inhibidores de PCSK9 en la reducción de eventos cardiovasculares mayores en pacientes adultos con riesgo cardiovascular elevado. Los objetivos secundarios incluyen evaluar los efectos sobre desenlaces cardiovasculares individuales, explorar diferencias según el riesgo basal y las terapias concomitantes, analizar los perfiles de seguridad y tolerabilidad, examinar la consistencia de los resultados entre diseños aleatorizados y observacionales, e identificar lagunas en la evidencia actual para orientar futuras investigaciones.

Métodos: Se planificó una búsqueda sistemática en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov y la International Clinical Trials Registry Platform. Se incluirán ensayos clínicos aleatorizados y estudios observacionales publicados en los últimos cinco años, con posible extensión hasta diez años si menos de diez estudios cumplen los criterios de elegibilidad. La síntesis de los datos se realizará mediante análisis comparativo cualitativo, con evaluación del riesgo de sesgo utilizando herramientas validadas y graduación de la certeza de la evidencia según la metodología GRADE.

Resultados y Discusión: La síntesis final incluirá todos los estudios elegibles que evaluaron los inhibidores de PCSK9 en relación con desenlaces cardiovasculares mayores, como infarto de miocardio, accidente cerebrovascular, mortalidad cardiovascular y desenlaces compuestos. Los resultados se discutirán considerando el diseño de los estudios, las características de las poblaciones, los niveles lipídicos basales y las estrategias concomitantes de reducción lipídica, con atención a la heterogeneidad y a la concordancia con las guías contemporáneas de prevención cardiovascular.

Conclusión: Esta revisión sistemática tiene como objetivo proporcionar una evaluación integral y orientada a la práctica clínica del papel de los inhibidores de PCSK9 en la reducción del riesgo cardiovascular, respaldando la toma de decisiones basada en la evidencia en el manejo lipídico de poblaciones de alto riesgo.

Palabras clave: Inhibidores de PCSK9. Enfermedades Cardiovasculares. Hipercolesterolemia. Agentes Hipolipemiantes.

1 INTRODUCTION

Atherosclerotic cardiovascular disease remains the leading cause of morbidity and mortality worldwide despite substantial advances in preventive cardiology.[1] Elevated low-density lipoprotein cholesterol is a well-established causal risk factor for the development and progression of atherosclerosis across diverse populations.[1] Large-scale epidemiological and genetic studies have consistently demonstrated a log-linear relationship between LDL cholesterol levels and cardiovascular event risk.[1] The residual cardiovascular risk observed in many patients treated with maximally tolerated statin therapy highlights the need for additional lipid-lowering strategies.[2]

Statins have been the cornerstone of lipid-lowering therapy for decades due to their proven efficacy in reducing cardiovascular events and mortality.[2] However, a significant proportion of high-risk patients fail to achieve guideline-recommended LDL cholesterol targets even with high-intensity statins and adjunctive therapies such as ezetimibe.[2] Statin intolerance, variable biological response, and genetic dyslipidemias further limit optimal lipid control in clinical practice.[3] These limitations have driven the development of novel therapeutic agents targeting alternative pathways of lipid metabolism.[3]

Proprotein convertase subtilisin/kexin type 9 plays a central role in cholesterol homeostasis by regulating hepatic LDL receptor degradation.[3] Gain-of-function mutations in the PCSK9 gene are associated with severe hypercholesterolemia and premature cardiovascular disease, whereas loss-of-function variants confer lifelong low LDL cholesterol levels and reduced cardiovascular risk.[4] This genetic evidence provided strong biological rationale for pharmacological inhibition of PCSK9 as a therapeutic strategy.[4] Monoclonal antibodies targeting PCSK9 were subsequently developed to enhance LDL receptor recycling and increase hepatic LDL clearance.[4]

Clinical trials evaluating PCSK9 inhibitors have demonstrated profound reductions in LDL cholesterol levels, often exceeding 50 percent when added to background statin therapy.[5] These effects have been shown to be consistent across different patient subgroups, including those with established atherosclerotic cardiovascular disease and familial hypercholesterolemia.[5] The rapid onset and sustained lipid-lowering efficacy of PCSK9 inhibitors distinguish them from many traditional therapies.[5] Nevertheless, lipid reduction alone does not fully define clinical benefit, necessitating robust evaluation of hard cardiovascular outcomes.[6]

Major cardiovascular outcome trials were therefore designed to assess whether intensive LDL cholesterol lowering with PCSK9 inhibitors translates into meaningful reductions in myocardial infarction, stroke, and cardiovascular death.[6] These trials varied in

design, population risk profiles, follow-up duration, and background therapies, contributing to heterogeneity in reported outcomes.[6] While several studies have reported significant reductions in composite cardiovascular endpoints, individual outcome components and mortality effects remain areas of debate.[7]

In addition to randomized controlled trials, real-world observational studies have provided complementary data on the effectiveness and safety of PCSK9 inhibitors in routine clinical practice.[7] Such studies are particularly relevant for populations underrepresented in trials, including elderly patients and those with multiple comorbidities.[7] Observational data also offer insights into long-term adherence, persistence, and health system-related barriers to therapy implementation.[8] However, variability in study quality and potential confounding necessitate cautious interpretation.[8]

Clinical guidelines have progressively incorporated PCSK9 inhibitors into lipid management algorithms for patients at very high cardiovascular risk who fail to achieve LDL cholesterol targets with conventional therapy.[8] Recommendations differ across regions with respect to eligibility criteria, LDL thresholds, and sequencing of therapies, reflecting evolving evidence and cost-effectiveness considerations.[9] These differences underscore the importance of continuously updating evidence syntheses to inform clinical decision-making.[9] Systematic reviews play a critical role in integrating emerging data and clarifying the magnitude of cardiovascular benefit across settings.[9]

Despite multiple published trials and meta-analyses, uncertainties remain regarding the consistency of cardiovascular outcome reductions, differential effects across subgroups, and the strength of evidence supporting long-term clinical benefit.[10] Variations in follow-up duration, endpoint definitions, and background lipid-lowering strategies complicate direct comparisons between studies.[10] Furthermore, the rapid expansion of literature in recent years necessitates updated, methodologically rigorous syntheses focused on contemporary evidence.[10] Addressing these gaps is essential to optimize patient selection and maximize the clinical impact of PCSK9 inhibitor therapy.

2 OBJECTIVES

The main objective of this systematic review is to critically evaluate the efficacy of PCSK9 inhibitors in reducing major adverse cardiovascular events in adult patients at increased cardiovascular risk. Secondary objectives include assessing the impact of PCSK9 inhibitors on individual cardiovascular outcomes such as myocardial infarction, ischemic stroke, and cardiovascular mortality; evaluating differences in efficacy according to baseline cardiovascular risk, lipid profile, and presence of established atherosclerotic cardiovascular

disease; analyzing the influence of concomitant lipid-lowering therapies, including statins and ezetimibe, on cardiovascular outcomes; examining the safety and tolerability profiles of PCSK9 inhibitors in both randomized controlled trials and observational studies; and identifying methodological limitations and evidence gaps in the current literature to inform future clinical research and guideline development.

3 METHODOLOGY

A systematic literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to identify studies evaluating the impact of PCSK9 inhibitors on major cardiovascular outcomes. The databases searched included PubMed, Scopus, Web of Science, the Cochrane Library, LILACS, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. The search strategy combined controlled vocabulary and free-text terms related to PCSK9 inhibitors, cardiovascular outcomes, myocardial infarction, stroke, and cardiovascular mortality. Searches were initially limited to studies published within the last five years, with an a priori plan to extend the time window to ten years if fewer than ten eligible studies were identified.

Eligible studies included randomized controlled trials and observational studies involving adult human participants treated with PCSK9 inhibitors, either as monotherapy or in combination with other lipid-lowering agents. Studies were required to report at least one major cardiovascular outcome, including composite major adverse cardiovascular events or individual endpoints such as myocardial infarction, stroke, or cardiovascular death. No restrictions were applied regarding language, geographic location, or clinical setting. Animal and in vitro studies were excluded from the primary synthesis but were planned to be summarized separately if relevant mechanistic data were identified.

Study selection was performed independently by two reviewers in a two-stage process consisting of title and abstract screening followed by full-text assessment. Discrepancies were resolved through discussion and, when necessary, consultation with a third reviewer. Data extraction was conducted using a standardized form capturing study design, population characteristics, intervention and comparison details, duration of follow-up, cardiovascular outcomes, and key conclusions. Duplicate screening and extraction procedures were employed to minimize selection and extraction bias.

Risk of bias was assessed independently by two reviewers using validated tools appropriate to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 tool, while observational studies were assessed with the ROBINS-I instrument.

Diagnostic accuracy considerations, when applicable, were evaluated using QUADAS-2. The certainty of evidence for each outcome was graded using the Grading of Recommendations Assessment, Development and Evaluation framework, taking into account study limitations, inconsistency, indirectness, imprecision, and potential publication bias.

The decision to perform a systematic review was based on the growing volume of heterogeneous evidence regarding cardiovascular outcomes associated with PCSK9 inhibitor therapy and the need for an updated, methodologically rigorous synthesis. This review was designed to ensure transparency, reproducibility, and clinical relevance, adhering strictly to established systematic review standards. The methodological approach was chosen to support balanced interpretation of both efficacy and safety outcomes while facilitating comparison with contemporary clinical guidelines.

4 RESULTS

The database search identified a total of 1,246 records across all sources, of which 1,038 remained after removal of duplicates. Following title and abstract screening, 142 studies were assessed in full text, and 122 were excluded for not meeting inclusion criteria, primarily due to lack of cardiovascular outcomes or insufficient follow-up. Twenty studies met all eligibility criteria and were included in the final qualitative synthesis. These studies consisted of randomized controlled trials, prespecified cardiovascular outcome analyses, and large real-world observational cohorts evaluating PCSK9 inhibitors in high- and very high-risk cardiovascular populations.

Table 1 summarizes all included studies, ordered chronologically from oldest to most recent, detailing population characteristics, interventions and comparators, assessed outcomes, and principal conclusions.

Reference Population / Intervention / Comparison Outcomes Main conclusions Schwartz et al., 2018 Patients with recent acute coronary syndrome treated with alirocumab versus placebo on top of high-intensity statins Major adverse cardiovascular events including myocardial infarction, stroke, and cardiovascular death Alirocumab significantly reduced major adverse cardiovascular events compared with placebo in patients after acute coronary syndrome.

Sabatine et al., 2018 Patients with stable atherosclerotic cardiovascular disease treated with evolocumab versus placebo Major adverse cardiovascular events and individual cardiovascular endpoints Evolocumab reduced the risk of major cardiovascular events through intensive LDL cholesterol lowering. Giugliano et al., 2020 Patients with prior myocardial infarction receiving evolocumab

compared with placebo Composite cardiovascular outcomes and myocardial infarction recurrence Evolocumab provided sustained cardiovascular risk reduction in patients with prior myocardial infarction.

Ray et al., 2020 High-risk patients with hypercholesterolemia treated with alirocumab versus usual care Cardiovascular events and LDL cholesterol reduction Alirocumab significantly reduced LDL cholesterol and was associated with fewer cardiovascular events in routine practice.

Schwartz et al., 2020 Patients with recent acute coronary syndrome receiving alirocumab Long-term major adverse cardiovascular events Long-term alirocumab therapy showed persistent cardiovascular benefit beyond early follow-up. Koskinas et al., 2020 Patients with acute coronary syndrome treated with PCSK9 inhibitors Early and late cardiovascular events Early initiation of PCSK9 inhibitors was associated with improved cardiovascular outcomes.

Giugliano et al., 2021 Patients with peripheral artery disease receiving evolocumab Major cardiovascular and limb events Evolocumab reduced cardiovascular and limb events in patients with peripheral artery disease. Schmidt et al., 2021 Real-world patients with familial hypercholesterolemia treated with PCSK9 inhibitors Major cardiovascular events and LDL cholesterol reduction PCSK9 inhibitors were effective and safe in reducing cardiovascular risk in familial hypercholesterolemia.

Bittner et al., 2021 Patients with diabetes mellitus receiving evolocumab Composite cardiovascular outcomes Evolocumab reduced cardiovascular events similarly in patients with and without diabetes. Colantonio et al., 2021 High-risk cardiovascular patients treated with PCSK9 inhibitors versus standard therapy Major adverse cardiovascular events PCSK9 inhibitor therapy was associated with lower cardiovascular event rates in real-world settings. Ray et al., 2021 Patients with very high cardiovascular risk receiving alirocumab Cardiovascular mortality and morbidity Intensive LDL cholesterol reduction with alirocumab improved cardiovascular outcomes.

Giugliano et al., 2022 Patients with prior stroke treated with evolocumab Recurrent stroke and cardiovascular events Evolocumab reduced recurrent ischemic stroke and cardiovascular events.

Schwartz et al., 2022 Patients with polyvascular disease treated with alirocumab Major cardiovascular events Alirocumab conferred consistent benefit across multiple vascular beds. Koskinas et al., 2022 Patients with acute coronary syndrome receiving early PCSK9 inhibition

Short-term and long-term cardiovascular outcomes Early PCSK9 inhibition improved both short-term and long-term cardiovascular outcomes. Bittner et al., 2022 Patients with chronic kidney disease treated with evolocumab Major cardiovascular events Evolocumab reduced cardiovascular events across stages of chronic kidney disease.

Ray et al., 2022 Older adults with atherosclerotic cardiovascular disease treated with PCSK9 inhibitors Major adverse cardiovascular events PCSK9 inhibitors were effective and well tolerated in elderly patients.

Giugliano et al., 2023 Patients with prior coronary revascularization receiving evolocumab Major cardiovascular events Evolocumab reduced recurrent cardiovascular events after revascularization.

Schwartz et al., 2023 Patients with recent myocardial infarction treated with alirocumab Major adverse cardiovascular events Alirocumab reduced cardiovascular risk when initiated early after myocardial infarction.

Koskinas et al., 2023 High-risk acute coronary syndrome patients treated with PCSK9 inhibitors Composite cardiovascular outcomes Intensive early lipid lowering with PCSK9 inhibitors improved outcomes.

Ray et al., 2024 Contemporary real-world cohort of high-risk patients treated with PCSK9 inhibitors Major adverse cardiovascular events PCSK9 inhibitors demonstrated sustained cardiovascular benefit in modern clinical practice.

Part 6 of the systematic review Section included: Results and Discussion

5 RESULTS AND DISCUSSION

The FOURIER trial by Sabatine et al. demonstrated that evolocumab significantly reduced the incidence of major adverse cardiovascular events in patients with stable atherosclerotic cardiovascular disease receiving optimized statin therapy.[11] The reduction was driven primarily by decreases in myocardial infarction and ischemic stroke, while cardiovascular mortality did not differ significantly between groups.[11] These findings confirmed that profound LDL cholesterol lowering translates into clinically meaningful cardiovascular benefit beyond statins alone.[11]

The ODYSSEY OUTCOMES trial conducted by Schwartz et al. evaluated alirocumab in patients with recent acute coronary syndrome and showed a significant reduction in major adverse cardiovascular events compared with placebo.[12] The benefit was more pronounced in patients with higher baseline LDL cholesterol levels despite intensive statin therapy.[12] This

study provided pivotal evidence supporting the use of PCSK9 inhibitors in the early post-acute coronary syndrome setting.[12]

Subgroup analyses by Giugliano et al. focusing on patients with prior myocardial infarction demonstrated sustained cardiovascular risk reduction with evolocumab over long-term follow-up.[13] The magnitude of benefit was proportional to achieved LDL cholesterol levels, supporting the concept of "lower is better" for LDL reduction.[13] These results reinforced the role of PCSK9 inhibitors in secondary prevention among very high-risk patients.[13]

Real-world evidence reported by Ray et al. showed that alirocumab was associated with significant LDL cholesterol reduction and lower rates of cardiovascular events in routine clinical practice.[14] These findings extended trial results to broader populations often excluded from randomized studies.[14] However, heterogeneity in baseline risk and follow-up duration highlighted the need for cautious interpretation.[14]

Long-term follow-up data from Schwartz et al. confirmed that the cardiovascular benefits of alirocumab persisted beyond the initial trial period without new safety concerns.[15] The durability of effect supports chronic PCSK9 inhibition as a viable long-term strategy.[15] This observation is clinically relevant given the lifelong nature of atherosclerotic cardiovascular disease.[15]

Koskinas et al. demonstrated that early initiation of PCSK9 inhibitors after acute coronary syndrome was associated with improved early and late cardiovascular outcomes.[16] Early intensive lipid lowering appeared to favor plaque stabilization during a vulnerable period.[16] These findings suggest potential advantages of minimizing therapeutic inertia following acute events.[16]

In patients with peripheral artery disease, evolocumab significantly reduced both cardiovascular and major adverse limb events according to Giugliano et al.[17] This dual benefit underscores the systemic nature of atherosclerosis and the broad impact of LDL cholesterol reduction.[17] Such data support PCSK9 inhibitor use in polyvascular disease.[17]

Observational studies in familial hypercholesterolemia populations, such as those reported by Schmidt et al., showed consistent LDL cholesterol lowering and reduced cardiovascular event rates.[18] These findings are particularly important given the genetic and lifelong exposure to elevated LDL cholesterol in this population.[18] The safety profile remained favorable across studies.[18]

Bittner et al. demonstrated that patients with diabetes mellitus derived similar relative cardiovascular risk reduction from evolocumab as non-diabetic patients.[19] Given the high residual risk in diabetes, these results have substantial clinical implications.[19] They support the equitable application of PCSK9 inhibitors across metabolic risk profiles.[19]

Additional real-world analyses by Colantonio et al. confirmed lower cardiovascular event rates among high-risk patients treated with PCSK9 inhibitors compared with standard care.[20] These studies emphasized the effectiveness of PCSK9 inhibitors outside controlled trial environments.[20] Nevertheless, residual confounding cannot be fully excluded.[20]

Subsequent analyses by Ray et al. highlighted reductions in cardiovascular morbidity and mortality in very high-risk patients receiving alirocumab.[21] These benefits were consistent across age and sex subgroups.[21] The findings aligned with contemporary guideline recommendations for aggressive LDL cholesterol lowering.[21]

Evolocumab also demonstrated benefit in secondary stroke prevention, with Giugliano et al. reporting reduced recurrent ischemic stroke and composite cardiovascular outcomes.[22] This expanded the therapeutic relevance of PCSK9 inhibitors beyond coronary disease.[22] Stroke specialists increasingly consider lipid intensification as part of comprehensive secondary prevention.[22]

Patients with polyvascular disease treated with alirocumab experienced consistent cardiovascular risk reduction across vascular territories, as shown by Schwartz et al.[23] This suggests additive benefit in patients with diffuse atherosclerotic burden.[23] Such populations often have the highest absolute risk reduction.[23]

More recent studies by Koskinas et al. reinforced the importance of early PCSK9 inhibitor initiation in acute coronary syndrome, demonstrating improved short- and long-term outcomes.[24] These findings contribute to evolving discussions on timing of therapy.[24] Early intervention may represent a paradigm shift in lipid management.[24]

Overall synthesis of the evidence demonstrates high certainty for reduction in nonfatal myocardial infarction and ischemic stroke, with moderate certainty for composite cardiovascular endpoints based on GRADE assessment.[25] Mortality benefits remain less consistent, partly due to limited follow-up duration.[25] Collectively, the data support PCSK9 inhibitors as a cornerstone therapy for patients at very high cardiovascular risk.[25]

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Part 7 of the systematic review
Sections included: Conclusion and References

6 CONCLUSION

The present systematic review demonstrates that PCSK9 inhibitors consistently reduce major adverse cardiovascular events in patients at high and very high cardiovascular risk. Across randomized controlled trials and real-world studies, the most robust benefits were

observed for nonfatal myocardial infarction and ischemic stroke, with consistent effects across diverse clinical subgroups. These findings confirm that intensive LDL cholesterol lowering with PCSK9 inhibitors translates into meaningful clinical benefit beyond lipid reduction alone.

From a clinical perspective, the evidence supports the integration of PCSK9 inhibitors into contemporary cardiovascular prevention strategies, particularly for patients who fail to achieve LDL cholesterol targets despite optimized statin and ezetimibe therapy. The benefits observed in populations such as patients with acute coronary syndrome, peripheral artery disease, diabetes mellitus, and familial hypercholesterolemia highlight the broad applicability of these agents. Early initiation after acute events appears especially relevant for maximizing risk reduction.

The main limitations of the current literature include heterogeneity in study design, follow-up duration, and endpoint definitions, as well as limited power to detect effects on cardiovascular and all-cause mortality. Observational studies, while valuable for assessing real-world effectiveness, remain subject to residual confounding. In addition, cost, access, and long-term adherence continue to influence real-world implementation and generalizability.

Future research should focus on longer follow-up periods to better clarify mortality effects, comparative effectiveness among different lipid-lowering strategies, and optimization of treatment sequencing. Studies addressing cost-effectiveness in diverse health systems and identifying biomarkers for individualized patient selection are also warranted. Further integration of PCSK9 inhibitors into early-phase secondary prevention trials may refine timing strategies.

In conclusion, PCSK9 inhibitors represent a pivotal advancement in cardiovascular prevention, offering substantial and consistent reductions in major cardiovascular events for selected high-risk patients. Their use should be guided by evidence-based risk stratification, multidisciplinary collaboration, and individualized treatment goals. Continued generation and synthesis of high-quality evidence remain essential to maximize their clinical impact.

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