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Risk of Adverse Health Outcomes in Patients with Poor Adherence to Cardiovascular Medication Treatment: a Systematic Review

Risco de Desfechos Adversos à Saúde em Pacientes com Baixa Adesão ao Tratamento Medicamentoso Cardiovascular: uma Revisão Sistemática

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Abstract

Background: Cardiovascular diseases (CVD) remain the leading cause of mortality worldwide. Medication adherence is an important issue in managing chronic CVD, directly influencing outcomes and healthcare costs.
Objectives: This systematic review, supported by the Brazilian Society of Cardiology, evaluates the impact of poor adherence to cardiovascular medications on critical clinical outcomes such as death and cardiovascular events.
Methods: A comprehensive search was conducted across four databases, including Medline, Embase, Lilacs, and the Cochrane Library. The review included systematic reviews with meta-analyses that reported risk estimates for adherence to cardiovascular medications. Four systematic reviews, each incorporating observational studies, were selected.
Results: The principal findings indicate that an increase in adherence to medications significantly reduces the risk of cardiovascular events, stroke, and all-cause death. Specifically, a 20% improvement in adherence to antihypertensive, lipid-lowering, and other cardiovascular medications correlated with reductions in cardiovascular events by 7%, 10%, and 9%, respectively; stroke by 17%, 13%, and 18%; and death by 12%, 9%, and 10%. The certainty of the evidence was moderate, suggesting that these effects are likely present. These findings emphasize the importance of enhancing medication adherence to improve clinical outcomes in CVD management.
Conclusions: Evidence has demonstrated reductions in hard endpoints in both primary and secondary prevention through the control of conditions such as hypertension and elevated LDL cholesterol concentrations, as well as the benefits of antiplatelet therapy in atherosclerotic disease. However, additional studies are needed to better elucidate the relationship between adherence to cardiovascular medications and the improvement of critical clinical outcomes.

Resumo

Introdução: As doenças cardiovasculares (DCV) continuam a ser a principal causa de mortalidade em todo o mundo. A adesão ao tratamento medicamentoso é uma questão importante no manejo das DCV crônicas, influenciando diretamente os resultados e os custos com saúde.

Objetivos: Esta revisão sistemática, apoiada pela Sociedade Brasileira de Cardiologia, avalia o impacto da baixa adesão aos medicamentos cardiovasculares em desfechos clínicos críticos, como morte e eventos cardiovasculares.

Métodos: Foi realizada uma busca abrangente em quatro bases de dados, incluindo Medline, Embase, Lilacs e Cochrane Library. A revisão incluiu revisões sistemáticas com meta-análises que relataram estimativas de risco para a adesão aos medicamentos cardiovasculares. Foram selecionadas quatro revisões sistemáticas, cada uma incorporando estudos observacionais.

Resultados: Os principais achados indicam que um aumento na adesão aos medicamentos reduz significativamente o risco de eventos cardiovasculares, acidente vascular cerebral (AVC) e morte por todas as causas. Especificamente, uma melhoria de 20% na adesão a medicamentos antihipertensivos, hipolipemiantes e outros medicamentos cardiovasculares correlacionou-se com reduções nos eventos cardiovasculares de 7%, 10% e 9%, respectivamente; AVC de 17%, 13% e 18%; e morte de 12%, 9% e 10%. A certeza das evidências foi moderada, sugerindo que esses efeitos provavelmente estão presentes. Esses achados enfatizam a importância de melhorar a adesão ao tratamento medicamentoso para aprimorar os resultados clínicos no manejo das DCV.

Conclusões: As evidências demonstraram reduções em desfechos duros tanto na prevenção primária quanto secundária através do controle de condições como hipertensão e concentrações elevadas de colesterol LDL, bem como os benefícios da terapia antiplaquetária em doenças ateroscleróticas. No entanto, são necessários estudos adicionais para elucidar melhor a relação entre a adesão aos medicamentos cardiovasculares e a melhoria dos desfechos clínicos críticos.

Keywords: medication adherence; patient compliance; cardiovascular diseases.

Palavras-chave: adesão ao tratamento medicamentoso; conformidade do paciente; doenças cardiovasculares.

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Potencial Conflito de Interesse

Declaramos não haver conflito de interesses pertinentes.

Contribuição dos Autores

Revisão crítica do manuscrito quanto ao conteúdo intelectual importante: Malachias MVB, Kaiser SE, Albuquerque DC, Brandão AA, Sposito AC, Moura LZ, Magalhães LBNC, Mota-Gomes MA, Clausell N, Jardim PCV, Nadruz W, Barroso WKS.

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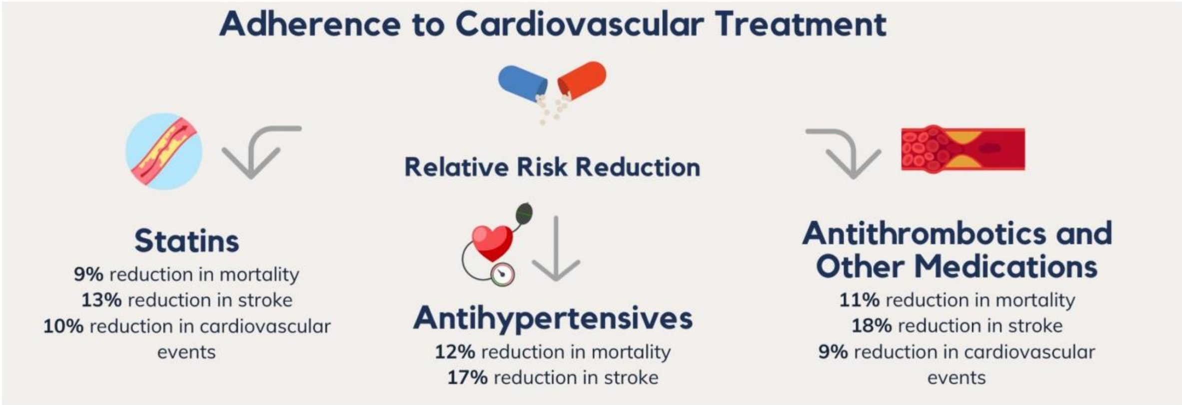

Central Illustration: Adherence to Cardiovascular Treatment.

PICO Question: In adults aged 18 and older, what are the differences in critical outcomes (death, myocardial infarction, and stroke) between patients who adhere to cardiovascular medications and those who do not?

Method: Systematic reviews of observational studies with good methodological quality and meta-analysis of observed effects.

Reference Study: Liu M. et al - (https://doi.org/10.3390/jcdd8110146)

Primary Studies Included: 46

Participants: 4,051,338 individuals

Mean Age: 60 years

Medications Evaluated: Antihypertensives, antidiabetics, antithrombotics, and statins.

Results:

	Relative Risk (all-cause mortality)	Relative Risk (stroke)	Relative Risk (cardiovascular events)	Dose-dependent effect (Y/N)
All classes (*)	RR 0.90 (0.87-0.92), 26 studies	RR 0.84 (0.81-0.87), 23 studies	RR 0.91 (0.88-0.94), 35 studies	Y
Statins (*)	RR 0.91 (0.89-0.94), 12 studies	RR 0.87 (0.84-0.91), 7 studies	RR 0.90 (0.88-0.92), 17 studies	
Antihypertensives (*)	RR 0.88 (0.82-0.94), 8 studies	RR 0.83 (0.78-0.89), 12 studies	RR 0.93 (0.84-1.03), 13 studies	
Antithrombotics and multiple medications (*)	RR 0.89 (0.84-0.94), 6 studies	RR 0.82 (0.74-0.92), 4 studies	RR 0.91 (0.84-0.98), 5 studies	

(*) RR calculated for each 20% increment in medication adherence

Effect Size: The table shows the relationship between clinical outcomes (death, stroke, and cardiovascular events) and adherence to prescribed medications, measured by Relative Risk. For example, the Relative Risk for mortality across all medication classes combined was 0.90), indicating a 10% lower chance of complications for those who adhered to their medications. The Confidence Interval (Cl) is shown in parentheses (when it exceeds 1.00 , the effect is not statistically significant).

Certainty of Evidence: Observational studies generally have low certainty of evidence according to the GRADE framework. However, in this study, the dose-dependent effect (greater adherence, greater protection) increases the certainty of evidence to moderate.

Comments: The results table clearly shows the reduction in outcomes (mortality, stroke, and cardiovascular events) among those who adhere well to the use of medications, including antihypertensives, statins, and antithrombotics, with moderate certainty of evidence. Strategies to improve adherence should be promoted by everyone directly or indirectly involved in the healthcare field.

Introduction

Cardiovascular diseases (CVD) remain a significant global health challenge and are the leading cause of mortality worldwide, responsible for an estimated 17.9 million deaths annually, accounting for 31% of all global deaths[1]. Key risk factors such as hypertension, hypercholesterolemia, diabetes, smoking, obesity and sedentary lifestyle greatly contribute to the prevalence of cardiovascular diseases and the occurrence of premature deaths. The need to implement public health strategies focused on lifestyle modifications and preventive care is crucial[2].

Economically, CVD impose a significant burden, not only due to direct healthcare expenses but also because of the indirect costs associated with lost productivity and long-term disability[3].

The aim of this systematic review is, through the search for the best available scientific evidence, to evaluate the impact of adherence to cardiovascular medication treatments on clinical outcomes. This document will support a Clinical Statement from the Brazilian Society of Cardiology on the topic.

Methods

The research question, framed in the PICO (patient/population, intervention, comparison and outcomes) format, was: in the adult population, aged 18 or over, what are the differences in clinical outcomes (death, stroke and myocardial infarction) between patients who adequately adhere or not to cardiovascular medication treatment? The protocol for this document was approved by the sponsor and is available for consultation upon request from the authors.

The rapid systematic review, which is the methodology employed in this document, belongs to the family of systematic reviews. It is a tool developed over the last decade aimed at maintaining methodological rigor while seeking the best possible evidence, but with modifications that expedite the execution time. Typically, these reviews inform medical societies or health-related institutions about the best available evidence based on a PICO-formatted question in a sensitive, transparent, and systematic manner. Leading institutions in the field of methodology have described the methods of this type of document[4,5,6].

A comprehensive search was conducted across four databases: Medline, Embase, Lilacs, and the Cochrane Library, including all records from their inception until March 1, 2024.

Two researchers independently conducted the selection of studies and the quality assessment of the systematic reviews through an initial phase where both worked together until achieving a 90% agreement rate, after which each document could be evaluated by a single author. For data extraction, one researcher extracted all predefined variables onto a spreadsheet, while the second researcher independently extracted only the effect data. The quality assessment of the systematic reviews was conducted using two specific tools (AMSTAR 2 - A Measurement Tool to Assess Systematic Reviews and The Joanna Briggs Institute (JBI) Systematic Review Checklist)[7,8], and the GRADE framework was employed to evaluate the evidence quality and determine the strength of the recommendations where feasible.

Articles selected for full reading were considered for inclusion in the study if they met the following criteria: (1) they were systematic reviews that included meta-analysis; (2) they reported risk estimates to assess the impact of adherence on major cardiovascular events (death from any cause, stroke, and myocardial infarction); (3) included patients aged 18 years or older; (4) evaluated at least one cardiovascular medication group such as antihypertensives, lipid-lowering, antithrombotic, or antiplatelet agents.

The following exclusion criteria were applied: (1) reviews that utilized fewer than two databases in their search; (2) reviews lacking detailed meta-analysis; (3) reviews that did not analyze the methodological quality of primary studies; (4) studies with low evidence quality as assessed by both tools (AMSTAR-2 and JBI). There were no language restrictions in the selection of studies.

Details of the search strategies and methodology employed in this rapid systematic review are provided in the supplementary material (Table 1S).

Results

Of the 643 identified records identified, 15 were selected for full reading as they met the eligibility criteria. At the end, four systematic reviews with meta-analyses were included (Figure 1S, supplementary material). A list of excluded studies and reasons for exclusions are presented in the supplementary material (Table 2S).

All four systematic reviews included only observational studies, as expected. One review evaluated adherence to various types of cardiovascular medications and a broader range of outcomes[9], in addition to measuring the dose-response curve between adherence and complications. This review is considered the best available evidence and serves as the basis for the conclusions of this article. The other three reviews focused exclusively on one drug group, namely, antihypertensives[10], statins[11], or aspirin[12]. Table 1 presents the main characteristics evaluated in the included studies.

Liu et al. (2021)[9] evaluated the association between vascular medication adherence and the risk of cardiovascular events, stroke, and all-cause mortality. The studies included patients in both primary and secondary prevention, involving healthy individuals, and individuals with hypertension, diabetes, dyslipidemia, and those with pre-existing CVD. The evaluated medications evaluated were lipid-lowering, antihypertensives, antidiabetics, and antithrombotic agents. The evaluated outcomes evaluated were death from all causes, stroke, and cardiovascular events (defined as any fatal or non-fatal coronary heart disease, myocardial infarction, heart failure, ischemic heart disease, or stroke or sudden cardiac death). Study-specific risk relative (RR) estimates were calculated per 20% increment of medication adherence and then pooled. Over 4 million patients distributed across 46 observational studies were included in the analysis, with quality assessment using the mean The Newcastle–Ottawa Scale score of 7.9 (maximum of 9), and an average follow-up period of 4.6 years. The analysis showed that increasing adherence to antihypertensive, lipid-lowering, and other cardiovascular medications by 20% reduced the risk of cardiovascular events by 7% [RR 0.93 (95% CI, 0.84-1.03), not significant], with the other findings demonstrating significance, 10% [RR 0.90 (0.88-0.92)], and 9% [RR 0.91 (0.84-0.98)], respectively. This increase in adherence also lowered the risk of stroke by 17% [RR 0.83 (0.78-0.89)], 13% [RR 0.90 (0.88-0.92)], and 18% [RR 0.91 (0.84-0.98)], and reduced all-cause mortality by 12% [RR 0.88 (0.82-0.94)], 9% [RR 0.91 (0.89-0.94)], and 10% [RR 0.89 (0.84-0.94)], respectively. A sensitivity and subgroup analysis performed for the various outcomes did not show any significant difference in the pooled estimates associated with good adherence to cardiovascular medication.

Lee et al. (2022)[10] conducted a systematic review and meta-analysis to estimate the global prevalence and consequences of nonadherence to antihypertensive medications among adult hypertensive patients. The analysis included several methods of measuring treatment adherence and involved 161 observational studies. This prevalence meta-analysis primarily aimed to assess blood pressure control, while also estimating secondary outcomes such as hypertension-related complications, all-cause hospitalization, and all-cause mortality. The results indicated that nonadherence to antihypertensive medications was associated with an increased odds ratio (OR) of death of 1.38 [95% CI, 1.35-1.41]. However, these results were based on only two studies with 1,653,763 patients and a median follow-up of 4.5 years. The analysis of certainty in the body of evidence, using the GRADE analysis, was deemed low for all outcomes[5]. This result stem particularly from the observational nature of the studies.

Xu et al. (2016)[11] evaluated, through a meta-analysis, the relationship between adherence to the use of statins and long-term clinical consequences in patients with CVD (secondary prevention). The primary endpoint was all-cause mortality, measured by risk ratio (Rr). The method of proportion of days covered (PDC) was used to quantify statin adherence (PDC ≥80% - good adherence and PDC <80% - poor adherence). A total of six studies were included in this meta-analysis, and the pooled risk ratio favoring good statin adherence was 0.64 (indicating a 36% reduction in the risk of death from any cause) [95% CI, 0.52-0.80]. There was statistical significance, although the wide confidence interval indicated notable imprecision.

The last meta-analysis included was that of Biondi-Zoccai et al. (2006)[12] in which the dangers inherent to aspirin withdrawal or non-compliance in subjects at risk for or with coronary artery disease were evaluated. Six studies were selected, and the result of the pooled estimate revealed that aspirin nonadherence/withdrawal was associated with a three-fold higher risk of major adverse cardiac events.

Table 2 provides the relative risk of the assessed outcomes and the number of studies included in each summarized estimate.

The result of the AMSTAR-2 analysis and the JBI critical appraisal checklist are presented in Tables 3S and 4S (supplementary material). Despite the differing results between these two tools, the authors deemed the overall quality of the four included systematic reviews to be satisfactory.

The authors performed a separate GRADE assessment for the study by Liu et al. (2021)[9], based on the risk of bias and the characteristics extracted from the study. This evaluation addressed all the drug groups and the various outcomes. In nearly all instances, the evidence achieved a moderate level of certainty, largely due to the presence of a dose-response gradient. However, the certainty of the evidence for cardiovascular event (CVE) outcomes associated with hypertensive medications was deemed very low. This assessment was based on the imprecision of the relative risk (RR) estimates, which intersected the null effect line. Consequently, it was recommended not to increase the certainty score for these specific outcomes

The evidence summary table is presented in the supplementary material (Table 5S).

The Central Illustration graphically presents the relative risk reduction when medication adherence to the three classes studied is increased by 20%, based on the information from the reference article.

Discussion

Medication adherence is a significant health issue today, and the Brazilian Society of Cardiology has taken a pioneering approach by addressing this topic, seeking the best scientific evidence to support their position statement.

Answering the questions posed for this review is not a simple task. It was anticipated that there would be no clinical trials on this topic, as it is not feasible to randomize patients to adhere or not adhere to cardiovascular medications with proven benefits. Therefore, it was necessary to use systematic reviews of observational studies, which start with a low degree of certainty of evidence but attempt to aggregate the results of multiple studies in order to improve confidence in the effect estimate.

Additionally, it was expected that these studies on adherence would exhibit significant heterogeneity for multiple reasons: the wide variety of methods for measuring adherence, the different groups of cardiovascular medications, the diverse populations (primary vs. secondary prevention, adults vs. elderly, etc.), the plurality of clinical outcomes, and the varying quality of the studies, among other possibilities.

Medication adherence is often quantified using various cutoff points and categorized into distinct levels, providing essential insights into patient behavior and treatment efficacy. Adherence is typically categorized based on percentage thresholds reflecting the proportion of prescribed doses a patient takes over a specific period. Commonly, "high adherence" is defined as taking 80% or more of the prescribed doses, "medium adherence" as taking 50-79%, and "low adherence" as taking less than 50%. These thresholds are extensively utilized in clinical research to assess intervention effectiveness and are crucial for understanding their impact on clinical outcomes[13]. The reference study by Liu et al. evaluated the impact of a 20% increase in medication adherence (for instance, from 80% - the most used cutoff in the literature to distinguish good adherence - to 100%). The study demonstrated a significant decrease in major cardiovascular outcomes when the cardiovascular drugs were used as prescribed.

A meta-analysis examining statin therapy revealed that adherence rates at one year of follow-up differed significantly between study designs: 49.0% in observational studies compared to 90.3% in randomized controlled trials. This discrepancy suggests that adherence in randomized RCTs, where there is greater control, may be overestimated compared to reality.[14]

These adherence cutoffs are employed across various medication types, including both chronic and acute therapies, to standardize research methodologies and enable meaningful comparisons. For example, the World Health Organization indicates that adherence levels above 80% are generally required to achieve optimal therapeutic outcomes in most chronic conditions[15]. However, certain conditions demand more specific adherence rates; for instance, antiretroviral therapy for HIV may require adherence levels as high as 95% to effectively suppress viral loads[16]. While these thresholds are pivotal for research uniformity, their applicability can vary based on the therapeutic window of the medication, the specific health condition, and individual patient factors. This variability underscores the need for adherence strategies that are tailored to maximize patient outcomes, suggesting a more nuanced application of these metrics depending on the therapeutic requirements and patient circumstances.

Establishing the multifaceted barriers to adherence is essential for optimizing cardiovascular outcomes. Factors such as patient-related issues (e.g., forgetfulness, beliefs about medication, perceived side effects), socioeconomic challenges (e.g., medication cost, patient education), and healthcare system obstacles (e.g., complex medication regimens, lack of follow-up) must be systematically addressed to enhance adherence rates[15,17]. Different models and theories attempt to address the complexities underlying these behaviors. For example, the Health Belief Model suggests that patient perceptions of the severity of their condition, the potential benefits of treatment, and barriers to care can influence adherence and persistence[18]. Furthermore, the World Health Organization identifies some factors that impact adherence, categorizing them into patient-related, condition-related, therapy-related, socioeconomic, and healthcare system factors [15]. Patient education, simplified drug regimens, and improved healthcare provider-patient communication are essential for enhancing adherence and ultimately improving clinical outcomes in CVD management[17].

One aspect warranting also consideration in medication adherence studies is dosage intensity. For example, one investigation evaluated adherence across different statin intensity levels — low, moderate, and high. The findings indicated that adherence rates at 12 months were 57.2% for low-intensity statins, 46.5% for moderate-intensity statins, and 37.9% for high-intensity statins, with adherence defined as achieving at least 80% medication compliance[19]. A further study identified a statistically significant disparity in adherence between low and high-dosage statins, suggesting that regimes involving high-intensity statins are linked to reduced adherence compared to those involving lower-intensity statins[20]. This observation appears to contradict a more recent article, which posits that following the introduction of new American College of Cardiology/American Heart Association (ACC/AHA) guidelines, a higher proportion of patients with atherosclerotic CVD are not only prescribed high-intensity statins but are also more likely to adhere to their treatment regimen[21].

Another aspect on this subject is the use of fixed-dose combination (FDC) therapy, which has emerged as a promising strategy to enhance medication adherence in patients with CVD. FDC therapy simplifies the treatment regimen by combining multiple medications into a single pill, which can reduce pill burden and improve patient compliance. Studies have demonstrated that FDC therapy is associated with higher adherence rates and better clinical surrogate outcomes compared to multiple-pill regimens. For instance, a study found that patients on FDC therapy had a 24% higher adherence rate and significantly improved blood pressure control[22]. Similarly, a meta-analysis reported that FDC therapy led to a 26% reduction in the risk of nonadherence and better management of cardiovascular risk factors[23]. These findings indicate the potential benefits of FDC therapy in optimizing cardiovascular treatment and enhancing patient adherence.

This review is not free of limitations. Firstly, only systematic reviews that included observational studies were selected. Observational studies, by their nature, have a greater margin of imprecision, primarily due to unmeasured or even unknown confounding factors. This justifies the requirement for primary studies to identify and adjust for confounding factors deemed important, and for systematic reviews to assess the quality of the primary studies, ideally including only high-quality research. Because some of the selected documents did not meet these criteria, they were excluded from our review.

Secondly, given the Brazilian Society of Cardiology's interest in various classes of cardiovascular medications and critical clinical outcomes, as well as the significant variability in adherence measurement methods, substantial heterogeneity among the studies was anticipated. In reference to the document by Liu et al.[9], it was decided not to penalize the study for heterogeneity, despite the Cochran Q and I^2 statistics indicating significant variability across studies. It presented similar effect estimates with consistent direction when analyzing the different medication groups by outcome. Furthermore, the confidence intervals demonstrated overlap, and several subgroup analyses did not alter the overall results, nor did the sensitivity analysis. Despite the heterogeneity being only partially explained, the potential benefits of good adherence to effective cardiovascular medications are substantial and should not be underestimated. The decision not to penalize the GRADE assessment in relation to this characteristic may not be unanimous.

Finally, regarding the assessment of the certainty of evidence using the GRADE tool, ideally, it should be conducted by the authors in each systematic review with meta-analysis. However, of the four studies included, only one presented such an analysis. In the reference study, this assessment was conducted based solely on the extracted information, without access to the primary sources.

While robust evidence supports reductions in hard endpoints in both primary and secondary prevention through the control of clinical variables such as blood pressure[24,25] and LDL-cholesterol concentrations[26,27], as well as the benefits of antiplatelet therapy in atherosclerotic disease[28], there remains a scarcity of studies demonstrating correlations between adherence to cardiovascular medications and attenuation of critical clinical outcomes.

Despite the limitations inherent to observational studies, the evidence of the risks of poor medication coverage reinforces the global need to implement strategies that improve adherence to cardiovascular treatments.

Conclusion

This systematic review demonstrates the significant impact of good adherence to cardiovascular medication treatment on clinical outcomes.

According to the GRADE methodology, there is moderate certainty of evidence that patients who adhere to their prescribed cardiovascular medications experience a reduction in death, stroke, and cardiovascular events compared to individuals with lower adherence.

Table 1 – Characteristics of studies included in the rapid review

Author/Year	Nº of studies included	Type of studies	Medication	Outcomes	Population	Adherence measure	Participants (n)	Median age	Female (%)	Funding
Liu/2021[9]	46	Observational	Statins, anti-hypertensive, antidiabetics, and antithrombotic agents	Cardiovascular events, stroke, and all-cause mortality	Hypertension / Dyslipidemia	MPR, PMC, CMA, PDC	4,051,338	60.1	44	No
Lee/2022[10]	161	Observational	Anti-hypertensive agents	Death and hospitalization	Patients with hypertension, >18 years; excluded: pregnant resistant hypertension	4-itemor 8-item MMAS, pill counting, prescription refills, electronic pill boxes, biochemical	27,785,595	57	57.1	No

						assays, or electronic medication monitoring				
Xu/ 2016[11]	6	Observational	Statin	All-cause mortality recurrence of CVD and revascularizetion	CVD	PDC	38,301	NR	NR	No
Biondi-Zoccai/ 2006[12]	6	Observational	Aspirin	Cardiovascular events	Patients at risk for or with CAD	NR	50,279	NR	NR	NR

CAD: coronary artery disease; CMA: cumulative medication adherence; CVD: cardiovascular disease; MMAS: Morisky Medication Adherence Scale; MPR: medication possession ratio; NR: not reported; PDC, Proportion of Days Covered; PMC: proportion of months covered by prescribed. Source: Authors.

Table 2 – Results of the meta-analysis of the included studies

Main author / Year	**Medication group**	**All-cause mortality** Measure (95% CI)	**Nº of studies**	**Stroke** Measure (95% CI)	**Nº of studies**	**Cardiovascular events** Measure (95% CI)	**Nº of studies**	**Dose-response effect**
Liu/ 2021[9]	Any cardiovascular medications*	RR 0.90 (0.87-0.92)	26	RR 0.84 (0.81-0.87)	23	RR 0.91 (0.88-0.94)	35	Yes
	Lipid-lowering agents*	RR 0.91 (0.89-0.94)	12	RR 0.87 (0.84-0.91)	7	RR 0.90 (0.88-0.92)	17	Yes

	Antihypertensives*	RR 0.88 (0.82-0.94)	8	RR 0.83 (0.78-0.89)	12	RR 0.93 (0.84-1.03)	13	Yes
	Others*†	RR 0.89 (0.84-0.94)	6	RR 0.82 (0.74-0.92)	4	RR 0.91 (0.84-0.98)	5	Yes
Lee/ 2022[10]	Antihypertensives	RR 0.75 (0.73-0.76) ‡	2	NR	-	NR	-	No
Xu/ 2016[11]	Statins	RR 0.64 (0.52-0.80)	6	NR	-	NR	-	No
Biondi-Zoccai/ 2006[12]	Aspirin	NR	-	NR	-	RR 0.37 (0.24-0.60) §	6	No

(*) RR calculated for each 20% increase in medication adherence. (†) Others: antithrombotic and multiple medications

(‡) inverse relative risk, calculated from the original Odds Ratio result (1.38 [CI 1.35-1.41]) and a weighted baseline probability of 8.01% of events over the follow-up period.

(§) inverse relative risk, calculated from the original Odds Ratio result (3.14 [1.75-5.61]) and a weighted baseline probability of 7.5% of events over the follow-up period.

NR: not reported; OR: odds ratio; RR: relative risk; Rr: risk ratio. The statistical significance level adopted across all studies was 5%. Source: Authors.

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Supplemental Material

1. Methodology details of the rapid systematic review.

Literature search:

A comprehensive search was conducted in four databases: Medline, Embase, Lilacs, and the Cochrane Library, covering all records from inception up to the access date (March 1, 2024). The type of evidence consisted of systematic reviews, for which filters for this type of review were used in the different databases.

Data management and selection:

All search strategies and selection processes were conducted using Rayyan software, with other documents stored in PDF or Microsoft formats in OneDrive, accessible to editors and researchers.

Rayyan's automatic detection feature was used to find duplicates at the beginning of the review, setting the agreement threshold at 95%. To ensure consistency, two independent reviewers (BB and LL) screened 10% of the studies by titles and abstracts, continuing this collaborative review until a 90% consensus was reached. Subsequently, one reviewer completed the evaluation of the remaining studies.

For quality assurance, two researchers re-evaluated either 10% or a minimum of two full-text documents of potentially eligible studies, specifically focusing on identifying systematic reviews that included meta-analyses. This paired review continued until a 90% consensus was again achieved. Thereafter, the selection process was concluded by one investigator.

Data and outcomes:

Data from the selected systematic reviews were meticulously extracted by a skilled methodologist into a comprehensive results spreadsheet. A second researcher verified the accuracy of this data, ensuring the reliability of our findings. This dual-step validation process aimed to uphold the highest precision in our analysis. Data collected included the principal author, publication year, studied population, medication type, study origin, funding sources, participant median age, female participant percentage, the total number of participants and events, adjustments of primary studies for confounders, and application of quality assessment tools.

The review focused on major cardiovascular events (death, myocardial infarction, and stroke) as critical outcomes.

Risk of bias in individual studies and certainty of the evidence:

The methodological quality of included systematic reviews was assessed by the two researchers, independently, using the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) tool and The Joanna Briggs Institute (JBI) Systematic Review Checklist. Both methods were published in 2017 to evaluate the quality of systematic reviews. They assess different characteristics, and thus, produce results and insights that can be complementary. The GRADE framework was used to evaluate the quality of evidence and determine the strength of the recommendations where feasible.

Table 1S – Bibliographic search strategy

Base	Search strategy	Recovered registries
Medline	(((((((("Cardiovascular Agents"[Mesh]) OR "Antihypertensive Agents"[Mesh]) OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR "Diuretics"[Mesh]) OR "Adrenergic beta-Antagonists"[Mesh]) OR "Adrenergic alpha-Antagonists"[Mesh]) OR "Vasodilator Agents"[Mesh]) OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]) OR "Aspirin"[Mesh]) AND ("adherence" OR "medication adherence" [Mesh] OR "patient compliance" [Mesh] OR "persistence" [Title/Abstract]) Filter: Systematic Review	195
EMBASE	#1 'medication adherence assessment'/exp OR 'medication adherence assessment' OR 'patient compliance'/exp OR 'patient compliance' OR 'persistence'/exp OR 'persistence' OR 'adherence'/exp OR 'adherence' #2 'cardiovascular agent' OR 'antihypertensive agent' OR 'dipeptidyl carboxypeptidase inhibitor' OR 'diuretic agent' OR 'beta adrenergic receptor blocking agent' OR 'alpha adrenergic receptor blocking agent' OR 'vasodilator agent' OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor' OR 'acetylsalicylic acid' #3 #1 AND #2 #4 #3 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) #5 #4 AND ('meta analysis'/de OR 'systematic review'/de)	382
LILACS e BDENF	Mh: ("Cardiovascular Agents" OR "Antihypertensive Agents" OR "Angiotensin-Converting Enzyme Inhibitors" OR "Diuretics" OR "Adrenergic beta-Antagonists" OR "Adrenergic alpha-Antagonists" OR "Vasodilator Agents" OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors" OR "Aspirin") AND (tw:("adherence" OR "persistence") OR mh:("medication adherence" OR "patient compliance")) Filter: Systematic Review	6
COCHRANE (CENTRAL)	#1 MeSH descriptor: [Medication Adherence] explode all trees #2 MeSH descriptor: [Patient Compliance] explode all trees #3 MeSH descriptor: [Medication Adherence] explode all trees #4 adherence OR #1 OR #2 OR #3 #5 MeSH descriptor: [Cardiovascular Agents] explode all trees #6 MeSH descriptor: [Antihypertensive Agents] explode all trees #7 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees #8 MeSH descriptor: [Diuretics] explode all trees #9 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees #10 MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees #11 MeSH descriptor: [Vasodilator Agents] explode all trees #12 MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees #13 MeSH descriptor: [Aspirin] explode all trees #14 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 #15 #4 AND #14 #16 "Systematic Review" OR "meta-analysis" #17 #15 AND #16	60
Total		643

Figure 1S – PRISMA flowchart

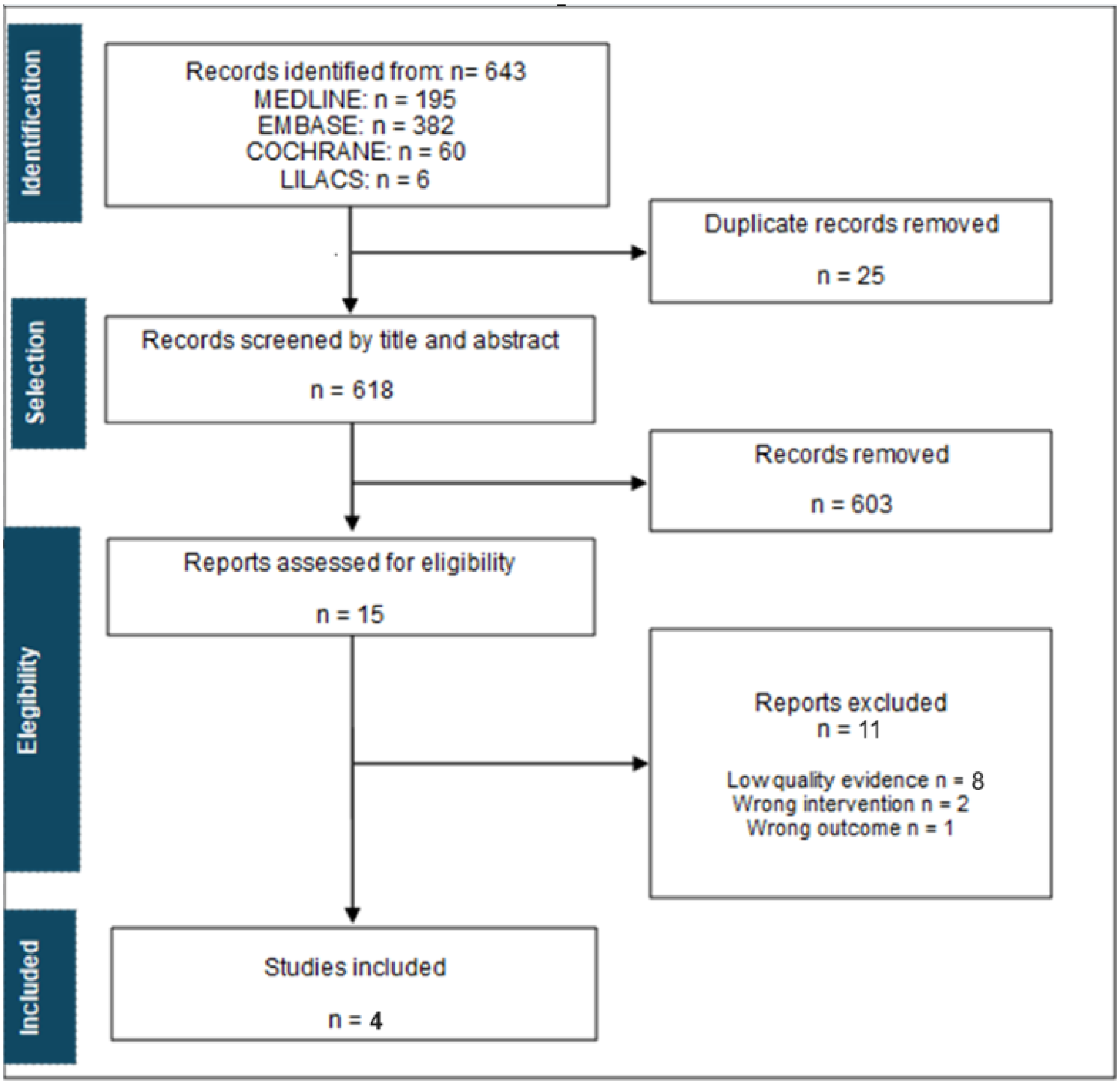

Table 2S – Excluded studies and reasons for exclusion

Author / Year	Title	Reasons for exclusion
Kengne /2024	Impact of poor medication adherence on clinical outcomes and health resource utilization in patients with hypertension and/or dyslipidemia: systematic review.	Low quality evidence
Li/ 2023	The Increased Ischemic Risk During the Early Period After Clopidogrel Noncompliance in Patients with Acute Coronary Syndrome: A Meta-Analysis	Wrong outcome
Tsigkas/ 2022	Real-world implementation of guidelines for heart failure management: A systematic review and meta-analysis.	Wrong intervention. Evaluated the rate of patients who received guideline-guided treatments and assessed the association of under-treatment patients with the composite

		outcome of rehospitalization and mortality
Elnaem/ 2020	Impact of medication regimen simplification on medication adherence and clinical outcomes in patients with long-term medical conditions	Wrong intervention. This study aims to identify interventions used to reduce medication regimen complexity and to assess their impact on medication adherence and clinical outcomes.
Martin-Ruiz/2018	Systematic Review of the Effect of Adherence to Statin Treatment on Critical Cardiovascular Events and Mortality in Primary Prevention.	Low quality evidence
Deshpande/ 2017	A systematic review to assess adherence and persistence with statins.	Low quality evidence
De Vera/ 2014	Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review.	Low quality evidence
Bitton/ 2013	The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review.	Low quality evidence
Chowdhury/ 2013	Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences.	Absence of analysis of methodological quality
Gomez Sandoval/ 2011	Statin discontinuation in high-risk patients: a systematic review of the evidence.	Low quality evidence
Simpson Jr/ 2010	The effects of adherence and persistence on clinical outcomes in patients treated with statins: a systematic review.	Low quality evidence

Table 3S – Appraisal of methodological quality of systematic reviews with AMSTAR-2 tool.

AMSTAR 2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	OVERALL
Lee 2022	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	**Low**
Liu 2021	Y	N	Y	PY	N	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	**Critically low**
Xu 2016	Y	Y	Y	PY	N	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	**Critically low**
Chowdhury 2013	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	N	N	Y	Y	Y	**Critically low**
Biondi-Zoccai 2006	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	**Critically low**

AMSTAR-2 critical domains appear in red.

Table 4S – Appraisal of methodological quality of systematic reviews with Joanna Briggs Institute Systematic Reviews Checklist.

JBI Checklist	1	2	3	4	5	6	7	8	9	10	11	
Lee 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**Include**

Liu 2021	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Include
Xu 2016	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Include
Biondi-Zoccai 2006	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Include

Table 5S – Summary of evidence Summary of evidence for evaluating adherence to treatment with any cardiovascular medications, lipid-lowering agents, hypertensive medications and other medications.

Setting:
Adherence of cardivascular medications in healthy, hypertensive, hypercholesterolemia, diabetic and know prior CVD patients.
Bibliography: Liu et al. 2021

Question:
20% increment of any cardiovascular medication compared to any cardiovascular medication for cardiovascular outcomes

Certainty assessment							Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)		
All-cause mortality									
26	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.90** (0.87 to 0.92)	⊕⊕⊕◯ Moderate	CRITICAL
Stroke									
23	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.84** (0.81 to 0.87)	⊕⊕⊕◯ Moderate	CRITICAL
Cardiovascular events									
35	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.91** (0.88 to 0.94)	⊕⊕⊕◯ Moderate	CRITICAL

Question:
20% increment of lipid-lowering agents compared to lipid-lowering agents for cardiovascular outcomes

Certainty assessment							Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)		
All-cause mortality									
12	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.91** (0.89 to 0.94)	⊕⊕⊕◯ Moderate	CRITICAL
Stroke									
7	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.87** (0.84 to 0.91)	⊕⊕⊕◯ Moderate	CRITICAL
Cardiovascular events									
17	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.90** (0.88 to 0.92)	⊕⊕⊕◯ Moderate	CRITICAL

Question:
20% increment of hypertensive medication compared to hypertensive medication for cardiovascular outcomes

Certainty assessment							Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)		

Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Certainty	Importance
All-cause mortality									
8	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.88** (0.82 to 0.94)	⊕⊕⊕◯ Moderate	CRITICAL
Stroke									
12	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.83** (0.78 to 0.89)	⊕⊕⊕◯ Moderate	CRITICAL
Cardiovascular events									
13	non-randomised studies	not serious	not serious	not serious[a]	serious[b]	dose response gradient	**RR 0.93** (0.84 to 1.03)	⊕◯◯◯ Very low	CRITICAL

Question:
20% increment of other medication compared to other medication for cardiovascular outcomes

Certainty assessment							Effect	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)		
All-cause mortality									
6	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.89** (0.84 to 0.94)	⊕⊕⊕◯ Moderate	CRITICAL
Stroke									
4	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.82** (0.74 to 0.92)	⊕⊕⊕◯ Moderate	CRITICAL
Cardiovascular events									
5	non-randomised studies	not serious	not serious	not serious[a]	not serious	dose response gradient	**RR 0.91** (0.84 to 0.98)	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Although studies involved different adherence measurement strategies, subgroup analyzes demonstrated that there was practically no change in the effect estimate and, therefore, it was decided not to downgrade in this domain of indirectness.
b. Result crosses the null effect line