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Methods and validity indicators for measuring adherence to statins in secondary cardiovascular prevention: a systematic review

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Abstract

Background Adherence to statin therapy is crucial for reducing the recurrence of cardiovascular events. Numerous methods exist to measure medication adherence, including those based on prescription data, patient self-report, medication counting, and direct methods. It is important to determine which of these methods are appropriate for use in clinical practice. This systematic review aimed to identify the methods used to measure adherence and persistence to statins in patients undergoing cardiovascular secondary prevention and to evaluate the validity indicators of these methods.

Methods This systematic review included studies reporting methods to measure adherence and/or persistence to statins in cardiovascular secondary prevention. Medline, Embase, and Scopus databases were searched from inception to February 2025. Rayyan was used for the study selection and extraction data processes. Validity indicators of the adherence/persistence methods were collected; it was reported. Risk of bias of studies reporting the method validity was evaluated using the COSMIN (Consensus-based Standards for the Selection of Health Measurement Instruments) tool.

Results A total of 77 studies were included. Regarding adherence measurement, the most frequently used method was prescription refill records ($n=55$) and self-report methods ($n=20$). Electronic monitoring methods ($n=2$), self-perceived adherence by physician ($n=1$), and pill counting ($n=1$) were less frequently used methods. Direct methods, using HPLC–MS/MS, were used in combination with other indirect methods ($n=5$). For measuring persistence, prescription refill records were the predominant method ($n=9$), while self-report methods were used in three studies, and one study used a standardized questionnaire. Several of the indirect methods have validity indicators for measuring adherence in different study populations and to different medications. Only one study provides validity indicators for the MAT questionnaire specifically adapted for statins.

Conclusions The methods for measuring adherence to statins in secondary cardiovascular prevention were predominantly indirect, relying on prescription and supply records and self-report methods. Pill counting, electronic monitoring, and direct measurement via LC–MS/MS were less commonly used. Persistence was primarily measured through prescription refill records. None of the indirect methods was validated; thus, their use for measuring

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adherence to statins is not recommended. There is a need for new validated tools, incorporating a gender perspective, to measure adherence to statins in this population.

Systematic review registration PROSPERO CRD42023463981.

Keywords Cardiovascular diseases, Secondary prevention, Hydroxymethylglutaryl-CoA reductase inhibitors, Medication adherence, Patient compliance

Background

Cardiovascular diseases (CVDs) are among the most prevalent conditions worldwide, contributing to significant morbidity and mortality [1, 2]. The World Heart Federation (WHF) [3] estimates that approximately 35 million people experience a cardiovascular event each year. CVDs not only lead to a substantial decline in quality of life but also impose a heavy economic burden on healthcare systems [4]. The pathogenesis of these diseases is influenced by a range of risk factors, including modifiable and non-modifiable ones [5]. The inadequate control of cardiovascular risk factors has shifted attention toward secondary cardiovascular prevention. This approach combines lifestyle changes and pharmacological measures to reduce the risk of recurrence in patients who have already experienced a cardiovascular event [1, 6].

Dyslipidemia is a key focus in cardiovascular secondary prevention, with statin therapy recommended by the AHA/ACCF [7] alongside lifestyle changes [8]. However, despite its benefits, ensuring proper medication use is challenging, as studies show that only about 50% of patients in high-income countries adhere to their prescribed treatments [9, 10]. Poor adherence leads to worse disease management, lower survival rates, higher recurrence risks, reduced quality of life, and increased healthcare costs [11].

The World Health Organization (WHO) defines therapeutic adherence as "the extent to which a person's behavior—taking medications, following a diet, and/or making lifestyle changes—corresponds with the agreed recommendations from a healthcare provider." The WHO also emphasizes that improving adherence may be the most cost-effective strategy for managing chronic conditions [10]. Specifically, medication adherence is defined as "the process by which patients take their medications as prescribed, comprising initiation, implementation, and discontinuation" [12]. Medication adherence is a multifactorial phenomenon shaped by five interrelated domains [13] related to patient characteristics such as age, employment status, socioeconomic conditions, culture, educational level, geographic area, and race [14, 15]; social and familial support [16]; disease characteristics; therapeutic regimen; and healthcare system conditions, including healthcare professional characteristics [17, 18].

Treatment efficacy depends not only on daily drug intake but also on long-term continuation. Persistence, which refers to the time between the initiation of treatment and the last dose taken before discontinuation, measures how long a patient continues the medication according to the intended duration. It is typically measured as the proportion of days a patient adheres to the treatment or the average time until therapy discontinuation [12, 19].

Methods for measuring medication adherence are generally classified as direct or indirect. Direct methods include techniques such as directly observed therapy (DOT), therapeutic drug monitoring (TDM), and ingestible sensor-based systems. These methods are objective, specific, and highly accurate but are often costly and impractical for routine clinical practice. Indirect methods, on the other hand, include patient self-report questionnaires, pill counts, calculations of the proportion of days covered (PDC) or the medication possession ratio (MPR) based on dispensing records, and medication event monitoring systems (MEMS), among others [19–21]. Patient self-report questionnaires based on clinical interviews are particularly popular in clinical practice. While this approach has limitations—including subjectivity, recall bias, and response bias due to its reliance on self-reported data—it remains widely adopted because of its practicality, simplicity, and cost-effectiveness [20].

Notable self-report questionnaires include the Haynes-Sackett Test [22], the Morisky-Green Test [9, 10], and the 8-item Morisky Medication Adherence Scale (MMAS-8) [19–21, 23]. The MMAS-8, in particular, is one of the most widely used tools in clinical practice. However, despite being validated for use in populations and conditions different from its original context [24–26], the MMAS-8 has often been applied without prior validation, resulting in evidence of its limitations in certain populations, such as patients with type 2 diabetes in Spain [27]. Furthermore, the original study on the MMAS-8 was recently retracted due to inconsistencies in its reported sensitivity and specificity values [23]. Therefore, although questionnaires like the MMAS-8 are valuable in clinical practice, it is essential to consider their limitations and

the need for contextual-specific validations before their application, particularly in diverse populations and conditions different from the original ones [28]. This systematic review aimed to identify the methods used in research to measure adherence and persistence to statins in patients undergoing secondary cardiovascular prevention. It also sought to evaluate the validity and accuracy indicators of these methods.

Materials and methods

The protocol for this systematic review was registered in PROSPERO (Reference: CRD42023463981), and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [29] guidelines were followed to report the methodology and results. The Office of Responsible Research of the University Miguel Hernández approved the study (Reference: TFG.GME.VFGG.MMM.231103).

Eligibility criteria

This review included studies that measured adherence or persistence to any type of statin and reported the methods used. Studies that evaluated adherence or persistence to statins in combination with other treatments were excluded. Regarding the study population, articles were selected if they included individuals aged 18 and older undergoing secondary cardiovascular prevention. Conditions considered for secondary prevention included ischemic heart disease, acute myocardial infarction, stroke, cerebral hemorrhage, transient ischemic attack, renal failure, heart failure, peripheral artery disease, dissecting aortic aneurysm, and diabetic or hypertensive retinopathy. All participants had to be receiving statin therapy. Eligible study designs included observational studies (cross-sectional, case–control, and cohort studies) and experimental studies. Excluded materials comprised letters, editorials, case reports, reviews, opinion articles, abstracts, conference papers, study protocols, non-scientific studies, and those written in non-Latin alphabet languages.

Sources of information and search strategy

The databases Medline, Embase, and Scopus were searched to retrieve relevant studies. Articles published from the inception of each database until February 28, 2025, were included, with no language restrictions except for the requirement that studies be written in Latin alphabet. The search strategy combined controlled vocabulary and free text terms, including "Treatment Adherence and Compliance," "Medication Adherence," "Hydroxymethylglutaryl-CoA Reductase Inhibitors," "Cardiovascular Diseases," and "Acute Coronary Syndrome." Filters were applied for publication type and population age. The complete search strategies for each database are detailed in Supplementary Material 1.

Study selection

Articles identified were exported to the Rayyan platform for screening. After automatic detection of duplicates, manual removal was performed. Two independent researchers conducted a two-stage screening process: (1) title and abstract review and (2) full-text eligibility assessment. Discrepancies were resolved by consulting a third researcher. For studies with restricted access, university library services were utilized; studies that remained inaccessible were excluded from the review.

Data collection

Data from eligible studies were extracted by one researcher and verified by another. Extracted data included author, year, location, study design, population characteristics, whether adherence, persistence, or both were measured (considering adherence as the degree to which patients follow the prescribed dosage frequency and persistence as the continuity of medication use over time without interruption), sample size, study setting, type of statin for which adherence or persistence was measured, methods used for measurement (type and description), criteria for defining a patient as adherent/persistent or non-adherent/non-persistent, validity indicators of measurement methods (if available), and psychometric properties of the adherence questionnaire (if available).

Risk of bias

The primary objective of this review was to identify the methods used to measure adherence and persistence to statins in patients undergoing cardiovascular secondary prevention, without focusing on clinical outcomes or intervention effectiveness. Therefore, a formal risk of bias or methodological quality assessment of the included studies was deemed unnecessary, as these aspects do not directly impact the primary objective of this review, which centers on identifying measurement methods. However, for studies assessing the validity of the method in question, risk of bias was evaluated using the COSMIN (Consensus-based Standards for the Selection of Health Measurement Instruments) tool [30]. This was due to the fact that these studies provide key data (validation indicators) that may be influenced by methodological design quality, which is essential for the reliability of the identified adherence methods.

Data synthesis

A descriptive synthesis summarized study characteristics, and a narrative synthesis detailed the measurement methods for adherence and persistence separately. Validity indicators of validated methods and psychometric properties of questionnaires were tabulated. Due to insufficient studies reporting validity indicators for statin adherence measurement methods, a meta-analysis was not feasible. A meta-analysis was not feasible due to the insufficient number of studies reporting validated methods for measuring statin adherence. The lack of validated methods compromises data reliability and comparability, increasing heterogeneity and the risk of bias. Without standardized, validated measurement tools, pooling data would not yield meaningful or accurate conclusions.

Results

Following the database search, 1488 articles were identified, and after duplicate removal, 1340 titles and abstracts were screened. Of these, the full texts of 144 studies were assessed for eligibility, leading to the inclusion of 77 articles in this systematic review. The most common reason for exclusion was failure to meet the inclusion criteria for the study population. Figure 1 provides the PRISMA flow diagram [29], which details the study selection process.

The general descriptive characteristics of the articles are presented in Table 1. The included articles were published between 2002 and 2023. Most studies were conducted in the USA ($n=25$), followed by other countries such as Canada ($n=6$), the UK ($n=5$), and Taiwan ($n=3$). Regarding study design, cohort studies predominated ($n=45$), followed by experimental studies

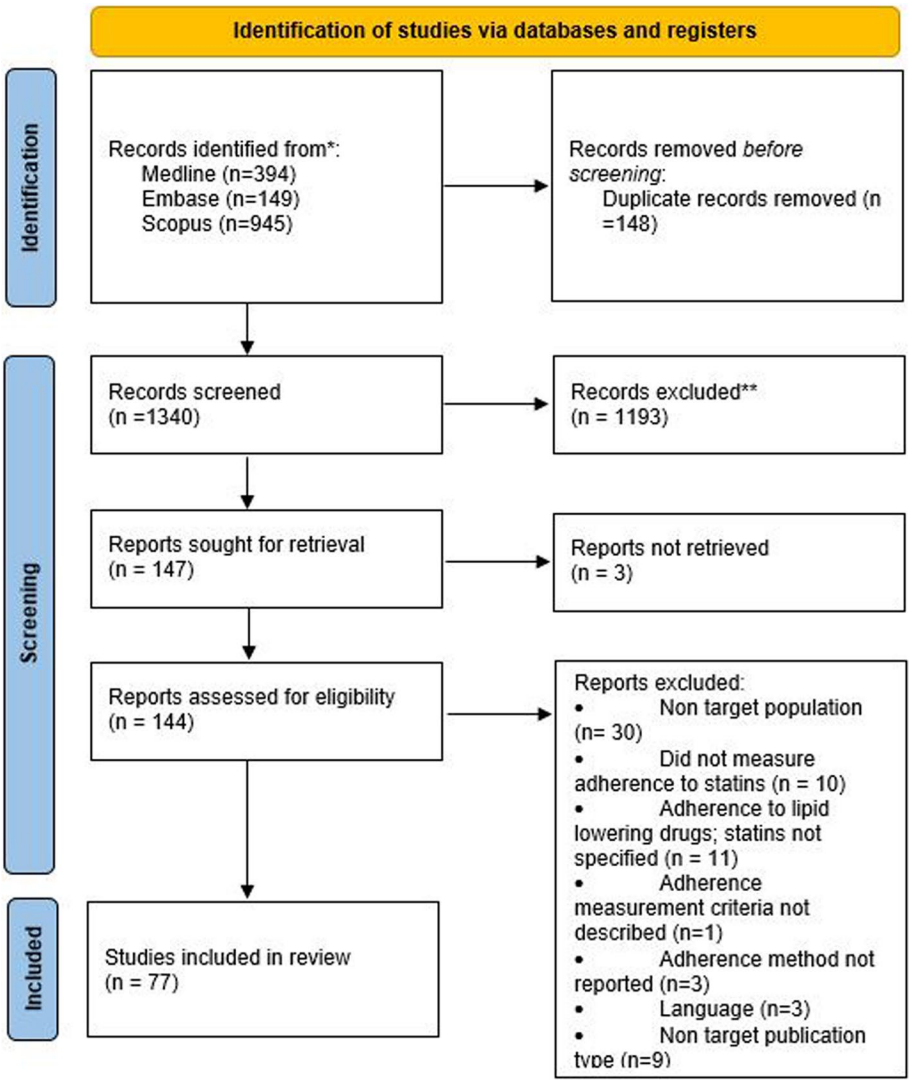

Fig. 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. Source: Page MJ, et al. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.814.

Table 1 General descriptive characteristics of the studies included in the review ($n=77$)

First author and publication year	Study location	Study design	Study population	Study setting	Adherence/persistence?	Sample size
Ali M, 2023 [24]	New Zealand	Cohort	Patients aged 35–84 years with ACS	Hospital	Adherence	30,452
Allonen J, 2012 [25]	Finland	Cohort	ACS patients undergoing CA	Hospital	Adherence and persistence	2091
Alsabbagh W, 2017 [26]	Canada	Cohort	Patients aged ≥ 30 who suffered an ACS after AH	Hospital	Adherence	9051
Al-Khadra S, 2014 [31]	Germany	RCT	Patients aged ≥ 65 discharged from HA after a first or recurrent AMI	Hospital	Persistence	259
Bell KJ, 2011 [32]	Australia and New Zealand	RCT	Patients 31–75 with high cholesterol and a history of AMI/UA	Outpatient clinic	Adherence	9014
Blackburn DF, 2005 [33]	Canada	Cohort	Patients aged 30–70 (first cardiovascular event in the last year)	Outpatient and inpatient setting	Adherence	1221
Booth JN, 2017 [34]	USA	Cohort	Patients aged ≥ 66 and ≤ 110 who suffered AMI	Hospital	Persistence	158,795
Brogaard HV, 2012 [35]	Denmark	Cohort	Patients discharged from HA after diagnosis of AMI	Hospital	Adherence	474
Brown R, 2021 [36]	UK	Cohort	Patients ≥ 18 years (HA for AMI)	Hospital	Adherence	11,031
Carey IM, 2012 [37]	UK	Cohort	Patients aged 30–84 after their first AMI	Outpatient clinic	Persistence	6988
Chan V, 2008 [38]	USA	Retrospective cohort study	Adults aged 18–64 years, discharged after MI	Inpatient and outpatient	Adherence	387
Chen PS, 2016 [39]	Taiwan	Cohort	Patients ≥ 18 years of age admitted for acute ischemic stroke or TIA	Hospital	Adherence	5354
Chen ST, 2019 [40]	Taiwan	Cohort	Patients aged 20–100, who were discharged from hospital for a new ASCVD episode, and initiated a statin within 90 days after hospital discharge	Hospital	Adherence and persistence	185,252
Chi MD, 2014 [41]	USA	Cross-sectional	Patients ≥ 18 years with a diagnosis of CAD	Outpatient and inpatient	Adherence	67,100
Choudhy NK, 2011 [42]	USA	RCT	Patients under 65 years of age with a diagnosis of AMI	Outpatient clinic	Adherence	5855
Chow CK, 2022 [43]	Australia	RCT	Patients with ACS, with mobile phone and reading ability	Outpatient clinic	Adherence	1424

Table 1 (continued)

First author and publication year	Study location	Study design	Study population	Study setting	Adherence/persistence?	Sample size
Chung PW, 2018 [44]	South Korea	Cohort	Patients ≥ 20 years with a diagnosis of acute ischemic stroke or TIA	Hospital	Adherence	991
Coberley C, 2008 [45]	USA	Observational	Patients with CHD and/or HF enrolled in disease management programs	Outpatient clinic	Adherence	20,202
Colantonio LD, 2017 [46]	USA	Cohort	Patients > 66 years hospitalized for MI, prescribed statins within 30 days of discharge	Hospital	Adherence and persistence	57,888
Cooke CE, 2006 [47]	USA	Cohort	Patients with chronic arterial disease	Outpatient and inpatient	Adherence and persistence	2095
Di Martino M, 2016 [48]	Italy	Cohort	Patients hospitalized with incident myocardial infarction (MI)	Hospital	Adherence	9606
Fanaroff AC, 2020 [49]	USA	RCT	Adult patients hospitalized for AMI, treated with P2Y12 with medical insurance	Hospital	Adherence and persistence	5109
Fang R, 2015 [50]	China	RCT	Patients with CAD	Outpatient clinic	Adherence	280
Faridi KF, 2016 [51]	USA	Retrospective cohort study	Patients > 65 years, Medicare-insured, discharged alive after AMI (STEMI/NSTEMI)	Outpatient and inpatient	Adherence	20,976
Griffiths B, 2014 [52]	South Africa	Cross-sectional	Adults discharged alive after ACS from a tertiary hospital CCU	Outpatient clinic	Adherence	125
Ho PM, 2014 [53]	USA	RCT	Patients with ACS cared for in the VA system	Outpatient clinic	Adherence	253
Hoang C, 2011 [54]	USA	Cohort	Patients with acute coronary syndrome (ACS)	Hospital	Adherence	1081
Hudson M, 2006 [55]	Canada	Cohort	Patients hospitalized with a primary diagnosis of AMI	Hospital	Persistence	20,239
Huynh T, 2018 [56]	Canada	Cohort	Patients who experienced a STEAMI	Hospital	Adherence	524
Jia X, 2019 [57]	USA	Cohort	Patients with ASCVD	Outpatient clinic	Adherence	813,887
Khunti K, 2018 [58]	UK	Retrospective cohort study	Patients who received their first statin and/or ezetimibe prescription with documented CVD	Outpatient clinic	Adherence	16,701

Table 1 (continued)

First author and publication year	Study location	Study design	Study population	Study setting	Adherence/persistence?	Sample size
Kirsch F, 2020 [59]	Germany	Observational	Patients with AMI	Outpatient and inpatient	Adherence	15,360
Kocas C, 2013 [60]	Turkey	RCT	Patients with stable coronary artery disease, hospitalized for catheterization	Hospital	Adherence	252
Korol S, 2022 [61]	Ukraine	Observational	Patients with STEMI from the STIMUL registry	Outpatient clinic	Persistence	Not reported
Kristiansen O, 2021 [62]	Norway	Cross-sectional	Patients aged 18–80 years experiencing a first or recurrent coronary event	Hospital	Adherence	373
Kulik A, 2011 [63]	USA	Cohort	Patients who were treated with statins after chronic coronary artery disease	Hospital	Adherence	13,130
Lee JK, 2007 [64]	USA	RCT	Patients ≥ 30 years of age with coronary heart disease	Outpatient clinic	Adherence	148
Liao YB, 2023 [65]	New Zealand	Cohort	Patients admitted with ACS, treated with an invasive strategy	Hospital	Adherence	19,942
Librero J, 2016 [66]	Spain	Cohort	Patients discharged after hospitalization for CHD	Hospital	Adherence	7462
Lip GYH, 2023 [67]	USA	Cohort	Patients aged 18–90 years with a diagnosis of MI and claims between 2016 and 2021	Not reported	Adherence	31,029[a]
Maddison R, 2021 [68]	New Zealand	RCT	Adults with recent ACS, clinically, stable and able to read	Hospital	Adherence	306
McGinnis BD, 2009 [69]	USA	Cohort	AMI patients who underwent CABG or PCI	Hospital	Adherence	2201
Mechtouff L, 2018 [70]	France	Observational	Patients ≥ 18 with stroke or TIA	Outpatient setting	Adherence and persistence	210
Navar AM, 2019 [71]	Multicenter (30 countries)	RCT	Patients hospitalized for ACS	Hospital	Persistence	17,706
Padilla López A, 2021 [72]	Spain	Cohort	Patients > 18 years old who had a first episode of STEACS	Hospital	Adherence	552
Park LG, 2014 [73]	USA	RCT	Patients > 21 years of age hospitalized for AMI with or without ST-segment elevation or PCI	Hospital	Adherence	90
Phan DQ, 2019 [74]	USA	Cohort	Patients > 80 years of age hospitalized with AMI (2006–2016)	Hospital	Adherence	5629

Table 1 (continued)

First author and publication year	Study location	Study design	Study population	Study setting	Adherence/persistence?	Sample size
Pietrzykowski L, 2020 [75]	Poland	RCT	Adult patients hospitalized for AMI and treated with PCI	Inpatient, outpatient setting	Adherence and persistence	225
Qvist I, 2020 [76]	Denmark	RCT	Men aged 65–74 diagnosed with abdominal aortic aneurysm, peripheral arterial disease, or high blood pressure	Outpatient clinic	Adherence	1446
Rana JS, 2021 [77]	USA	Cohort	Patients aged 18–90 hospitalized for ASCVD (IM or ACV) with statin treatment	Hospital	Adherence	19,604
Rasmussen JN, 2007 [78]	Canada	Population-based, observational, longitudinal study	Patients (≥ 66 years) hospitalized with AMI between 1999 and 2003 who filled a prescription for a statin	Hospital	Adherence	17,823
Reddy A, 2016 [79]	USA	RCT	Veterans aged 30–75 years with CHD and poor adherence to statins (MPR < 80%)	Outpatient clinic	Adherence	126
Rodríguez F, 2019 [80]	USA	Cohort	Patients aged 18–85 years with established ASCVD	Outpatient clinic	Adherence	487,812
Schiele F, 2021 [81]	France	Retrospective cohort study	Patients with MI with an initial LLT prescription in 2011–2013 with no LLT prescription during the 2 years before LLT initiation	Outpatient clinic	Adherence	164,565
Schwalm JD, 2020 [82]	Canada	Quasi-experimental	Patients ≥ 65 who have suffered an AMI	Hospital	Adherence and persistence	20,896
Shalev V, 2014 [83]	Israel	Cohort	Patients had a diagnosis of AMI or vascular disease who initiated statin therapy between 1998 and 2008	Outpatient and inpatient setting	Persistence	15,139[a]
Shau WY, 2019 [84]	Taiwan	Cohort	Patients aged 20–100 years after hospitalization for ASCVD	Hospital	Adherence and persistence	185,252
Simonyi G, 2014 [85]	Hungary	Cross-sectional	Patients with atherosclerotic disease	Outpatient Clinic	Adherence and Persistence	1519
Sjölander M, 2016 [86]	Sweden	Cohort	Patients with ischemic stroke	Hospital	Adherence	15,192

Table 1 (continued)

First author and publication year	Study location	Study design	Study population	Study setting	Adherence/persistence?	Sample size
Soldati S, 2021 [87]	Italy	Retrospective follow-up study	Patients discharged from hospitals between 2012 and 2016 with a diagnosis of AMI	Hospital	Adherence	25,779
Souza Groia Veloso R, 2021 [88]	Brazil	Cross-sectional	Patients ≥ 18 years, with a diagnosis of CHD	Outpatient clinic	Adherence	148
Stuart B, 2013 [89]	USA	Observational	Medicare beneficiaries post-AMI	Outpatient clinic	Adherence	8900
Thompson D, 2021 [90]	UK	RCT sub-study	Patients aged 18–85 years with stable angina	Outpatient clinic (telemedicine)	Adherence	200
Vethe NT, 2019 [91]	Norway	Observational	Patients with CVD	Hospital	Adherence	Method validation: 6; pilot study: 2
Vethe NT, 2022 [92]	Norway	Cross-sectional	Adult patients with CHD	Outpatient clinic	Adherence	18
Virani SS, 2014 [93]	USA	Cohort	Patients with ≥ 2 outpatient diagnosis codes or 1 inpatient diagnosis code for UA, MI, PCI, or coronary bypass	Outpatient clinic	Adherence	629,005
Vitturi BK, 2021 [94]	Brazil	Cohort	Patients > 18 years with a first ischemic stroke	Hospital	Adherence	344
Volpp KG, 2017 [95]	USA	RCT	Patients aged 18–80 years, survivors of AMI	Outpatient clinic	Adherence	1509
Wake M, 2019 [96]	Japan	Cohort	Patients > 18 years of age with type 2 diabetes or a previous diagnosis of ASCVD with a diagnosis of hyperlipidemia	Not reported	Adherence and persistence	18,457[a]
Wawruch M, 2017 [97]	Slovakia	Cohort	Persons > 18 years after first diagnosis of TIA	Not reported	Persistence	797
Wei L, 2002 [98]	UK	Cohort	Patients hospitalized for recurrent MI	Hospital	Adherence	5590
Xie G, 2017 [99]	China	Cohort	Patients with ACS with no relapse 6 months after HA	Hospital	Adherence	12,516
Xie G, 2022 [100]	China	Cohort	Patients with ACS hospitalized	Hospital	Persistence	10,337
Yaglioglu H, 2022 [101]	Turkey	Cohort	Patients with a diagnosis of UA, STEACS, or NSTEACS	Outpatient clinic	Adherence	180
Yan LL, 2021 [102]	China	RCT	Stroke patients	Outpatient clinic	Adherence	1299

Table 1 (continued)

First author and publication year	Study location	Study design	Study population	Study setting	Adherence/persistence?	Sample size
Yao X, 2020 [103]	USA	Retrospective cohort	Adults with ASCVD (CHD, TIA, PAD)	Hospital	Adherence	284,954
Yu G, 2018 [104]	China	Cohort	Patients with CHD	Hospital	Adherence	615

ACS acute coronary syndrome, *AMI* acute myocardial infarction, *ANZACS-QI* All New Zealand ACS Quality Improvement, *ASCVD* atherosclerotic cardiovascular disease, *CA* coronary angiography, *CABG* coronary artery bypass graft, *CAD* coronary artery disease, *CHD* coronary heart disease, *CVD* cardiovascular disease, *HD* hospital discharge, *HF* heart failure, *LDL-C* low-density lipoprotein cholesterol, *MHS* Maccabi Healthcare Services, *MI* myocardial infarction, *MPR* medication possession ratio, *NSTEMI* non-ST-segment elevation acute coronary syndrome (non-ST-segment elevation myocardial infarction), *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *RCT* randomized clinical trial, *STEMI* ST-segment elevation acute coronary syndrome (ST-segment elevation myocardial infarction), *TIA* transient ischemic attack, *UA* unstable angina, *VA* Veterans Affairs Healthcare System

[a] Sub-cohort of patients in secondary cardiovascular prevention

($n=24$) and cross-sectional studies ($n=6$). Sample sizes ranged from two to 813,887 patients. Most studies were conducted in hospital settings ($n=40$). A significant proportion (74.0%, $n=57$) focused on adherence, with fewer studies measuring persistence (11.7%, $n=9$) or both adherence and persistence (14.3%, $n=11$). As for the types of statins evaluated, most studies assessed multiple types, with atorvastatin and rosuvastatin being the most frequently analyzed (Table 2).

Methods for measuring statin adherence

The reviewed studies employed various methods to measure adherence to statins. These included, in order of frequency, review of prescription refill records ($n=55$), self-report methods ($n=20$), direct monitoring methods via plasma or urine ($n=5$), electronic monitoring devices ($n=2$), self-perceived adherence by physicians ($n=1$), and pill count methods ($n=1$). Among prescription-based adherence indicators, the most commonly used were the PDC ($n=30$) and the MPR ($n=16$), with adherence thresholds typically defined as PDC or MPR $\geq 80\%$. Some studies further categorized MPR-based adherence into optimal, adequate, and suboptimal levels. Figure 2 summarizes all these adherence measurement methods grouped into six main groups.

Self-report tools used to measure statin adherence included:

- 8-item Morisky Medication Adherence Scale (MMAS-8) [23]: An 8-item scale scoring adherence from 0 to 8, where lower scores indicate higher adherence.
- 4-item Morisky Medication Adherence Scale (MMAS-4) [105]: A shorter version scoring adherence from 0 to 4, with lower scores reflecting higher adherence.
- 7-day recall: A single-item measure asking patients how many days they took their statin in the past week.
- Medication Adherence Tool (MAT) [108, 110]: A 7-item questionnaire rated on a 6-point Likert scale, evaluating various aspects of adherence from the patient's perspective.
- Visual analog scale (VAS): A line scale from 0 to 100% divided into 10 intervals, where patients mark their adherence level.
- Gehi et al. questionnaire [111]: A 3-item tool assessing adherence qualitatively, without generating a cumulative score.
- SEAMS Questionnaire [107]: A 13-item scale scored on a 3-point Likert scale, with scores ranging from 13 to 39, where higher scores indicate better adherence.
- 24-h recall: A single-item measure assessing whether the patient took their medication in the last 24 h.

Two studies used electronic devices to quantify statin adherence, without specifying thresholds for classifying patients as adherent or non-adherent:

- Medication event monitoring system (MEMS) [106]: Electronically records each time the medication container is opened, providing precise data on medication access frequency and timing.
- GlowCap®: An electronic cap device that emits visual or auditory reminders for medication intake, while logging the frequency of use.

One study [64] employed pill count methods, defining adherence as the consumption of 85–100% of the expected pills. Lastly, some studies used direct monitoring methods, such as tandem liquid chromatography-mass spectrometry (LC–MS/MS), which measures adherence by detecting drug levels in biological fluids, providing objective verification of recent statin consumption [61].

Regarding validity indicators for indirect methods, none was specifically designed or validated for measuring statin adherence. Table 2 summarizes the psychometric properties previously reported for the MMAS-8 (retracted), MMAS-4, SEAMS, and MAT scales for measuring adherence to other medications and populations. Only in the case of the MAT scale did authors test internal consistency when adapted for statins (Cronbach's alpha = 0.66) [88]. Direct measurement methods assessing adherence through statin detection (or its metabolites) in the patient's body provide objective verification of recent statin intake. The reliability of these results depends on the validity indicators of the analytical method, which were reported in five studies (Table 2). Thompson et al. [90] used the HPLC–MS/MS method to evaluate adherence with a detection limit of 1–200 ng/mL, stating that variations in drug pharmacokinetic parameters did not affect relative detection. This suggests the method's precision is reliable for identifying drug presence in urine, although full analytical validation details were not provided.

Methods for measuring statin persistence

Persistence in statin use was assessed through various methods, predominantly based on prescription refill records, each employing specific criteria to define continuity in medication acquisition (Table 2):

- Interruptions without renewal within a defined period: Patients were classified as persistent if they

Table 2 Methods of measuring adherence and persistence, and their validity indicators ($n = 77$)

First author and publication year	Type(s) of statin(s)	Measurement method	Definition adherent/ persistent patient	Validation evidence	Validation metrics	Psychometric properties questionnaire
Ali M, 2023 [24]	ATV, SIM, PRA, FLU	Adherence: PRR (MPR)	Optimal adherence: MPR ≥ 1.0 Adequate adherence: MPR > 0.8 and < 1.0 Sub-optimal adherence: MPR < 0.8	No	–	–
Allonen J, 2012 [25]	All types	Adherence: PRR (days counted from discharge date to purchase date)	Adherent: - Early: within 7 days - Delayed: between 7 and 120 days - Late: after 120 days Non-adherent: did not purchase medication	No	–	–
		Persistence: PRR (days counted from discharge date to purchase date)	Non-users: no purchase or only one purchase; first purchase > 180 days after prescription Irregular users: first purchase ≥ 30 days after discharge or multiple purchases with > 180-day gap Regular users: multiple purchases, first within 30 days of discharge, no long gaps			
Alsabbagh W, 2017 [26]	All types	Adherence: PRR (PDC)	Optimum: PDC ≥ 80%	No	–	–
Al-Khadra S, 2014 [31]	All types	Persistence: self-reported (direct questioning via phone or home visits)	Discontinuity if the treatment was interrupted for ≥ 90 days	No	–	–
Bell KJ, 2011 [32]	PRA	Adherence: self-reported (direct questioning)	Adherent: taking any pills Non-adherent: stopped taking them	No	–	–
Blackburn DF, 2005 [33]	All types	Adherence: PRR (supply frequency of medication)	Adherent: supply frequency > 80% Non-adherent: supply frequency ≤ 60%	No	–	–
Booth JN, 2017 [34]	All types	Persistence: PRR (PDC)	High persistence: PDC ≥ 80% (182 days post-discharge) Discontinuation: ≥ 60 days without statin supply after initial dose	No	–	–
Brogaard HV, 2012 [35]	All types	Adherence: PRR (MPR)	Adherent: MPR ≥ 80%	No	–	–
Brown R, 2021 [36]	All types	Adherence: PRR (MPR)	Adherent: MPR ≥ 80%, or ≥ 50% for patients with low tolerance taking it every other day	No	–	–
Carey IM, 2012 [37]	ATV, CER, FLU, PRA, ROS, SIM	Adherence: PRR (PDC)	Adherent: MPR ≥ 80% (over 1 year)	No	–	–
Chan V, 2008 [38]	All types	Adherence: PRR (MPR)	Optimal adherence: MPR ≥ 80%	No	–	–
Chen PS, 2016 [39]	All types	Adherence: PRR (MPR)	Adherence: - Good: MPR > 80% - Intermittent: MPR 40–80% - Poor: MPR < 40%	No	–	–

Table 2 (continued)

First author and publication year	Type(s) of statin(s)	Measurement method	Definition adherent/ persistent patient	Validation evidence	Validation metrics	Psychometric properties questionnaire
Chen ST, 2019 [40]	All types	Adherence: PRR (PDC and MPR)	Adherence: - Good: PDC ≥ 0.8 - Suboptimal: PDC < 0.8	No	–	–
		Persistence: PRR (time to non-renewal of medication)	Discontinuity: no renew the prescription for 90 days			
Chi MD, 2014 [41]	All types	Adherence: PRR (MPR)	Good adherence: MPR > 80%	No	–	–
Choudhy NK, 2011 [42]	All types	Adherence: PRR (MPR)	Adherent: MPR ≥ 80% Non-adherent: do not pick up prescribed medication	No	–	–
Chow CK, 2022 [43]	All types	Adherence: self-reported (direct questioning)	Adherent: take ≥ 80% of prescribed doses (maintain at 6 and 12 months)	No	–	–
Chung PW, 2018 [44]	All types	Adherence: self-reported (MMAS-8)	- High: score = 8 points - Moderate: score = 6–7 points - Low: score < 6 points	Yes, by previous authors for hypertensive patients (results retracted) [23]	Sensitivity = 93% Specificity = 53%	Internal consistency (Cronbach's alpha) = 0.83
Coberley C, 2008 [45]	All types	Adherence: PRR (supply frequency)	Adherence: having at least one pharmacy claim during each 12 months	No	–	–
Colantonio LD, 2017 [46]	ATV, ROS	Adherence: PRR (PDC)	- High adherence: PDC ≥ 80% - Low adherence: PDC < 80%	No	–	–
		Persistence: PRR (time to non-renewal of medication)	Discontinuity: no renew the prescription for or supply of statins in the last 60 days of the 6-month period			
Cooke CE, 2006 [47]	ATV, FLU, LOV, PRA, ROS, SIM	Adherence: PRR (MPR)	- Good: MPR ≥ 0.8 - Poor: MPR 0.5 ≤ MPR < 0.8 - Very poor: MPR < 0.5	No	–	–
		Persistence: PRR (time between prescription and supply dates)	Persistence: time between prescription and supply ≤ 30 days			
Di Martino M, 2016 [48]	All types	Adherence: PRR (MPR)	Adherence: MPR ≥ 0.75	No	–	–
Fanaroff AC, 2020 [49]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% (1 year) No adherence: PDC < 80%	No	–	–
		Persistence: PRR (PDC)	Persistence: supply without a break ≥ 30 days No persistence: break in supply > 30 days or never picked up			
Fang R, 2015 [50]	All types	Adherence: self-reported (MMAS-4)	- Good: MMAS = 0 - Fair: MMAS = 1–2 - Poor: MMAS = 3–4	Yes, by previous authors for hypertensive patients [105]	Sensitivity: 0.81 Specificity: 0.44	Cronbach's alpha: 0.61
Faridi KF, 2016 [51]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% at 90 days and 1 year	No	–	–
Griffiths B, 2014 [52]	All types	Adherence: self-reported (direct questioning via phone)	Adherence: continued use at 6–9 months after discharge	No	–	–
Ho PM, 2014 [53]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% (1 year) No adherence: PDC < 80%	No	–	–

Table 2 (continued)

First author and publication year	Type(s) of statin(s)	Measurement method	Definition adherent/persistent patient	Validation evidence	Validation metrics	Psychometric properties questionnaire
Hoang C, 2011 [54]	All types	Persistence: self-reported (direct questioning via phone)	Discontinuity: if they discontinued at 6–12 months after discharge	No	–	–
Hudson M, 2006 [55]	All types	Persistence: PRR (MPR)	Persistence: MPR ≥ 80% during the first year	No	–	–
		Persistence: PRR (continuity of prescription)	Persistence: active prescription at the end of follow-up (60 days)			
Huynh T, 2018 [56]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80%	No	–	–
Jia X, 2019 [57]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% No adherence: PDC < 80%	No	–	–
		Adherence: self-reported (24-h recall)	Adherence: reported taking all medications in the last 24 h			
		Adherence: PRR (CHCS)	Adherence: refills matched prescribed days, always within 90 days			
Kirsch F, 2020 [58]	All types	Adherence: PRR (PDC)	Not reported	No	–	–
Kocas C, 2013 [59]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% (1 year) No adherence: PDC < 80%	No	–	–
Korol S, 2022 [60]	All types	Persistence: PRR (supply frequency)	Persistence: regular use without discontinuation at 6, 12, and 24 months	No	–	–
Kristiansen O, 2021 [61]	ATV	Adherence: self-reported (MMAS-8)	Low adherence: score < 6	No	–	–
		Adherence: self-reported (Gehi's adherence question)	Reduced adherence: if they answer any of these options: "most of the time" (75%), "about half the time" (50%), or "less than half of the time" (< 50%)	No	–	
		Adherence: self-reported (7-day recall)	Adherence: < 6/7 days	No	–	
		Adherence: direct method (TDM: HPLC–MS/MS)	Partial adherence: ATV + metabolites < 0.10 nM/mg (≥ 2 consecutive skipped doses) Non-adherence: 2-OH atorvastatin acid < 0.014 nmol/L (> 3 consecutive missed doses)	Analytical method validated by the same authors [62] All ATV and metabolite analyses met the acceptance criteria for analytical runs in the EMA Guideline on Validation of Bioanalytical Methods	Sensitivity = 100% Specificity = 92%	
Khunti K, 2018 [62]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80%	No	–	–
Kulik A, 2011 [63]	ATV, FLU, LOV, PRA, ROS, SIM	Adherence: PRR (PDC)	Fully adherence: PDC > 80%	No	–	–
Lee JK, 2007 [64]	All types	Adherence: pill count method	Adherence: taking 85–100% of expected pills	No	–	–
		Adherence: self-reported (24-h recall)	Adherence: self-reported full medication intake in the last 24 h			
		Adherence: PRR (CHCS)	Adherence: refills aligned with prescribed days within 90 days			

Table 2 (continued)

First author and publication year	Type(s) of statin(s)	Measurement method	Definition adherent/ persistent patient	Validation evidence	Validation metrics	Psychometric properties questionnaire
Liao YB, 2023 [65]	All types	Adherence: PRR (MPR)	No adherence: MPR < 0.8	No	–	–
Librero J, 2016 [66]	All types	Adherence: PRR (MPR)	Adherence: PDC ≥ 0.8	No	–	–
Lip GYH, 2023 [67]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 0.8 No adherence: PDC < 0.8	No	–	–
Maddison R, 2021 [68]	All types	Adherence: PRR (MPR)	Adherence: MPR ≥ 80% No adherence: MPR < 80%	No	–	–
		Adherence: self-reported (MMAS-8)	- High: score = 0 - Medium: score = 1–2 - Low: score = 3–6	Yes, by previous authors for hypertensive patients (results retracted) [23]	Sensitivity = 93% Specificity = 53%	Internal consistency (Cronbach's alpha) = 0.83
McGinnis BD, 2009 [69]	PRA, LOV, ATV, SIM, ROS, FLU	Adherence: PRR (PDC)	- Adherence: PDC > 80% - Partial adherence: PDC = 20 to ≤ 80% - Non-adherence: PDC < 20%	No	–	–
Mechtouff L, 2018 [70]	All types	Adherence: PRR (CMA)	Adherence: CMA ≥ 0.8	No	–	–
		Persistence: PRR (supply frequency)	Persistence: if they purchase at least one prescribed treatment during the studied year			
Navar AM, 2019 [71]	SIM	Persistence: self-reported (direct questioning)	Discontinuation: permanent stop of medication - Early: < 30 days - Intermediate: 30 days to 1 year - Late: > 1 year	No	–	–
Padilla López A, 2021 [72]	All types	Adherence: PRR (PDC)	Adherence: PDC > 80%	No	–	–
Park LG, 2014 [73]	All types	Adherence: electronic monitoring device (MEMS: % of doses)	Adherence: quantitative measurement was used but threshold not reported	Adherence: yes, by previous authors in patients with hypertension [106]	Sensitivity = 76% Specificity = 83%	Correlation coefficient = 0.20
		Adherence: self-reported (SEAMS)	Good adherence: high scores	Adherence: yes, by previous authors [107]	Adherence: test–retest reliability:correlation = 0.57	Adherence: internal consistency (Cronbach's alpha) = 0.89
		Adherence: self-reported (MMAS-8)	Adherence: quantitative measurement was used but threshold not reported	Adherence: yes, by previous authors for hypertensive patients (results retracted) [23]	Adherence: sensitivity = 93% Specificity = 53%	Adherence: internal consistency (Cronbach's alpha) = 0.83
Phan DQ, 2019 [74]	All types	Adherence: PRR (PDC)	- High: PDC ≥ 80% - Partial: PDC ≥ 40 to < 80% - Low: PDC < 40%	No	–	–
Pietrzykowski L, 2020 [75]	ATV, SIM, ROS	Adherence: PRR (days on treatment and days of interruption)	Not reported	No	–	–
		Persistence: PRR (days of interruption)	- Short-term discontinuation: less than 30 days - Long-term discontinuation: 30 days or more - Permanent discontinuation: when the patient stops taking the medication permanently			
Qvist I, 2020 [76]	SIM, ATV	Adherence: PRR (PDC)	- Good: PDC ≥ 80%	No	–	–

Table 2 (continued)

First author and publication year	Type(s) of statin(s)	Measurement method	Definition adherent/persistent patient	Validation evidence	Validation metrics	Psychometric properties questionnaire
Rasmussen JN, 2007 [77]	All types	Adherence: PRR (PDC)	- High: PDC ≥ 80% - Intermediate: PDC 40–79% - Low: PDC < 40% (1 year)	No	–	–
Rana JS, 2021 [78]	All types	Adherence: PRR (CMG: % time without adequate supply)	- Good: CMG ≤ 20% - Inadequate: CMG > 20%	No	–	–
Reddy A, 2016 [79]	All types	Adherence: PRR (MPR)	Poor adherence: MPR < 80%	No	–	–
		Adherence: self-reported (MMAS-4)	- High: score = 0 - Medium: score = 1–2 - Low: score = 3–4	Adherence: yes, by previous authors for hypertensive patients [105]	Adherence: sensitivity = 0.81 Specificity = 0.44	Adherence: Cronbach's alpha = 0.61
		Adherence: electronic monitoring device (GlowCap®)	Adherence: number of days opening the jar over a period of time. No exact threshold specified	No	–	–
Rodríguez F, 2019 [80]	FLU, LOV, SIM, PIT, PRA, ATV, ROS	Adherence: PRR (MPR)	Adherence: MPR ≥ 80%	No	–	–
Schiele F, 2021 [81]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% (1 year)	No	–	–
Schwalm JD, 2020 [82]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80%	No	–	–
		Persistence: PRR (days between supply dates)	Persistence: no ≥ 30-day gap in supply during follow-up (1 year)			
Shalev V, 2014 [83]	SIM, PRA, LOV, FLU, ATV, CER, ROS, PIT	Persistence: PRR (PDC)	- Low: PDC ≤ 33% - Moderate: PDC = 34–79% - High: PDC ≥ 80%	No	–	–
Shau WY, 2019 [84]	All types	Adherence: PRR (PDC)	Good adherence: PDC ≥ 0.8 No adherence: PDC < 0.8	No	–	–
		Persistence: PRR (continuity of prescription)	- No persistence: discontinuity > 90 days - Intermittent use: resumption of statin prescription after non-persistent status - Recent suspension < 90 days - Consistent use: continuous administration or statins			
Simonyi G, 2014 [85]	ATV ROS SIM	Adherence: self-perceived adherence by physicians	Not reported	No	–	–
		Adherence: PRR (supply frequency)	Adherence: ≥ 8 prescriptions/year			
		Persistence: PRR (supply frequency)	- High: regular supply frequency - Low: low supply frequency			
Sjölander M, 2016 [86]	All types	Adherence: PRR (PDC)	Adherence: PDC > 80%	No	–	–
Soldati S, 2021 [87]	All types	Adherence: PRR (MPR)	Adherence: MPR ≥ 0.75 (6 months)	No	–	–

Table 2 (continued)

First author and publication year	Type(s) of statin(s)	Measurement method	Definition adherent/ persistent patient	Validation evidence	Validation metrics	Psychometric properties questionnaire
Souza Groia Veloso R, 2021 [88]	All types	Adherence: self-reported (MAT)	Adherence: score = 5–6 Non-adherent: score = 1–4	Yes, by authors for another drug and field; internal consistency analyzed for statin-adapted MAT [108]	–	MAT adapted to statins: Cronbach's alpha = 0.66
		Adherence: self-reported (VAS)	- Adherent patient: VAS score ≥ 80% - Non-adherent patient: VAS score < 80%	No	–	–
		Adherence: self-reported (7-day recall)	- Non-adherent: statin use ≤ 5 days - Adherent: use of statin 6 or 7 days	No	–	–
Stuart B, 2013 [89]	All types	Adherence: PRR (PDC)	Good adherence: PDC ≥ 80%	No	–	–
Thompson D, 2021 [90]	ATV or other	Adherence: self-reported (7-day recall)	Not reported	No	–	–
		Adherence: direct method, TDM (HPLC–MS/MS in urine sample analysis)	Adherence: detection of drug in urine (detection limit between 1 and 200 ng/mL)	Yes, by previous authors [109]	Sensitivity > 90%	–
Vethe NT, 2019 [91]	ATV	Adherence: direct method, TDM (LC–MS/MS)	Non-adherent: ≥ 3 days without medication. The threshold of adherence was not reported	Validated by the authors per EMA and FDA guidelines	Mean accuracy: 92 to 110% Coefficients of variation (CV): ≤ 8.1%	–
Vethe NT, 2022 [92]	SIM	Adherence: direct method, TDM (HPLC–MS/MS)	- Reduced adherence: dose omission (t48h, t72h, t96h) - Cutoff levels: simvastatin acid ≥ 1.0×10^{-2} nmol·L^{-1}·mg^{-1}; total components ≥ 2.0×10^{-2} nmol·L^{-1} - Detection: 100% for 2 missed doses, 60% for 1 missed dose	Yes, by the same authors. Plasma concentration normalized per dose after 2 missed doses vs. adherent dosing [92]	Sensitivity = 100% Specificity = 100%	–
Virani SS, 2014 [93]	ATV, FLU, LOV, PRA, ROS, SIM, PIT	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% Non-adherence: PDC < 80%	No	–	–
Vitturi BK, 2021 [94]	All types	Adherence: self-reported (MMAS-8)	- Poor: score < 6 points - Intermediate: score = 6 or < 8 points	Yes, by previous authors for hypertensive patients (results retracted) [23]	Sensitivity = 93% Specificity = 53%	Internal consistency (Cronbach's alpha) = 0.83
Volpp KG, 2017 [95]	All types	Adherence: PRR (PDC for 1 year)	Quantitative, but adherence threshold not defined	No	–	–
Wake M, 2019 [96]	PRA, SIM, FLU, ATV, ROS, PIT	Adherence: PRR (PDC)	Adherence: PDC ≥ 80%	No	–	–
		Persistence: PRR (time between prescription and supply dates)	Persistence: no gap > 1.5 × the median treatment duration			
Wawruch M, 2017 [97]	All types	Persistence: PRR (continuity of prescription)	Persistence: continuous treatment without interruption Non-persistence: ≥ 6 months without a prescription after the last covered day	No	–	–

Table 2 (continued)

First author and publication year	Type(s) of statin(s)	Measurement method	Definition adherent/ persistent patient	Validation evidence	Validation metrics	Psychometric properties questionnaire
Wei L, 2002 [98]	All types	Adherence: PRR (PDC)	- Non-adherent: no statin prescription - Good adherence: PDC > 80% - Maximum adherence: compliance > 100% (excess medication pickup)	No	–	–
Xie G, 2017 [99]	All types	Adherence: PRR (supply frequency)	- Good adherence: continuous statin use without tapering for 6 months post-discharge - Poor adherence: interruption or dosage reduction within 6 months post-discharge	No	–	–
Xie G, 2022 [100]	ATR SIM ROS PRA FLU	Persistence: standardized questionnaire (phone interview and personal visits)	Persistence: use at statins at either the 6- or 12-month follow-up	No	–	–
Yaglioglu H, 2022 [101]	ATV, ROS	Adherence: direct method, TDM (HPLC–MS/MS)	Non-adherence threshold: -ATV < 4.88 ng/mL, -ROS < 3.95 ng/mL (LLOQ)	Yes, by the same authors. Follow the recommendations of the FDA guidance [101]	LLOQ: ATV: 4.88 ng/mL ROS: 3.95 ng/mL Accuracy (intra-day and inter-day CV%): ATV: 1.7–5.9% ROS: 1.7–5.9% Accuracy (% recovery): -ATV: 93.8–110.4% -ROS: 93.8–110.4% Matrix effect (%): -ATV: – 7.63 to – 2.83% -ROS: – 8.84 to 3.65%	–
Yan LL, 2021 [102]	All types	Adherence: self-reported (MMAS-4)	Perfect adherence: score = 0	Yes, by previous authors for hypertensive patients [105]	Sensitivity: 0.81 Specificity: 0.44	Cronbach's alpha: 0.61
Yao X, 2020 [103]	ATV ROS SIM	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% within the first year	No	–	–
Yu G, 2018 [104]	All types	Adherence: PRR (PDC)	Adherence: PDC ≥ 80% Non-adherence: PDC < 80%	No	–	–

ATV atorvastatin, *CER* cerivastatin, *CHCS* Composite Health Care System, *CMA* continuous method of medication acquisition, *CMG* continuous medication gap, *FLU* fluvastatin, *HPLC–MS/MS* high-performance liquid chromatography-tandem mass spectrometry, *LLOQ* lower limit of quantification, *LOV* lovastatin, *MAT* measure of adherence to treatment, *MEMS* medication event monitoring system, *MMAS-4/8* Morisky Medication Adherence Scale, *MPR* medication possession ratio, *PDC* proportion of days covered, *PIT* pitavastatin, *PRA* pravastatin, *PRR* prescription refill records, *ROS* rosuvastatin, *SEAMS* Self-Efficacy for Appropriate Medication Use Scale, *SIM* simvastatin, *TDM* therapeutic drug monitoring, *VAS* visual analog scale

renewed their prescriptions without exceeding a predetermined interruption pe

- Time between prescription and supply: Persistence was determined by evaluating whether patients refilled their medication within a defined timeframe after the initial prescription.
- Proportion of days covered (PDC): Persistence was defined in several studies as a PDC ≥ 80% during the follow-up period, with lower values indicating prolonged treatment interruptions and classified as non-persistence.
- Medication possession ratio (MPR): In one study, patients were considered persistent if their MPR was ≥ 80% over a 1-year follow-up period.
- Continuity of prescription: Persistence was assessed by verifying whether patients had statins available on a specific date, regardless of prior supply interruptions.
- Supply frequency: Patients were classified as persistent if they maintain a consistent supply frequency or exceed a minimum threshold.

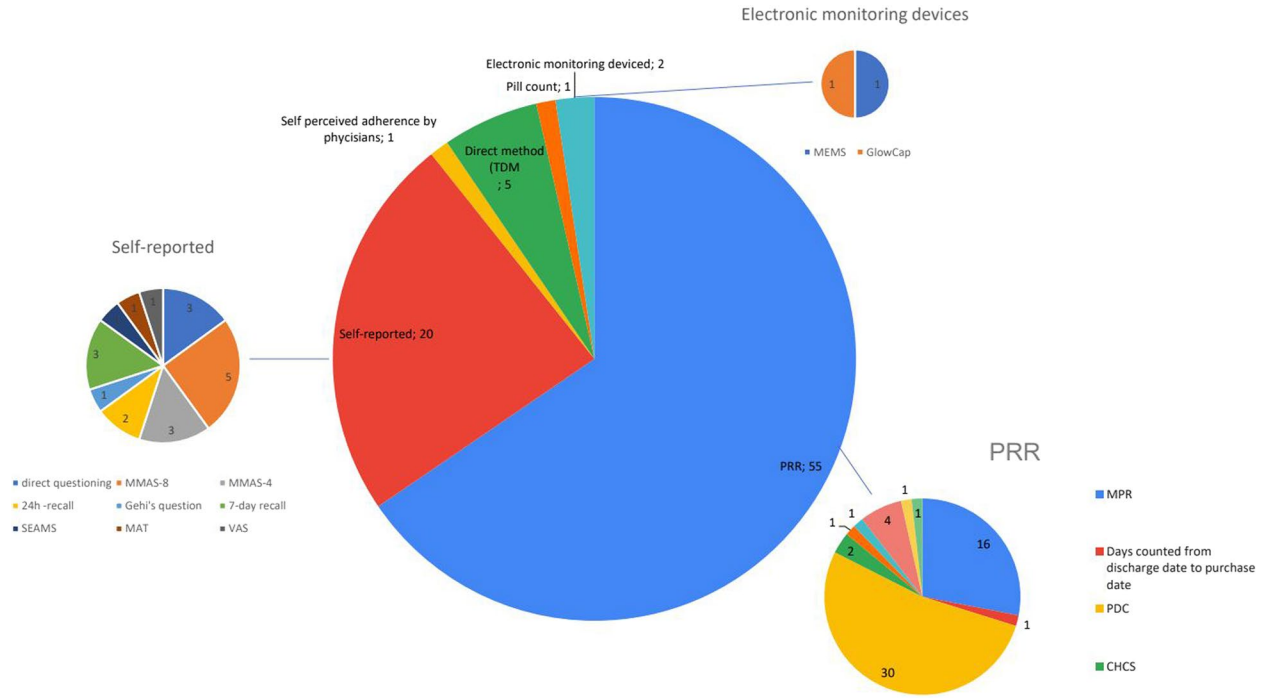

Fig. 2 Pie chart grouping adherence measurement methods into six main groups: pill counting methods, dispensation records, direct methods, electronic monitoring methods, self-perceived adherence by physician, and self-report methods

Three studies [31, 54, 71] employed a self-report approach, where patients were asked during follow-up phone calls or home visits about their medication use. Discontinuity was defined as an interruption in treatment lasting more than 90 days. One study [100] used a standardized questionnaire although no further details were provided.

Persistence measurement methods based on prescription refill records generally lack formal validation, as no standardized process ensures their accuracy or consistency across diverse contexts. However, sensitivity analyses were conducted in some studies to justify the chosen cutoff points: Allonen et al. [25] validated a 180-day cutoff for assessing statin use continuity through sensitivity analysis. Another study [97] defined non-persistence as a period exceeding 6 months without a prescription after the last covered day of statin supply, supported by sensitivity analyses conducted by the authors. Figure 3 summarizes all these persistence measurement methods grouped into the two main groups.

Quality assessment of validation studies for adherence measurement methods

Among all the reviewed studies, only one [88] specifically addresses the psychometric properties of a method for measuring adherence to statins: the MAT adapted for this medication type. This study assessed the internal consistency of the adapted MAT, reporting a Cronbach's alpha of 0.66, indicating low internal consistency. Using the COSMIN tool for evaluation, this study demonstrates several limitations in the psychometric validation of the adapted MAT. The instrument's reliability, assessed through internal consistency, is acceptable but low. Regarding content validity, the study did not conduct a comprehensive analysis or confirm the specific relevance of the items adapted for statins. Criterion validity is also insufficient, as the study did not compare the MAT against a reference standard, such as plasma statin levels. Construct validity was partially evaluated through concordance with other self-report methods; however, the low concordance suggests potential differences in the construct being measured, without an in-depth analysis. Finally, in terms of interpretability, the study provides a basic classification of adherence versus non-adherence but lacks validated cutoff points tailored to patients undergoing statin therapy.

Discussion

This systematic review identified various methods for measuring adherence to statins in secondary cardiovascular prevention, including prescription refill records, notably through the use of PDC and MPR, self-report tools (statin-adapted MAT [88], adherence VAS, 7-day recall, 24-h recall, MMAS-8 [23], MMAS-4 [105], SEAMS [107], and Gehi et al.'s adherence question [111]);

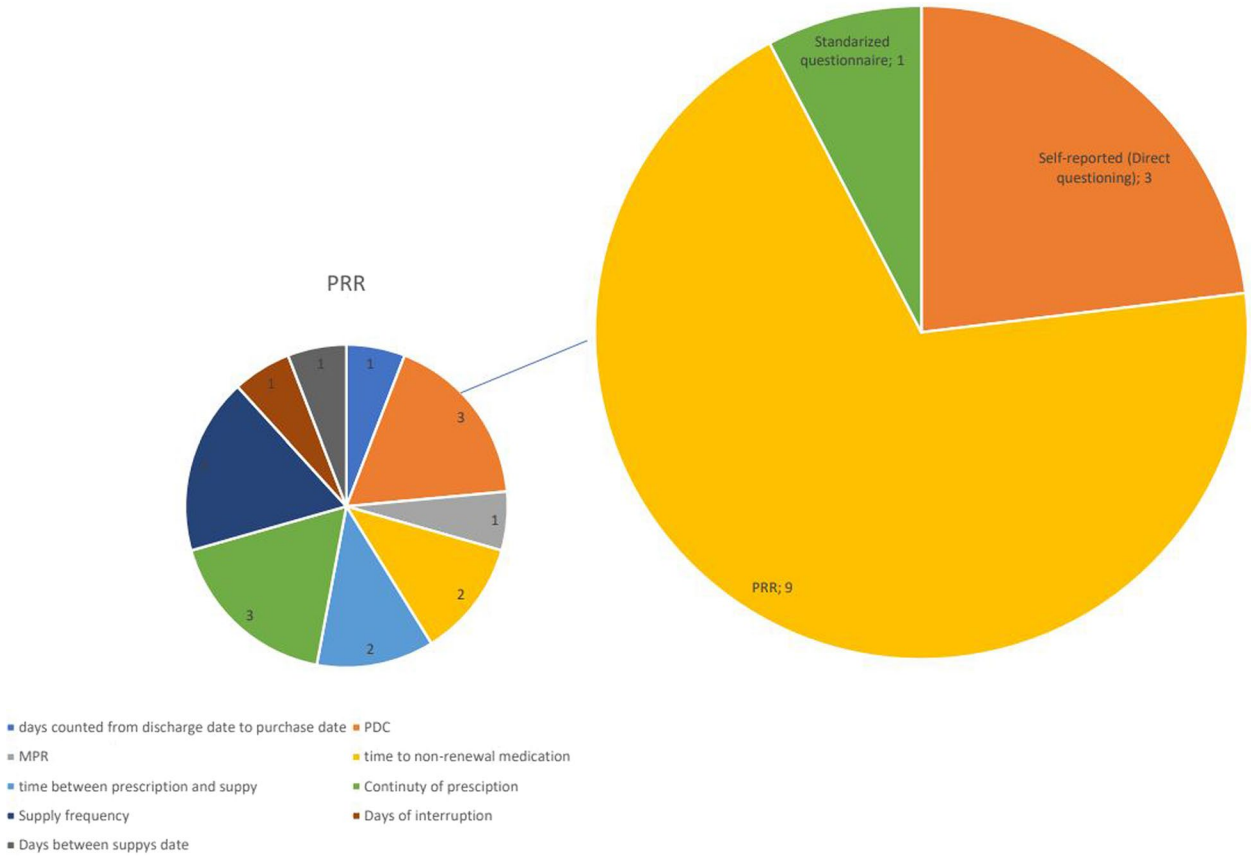

Fig. 3 Pie chart grouping persistence measurement methods. Self-report and dispensing records methods are the three main groups

and, less frequently, pill counting, electronic monitoring (MEMS [106] and GlowCap®), self-perceived adherence by physician, and direct measurement through detection of statins or their metabolites in blood or urine using LC–MS/MS [62]. For persistence, findings reveal that measurement methods are largely based on prescription refill records. Regarding the validity indicators of the methods used, none of the indirect methods included validity indicators specific to measuring adherence to statins, except for the statin-adapted MAT [88], which showed low internal consistency. Direct methods are considered valid as they provide acceptable validity indicators for the analytical technique employed.

Regarding the terminology used for adherence and persistence, it is not always consistent in the literature. Therefore, the nomenclature employed by various studies (adherence or persistence) was considered, regardless of whether it adhered strictly to the standard definitions [9]. Many studies use these terms interchangeably, even though adherence refers to the proportion of prescribed doses taken as directed, while persistence pertains to the continuation of treatment without interruptions. Additionally, other terms such as compliance and concordance have been used to describe different aspects of medication use. However, compliance often carries a negative connotation of subordination to the prescriber [112, 113], and concordance is frequently misinterpreted as synonymous with compliance [114–116]. This lack of clarity in terminology and measurement methods complicates the comparison of study results and leads to inconsistencies in conclusions about the effectiveness of adherence interventions. Greater consistency in terminology and methodology would help standardize the literature and facilitate evidence-based healthcare policy decisions.

Prescription and refill records are widely used tools for evaluating medication adherence, particularly for chronic treatments. The most commonly employed methods, PDC and MPR, are often assessed according to the interpretations of different study authors. The PDC is calculated as the percentage of days within a period during which the patient has the medication available, excluding duplicate supply days. This index is considered one of the most robust methods for measuring adherence, as it assesses whether the patient had the medication available each necessary day, excluding "overstocking" due to additional dispensations. Although PDC has not been

validated in the traditional psychometric sense, it is an accepted and reliable method in adherence research due to its consistency, broad applicability, and positive correlation with clinical outcomes [117]. In comparison, the MPR measures the proportion of time the patient has had the medication available during a given period but can exceed 100%, indicating surplus medication due to early refills. The primary limitation of these methods is that they cannot confirm whether the patient actually ingests the medication. A study by Márquez-Contreras et al. [118] demonstrates that MPR calculated from electronic prescription data is effective in measuring adherence in hypertensive patients using MEMS as the gold standard (sensitivity of 87% and specificity of 93.7%), although MPR may overestimate adherence when there is refill overlap. In contrast, CMG has been used far less frequently to measure statin adherence, and its correlation with pill count has been weak [119], suggesting limitations in accuracy and use compared to other adherence methods, particularly for different medication types.

Self-report methods are straightforward and practical tools for assessing adherence from the patient's perspective; however, their validity may be affected by recall bias or social desirability bias [88]. The MMAS-8 and its previous version, the MMAS-4, are widely used questionnaires in chronic conditions, though they were initially developed to measure adherence to antihypertensives. This questionnaire has been studied across numerous populations and contexts, with varying psychometric properties. In some studies, MMAS-8 has demonstrated good validity and reliability [24–26], while in others, its internal consistency and predictive adherence ability have been limited [27], suggesting that its accuracy may depend on the specific context and population. Notably, the original study by Morisky, which developed and validated the MMAS-8, has been retracted, raising concerns about the instrument's validity and the integrity of its psychometric properties [23]. In contrast, the MAT allows not only for assessing adherence levels but also for identifying possible reasons or barriers to non-adherence, such as forgetfulness, side effects, lack of understanding about treatment, or difficulties accessing medication. Although it has been adapted for patients on statins [88], it exhibits moderate internal consistency and does not meet COSMIN [30] quality standards, warranting additional validation. The Gehi method is based on only three questions, which may not capture all aspects of patient adherence behavior [20]. This tool is simple and practical but has limited predictive validity compared to more detailed scales. Although some studies have used VAS to assess adherence and found correlations with other self-report methods, no universal validation confirms its precision and reliability across all contexts or medications. The VAS may be useful as a complementary measure, but its validity for accurately and reliably measuring adherence is often limited [120, 121]. Reminder methods, such as the 7-day and 24-h recalls, have been used in adherence studies to provide a quick and point-in-time picture of patient treatment adherence. While these methods may correlate with other adherence measures, they are less detailed and may suffer from recall bias, limiting their accuracy in long-term adherence assessments.

Pill count is an indirect method used in some adherence studies, although its application in statin adherence evaluation is scarce. It involves counting the remaining pills in the container to infer adherence. While it is a cost-effective method, its validity is limited, as it cannot guarantee that the patient took the recorded doses. Electronic devices like MEMS are considered a reference standard in adherence assessment, offering a detailed record of patient behavior. However, their validity is limited, as they do not confirm ingestion when the patient opens the container. GlowCap® operates similarly, recording openings but not ensuring ingestion. Both devices, while useful as approximations, have significant limitations and are not recommended as the sole adherence reference.

Direct methods are based on detecting the drug or its metabolites in bodily fluids. For statins, this approach allows confirmation of the medication's presence in the body, ensuring it has been ingested and absorbed. However, this method has significant limitations: due to the half-life of statins, they may be undetectable in the blood shortly after the last dose, making them unsuitable for measuring short-term adherence. Establishing adherence thresholds or plasma concentration cutoff points is crucial to differentiate between adherence and non-adherence, as in the study by Kristiansen et al. [62], which calculated the theoretical plasma concentration range for statins in the steady state, classifying patients into three different adherence levels. Direct methods may be applicable in research or hospital settings, but their high cost and complexity make them less feasible for routine clinical practice. The present review shows that the main statins for which these methods were developed include atorvastatin, rosuvastatin, and simvastatin [62, 90, 92, 101].

Regarding persistence, it is generally measured through refill records, and although PDC may give an idea of adherence, it is not the ideal method for measuring persistence. PDC evaluates days covered by the medication but does not ensure uninterrupted treatment continuity, which is essential for accurate persistence measurement. Persistence is better assessed by analyzing periods without refill or long intervals without dispensing, providing a more realistic picture of patient behavior over the long term.

This review excluded studies in languages not using the Latin alphabet. However, this decision likely did not

have a significant impact, as most reviewed studies were in English. Additionally, the search was conducted using only three databases, without accounting for gray literature or articles in other databases.

This study highlights the scarcity of validated adherence measurement methods for statins in secondary cardiovascular prevention, underscoring the need to develop a method applicable in clinical practice for this purpose, with consideration for gender perspectives. Most studies do not consider gender disparities in medication adherence measurement in cardiovascular diseases, despite evidence that gender may influence adherence behaviors and that being female is an independent predictor of non-adherence to certain medications, including lipid-lowering agents post-myocardial infarction [122–124]. Considering this factor would enable more personalized, gender-specific interventions and adapted clinical approaches, as biological and perceptual differences may influence adherence and persistence behaviors in statin treatment. Integrating a gender perspective could provide more comprehensive results aligned with each population group's needs. Healthcare professionals must be familiar with tools to measure adherence to statins, given the severe implications of poor adherence in chronic conditions like CVDs. Failure to identify poor adherence as the underlying cause of inadequate disease control can lead to medications being incorrectly deemed ineffective, unnecessary treatment intensification, avoidable diagnostic testing, and even the misinterpretation of clinical trial results when adherence is not properly accounted for [28].

Consequently, we consider that direct methods, such as the detection of statins or their metabolites in blood or urine, are currently the most accurate tools available for measuring adherence to statins. However, their application in clinical practice is limited by cost and complexity. On the other hand, indirect methods such as prescription refill records and indices like PDC or MPR are practical and widely used, but do not guarantee that the medication has been taken. Notably, no indirect method has demonstrated sufficient validation metrics specific to statin adherence in secondary cardiovascular prevention, with the exception of the statin-adapted MAT, which showed low internal consistency. Thus, we highlight the need to develop and validate new tools that combine refill records and self-report. And we recommend using direct methods as the gold standard in research and validation studies to ensure reliable measurement of adherence. These tools should also incorporate a gender perspective, as gender differences can significantly influence adherence behaviors.

Conclusions

The methods used to measure adherence to statins in secondary cardiovascular prevention were mainly indirect, based on the review of prescription and supply records and self-report methods. Pill counting, electronic monitoring, and direct measurement through detection of statins and/or metabolites in blood or urine using the LC–MS/MS technique were used to a lesser extent. Regarding persistence, measurement methods were based on prescription refill records. None of the indirect methods identified was validated specifically for statin use in this population, and therefore, so their use to measure adherence to taking statins is not recommended. Based on current evidence, we consider that direct methods are the most accurate for measuring adherence and should serve as the gold standard in validation studies. In clinical settings, there is an urgent need to validate existing tools, originally developed for other conditions, and to develop new, mixed-method approaches that integrate refill data and self-report. We encourage future research and clinical efforts to prioritize the validation and implementation of reliable adherence measurement tools, as accurate assessment is essential for improving outcomes in cardiovascular disease prevention.

Abbreviations

ACS	Acute coronary syndrome
AH	Acute hospitalization
AMI	Acute myocardial infarction
ASCVD	Atherosclerotic cardiovascular disease
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHCS	Composite Health Care System
CMG	Continuous medication gap
CVDs	Cardiovascular diseases
DOT	Directly observed therapy
HPLC–MS/MS	High-performance liquid chromatography-tandem mass spectrometry
LC–MS/MS	Liquid chromatography-mass spectrometry
LDL-C	Low-density lipoprotein cholesterol
MHS	Maccabi Healthcare Services
MI	Myocardial infarction
MMAS- 4	4-Item Morisky Medication Adherence Scale
MMAS- 8	8-Item Morisky Medication Adherence Scale
MPR	Medication possession ratio
NSTEACS	Non-ST-segment elevation acute coronary syndrome
PCI	Percutaneous coronary intervention
PDC	Proportion of days covered
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized clinical trial
SEAMS	Self-Efficacy for Appropriate Medication Use Scale
STEMI	ST-segment elevation myocardial infarction
TIA	Transient ischemic attack
TDM	Therapeutic drug monitoring
UA	Unstable angina
VA	Veterans Affairs
VAS	Visual analog scale
WHO	World Health Organization
WHF	World Heart Federation

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
The idea for the systematic review was conceived by AL-P, RN-G, and VFG-G. The study design was carried out by AL-P, MM-M, RN-G, JAQ, CC-M, and VFG-G. The literature search was performed by ALP and MM-M. Article selection was conducted by ALP, MMM, RNG, AEA, ACS, and ERF. Data extraction was completed by AL-P, MM-M, AE-A, RN-G, JAQ, and CC-M. Quality analysis was undertaken by AL-P, MM-M, AC-S, RN-G, and JAQ. Data interpretation was done by AL-P, AE-A, MM-M, RN-G, VFG-G, AC-S, JAQ, and CC-M. The manuscript draft was written by MM-M, AL-P, RN-G, and AE-A. All authors critically reviewed and approved the final manuscript. VFG-G provided overall coordination and oversight of the project.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This systematic review was approved by the Office of Responsible Research of the University Miguel Hernández (Reference: TFG.GME.VFGG.MMM.231103). Consent to participate was not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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