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Prevalence, Associated Risk Factors, and Adverse Cardiovascular Outcomes of Statins Discontinuation: A Systematic Review

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ABSTRACT

Purpose: Statins are widely prescribed for cardiovascular diseases (CVD) prevention; however, a significant proportion of users discontinue the medication for various reasons. This review aimed to determine the prevalence of statin therapy discontinuation, its associated factors, and adverse cardiovascular outcomes within the first year of discontinuation.

Methods: The PubMed, EMBASE, ScienceDirect, SCOPUS, and Google Scholar databases were systematically searched from their inception to December 2022. Manual searches were also conducted on the bibliographies of relevant articles. Studies were included for qualitative data synthesis and assessed for methodological quality.

Results: Fifty-two studies, predominantly cohort studies ($n = 38$), involving 4 277 061 participants were included. The prevalence of statin discontinuation within the first year of statin initiation ranged from 0.8% to 70.5%, which was higher for primary prevention indications. Factors frequently associated with an increased likelihood of statin discontinuation included male sex, nonWhite ethnicity, smoking status, and being uninsured. Conversely, discontinuation was less likely in patients with CVD who received secondary prevention statin therapy and in patients with polypharmacy. Furthermore, age showed diverse and inconsistent relationships with statin discontinuation among various age categories. Five studies that reported the cardiovascular risk of statin discontinuation within the first year of initiation showed significantly increased risk of discontinuation, including all-cause mortality (hazard ratio: 1.36–3.65).

Conclusion: Our findings indicate a high prevalence of statin discontinuation and an increased likelihood of adverse cardiovascular outcomes within the first year of discontinuation, despite wide variability across published studies. This review highlights the importance of addressing the modifiable risk factors associated with statin discontinuation, such as smoking and lack of insurance coverage.

1 | Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. According to global statistics from the World Health Organization, approximately 17.9 million people died of CVDs in 2019 [1]. The global prevalence of CVD increased from 271 million in 1990 to 523 million in 2019 [2]. The burden of atherosclerotic cardiovascular disease (ASCVD) can be reduced through preventive strategies, such as managing modifiable risk factors (e.g., tobacco use, hypertension,

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Summary

- Statins are commonly prescribed for cardiovascular protection, but a significant proportion of patients either temporarily or permanently discontinue using them for various reasons.
- The rate of statin discontinuation and its associated risk factors can differ depending on the setting and population studied.
- This review estimated the discontinuation rate of statins within the first year of treatment, the risk factors associated with discontinuation, and the incidence of cardiovascular events during the first year following discontinuation.
- The review found a high rate of statin discontinuation and a greater likelihood of adverse cardiovascular outcomes within the first year after stopping the medication.
- Modifiable factors linked to statin discontinuation include smoking and the lack of health insurance.

diabetes, low high-density lipoprotein cholesterol, high low-density lipoprotein [LDL] cholesterol, and weight). The use of hydroxymethylglutaryl-CoA reductase inhibitors (statins class of medications) to reduce ASCVD risk in high-risk populations (i.e., primary prevention) and in those with a history of ASCVD (i.e., secondary prevention) is one of the most important prevention modalities in clinical practice [3, 4].

Prior to 2013, statin therapy was mainly used for secondary prevention and in high-risk individuals considered to have coronary heart disease-risk equivalent [5]. The 2013 updated clinical practice guidelines on the management of blood cholesterol to reduce ASCVD risk focused on lifestyle changes and expanded the eligibility of statin therapy for the primary prevention of ASCVD with high- or moderate-intensity statin therapy [6]. This has significantly increased the number of statin users, with an estimated 12.8 million adults in the United States becoming eligible for statin therapy initiation because of new guidelines [7]. Furthermore, both the 2018 cholesterol guidelines for ASCVD prevention and 2019 guidelines for CVD prevention reaffirmed the 2013 guideline recommendations for the use of statins as first-line pharmacotherapy for both the primary and secondary prevention of ASCVD [8, 9].

Statin therapy is required for the secondary prevention of CVD, such as myocardial infarction (MI) and stroke [10, 11]. However, its use for primary prevention is selective, with consideration of its risks and benefits, as well as discussion with the patient prior to therapy initiation [12]. Therefore, guidelines recommend the individualization of the use of statins for primary prevention in older adults (i.e., >75 years old) as the benefits may not outweigh the risks in this population [13].

High-intensity rosuvastatin and atorvastatin are the most commonly prescribed statins for CVD prevention [14, 15]. High doses of statins are associated with an increased risk of muscle-related side effects, such as myopathy and rhabdomyolysis, which occur in 10%–15% of patients on statin therapy. Other statin-related adverse effects (e.g., elevated liver enzymes, increased risk of diabetes mellitus, benign proteinuria, and neuropathy) occur at lower rates [16, 17]. These side effects increase the potential for reduced adherence among patients owing to statin intolerance. Some patients permanently discontinue statin therapy when temporary discontinuation and rechallenge fail to mitigate muscle-related side effects [18]. A large prospective cohort study of patients on statins for the primary and secondary prevention of CVD in the United Kingdom found that 47% of the patients temporarily or permanently discontinued statin therapy after a median follow-up of 137 weeks [19]. Large cohort studies have reported an increased risk of cardiovascular (CV) events and all-cause mortality in high-risk patients within the first year of statin discontinuation [20–23].

The prevalence of statin discontinuation and its associated factors vary significantly by setting, population, and country of study. The factors associated with statin discontinuation could be socioeconomic-related (e.g., cost of medication or lack of prescription medication insurance coverage), patient-related (e.g., low health literacy and multiple comorbidities), or medication-related (e.g., side effects). Aggregating regional and global data on the factors associated with and reasons for discontinuation of statin therapy is important. Therefore, clinicians and researchers, irrespective of their country or region of practice, may need to identify the reported factors and predict potential discontinuation of statin therapy among their patients, which may ultimately allow the modifications of amenable factors.

Accordingly, determining the magnitude of statin therapy discontinuation and factors associated with the likelihood of discontinuation is important for designing feasible intervention strategies to minimize the associated risks. To the best of our knowledge, no previous systematic review has provided a global landscape of statin therapy discontinuation, its associated risk factors, and CV risk within the first year of discontinuation. Since previous cohort studies have estimated high rates of statin discontinuation within the first year of initiation and the associated increased risk of CV events and all-cause mortality, we conducted a systematic review of published studies to (1) determine the discontinuation rate of statins within the first year of initiation, (2) identify the risk factors associated with statin therapy discontinuation, and (3) estimate the risk of CV events during the first year after statin therapy discontinuation.

2 | Methods

A systematic review protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol standards [24, 25]. The review protocol was registered with the International Prospective Register of Systematic Reviews (protocol registration number: CRD42020188801).

2.1 | Source of Data and Search Strategy

The following electronic bibliographic databases and search engines were searched from their inception to December 2022: PubMed, EMBASE, ScienceDirect, SCOPUS, and Google Scholar. Search keywords from different categories were combined using Boolean operators (AND/OR/NOT) to identify

eligible studies (Box 1). However, the search strategy varied for each electronic database based on its features and the availability of advanced search features and thesauri. For instance, MeSH terms were used in PubMed, whereas Emtree was used in EMBASE. Box 2 presents the examples of the search strategies applied in the different databases.

In addition, the bibliographies of relevant reviews and original research articles identified through the electronic searches were manually searched. Google Scholar was used for the supplementary search.

2.2 | Inclusion Criteria and Selection of Studies

A study was included in the review, if it fulfilled the following eligibility criteria: (1) the study population included patients with or at risk of CV events who discontinued statin therapy and (2) the study utilized any of the following study designs: randomized controlled trials (RCTs), nonRCTs, cohort, case–control, cross-sectional, or quasi-experimental study designs. In this review, eligible studies were limited to those published in English. Studies were excluded if they involved nonprimary studies (e.g., case reports, literature reviews, editorials, letters to the editor, and commentaries), or if the CV outcomes were surrogate markers. Table 1 shows the "Population, Intervention, Comparison, and Outcomes" approach used to define the study eligibility/inclusion criteria.

Various electronic databases were searched to identify studies that met the prespecified eligibility criteria. This resulted in the identification of potentially eligible studies for inclusion in this review. The selected studies were screened in two stages: title/abstract screening and full-text screening. The titles and abstracts identified from the electronic searches were screened for potential eligibility using predefined eligibility criteria. Potentially eligible articles were identified through title/abstract screening by one reviewer (A.A.B. or S.A.A.) and validated by a second reviewer (A.A.B. or S.A.A.). Furthermore, the full texts of the potentially eligible studies identified from the title/abstract screening were independently read and assessed for inclusion in the review by any two reviewers (A.A.B., S.A.A., H.E., Y.B.O., or A.A.). Articles were selected for inclusion in the review based on prespecified eligibility criteria. Any disagreements or discrepancies between the two reviewers were resolved through discussion and consensus among all the research team members.

BOX 1 | Search categories combined.

- **Category A**
  Hydroxymethylglutaryl-CoA reductase inhibitors, HMG-CoA reductase inhibitors, statins.
- **Category B**
  Withholding treatment, treatment withdrawal, discontinuation.
- **Category C**
  Cardiovascular disease, cardiovascular, atherosclerotic cardiovascular disease (ASCVD).

BOX 2 | Examples of search strategy used in different databases.

- **PubMed:**
  (Withholding Treatment [MeSH Terms]) AND (Hydroxymethylglutaryl-CoA Reductase Inhibitors [MeSH Terms]) AND (Cardiovascular Disease [MeSH Terms]).
- **EMBASE:**
  (Treatment Withdrawal) AND (Hydroxymethylglutaryl Coenzyme A Reductase Inhibitor) AND (Cardiovascular Disease).
- **Scopus:**
  Statins AND Discontinuation AND Cardiovascular.
- **ScienceDirect**
  Statins AND Discontinuation AND Cardiovascular.

2.3 | Definition of Study Outcome Measures

Statin discontinuation: A continuous period of >30 days without statin intake [26].

Cardiovascular events: A composite of various adverse events, including cardiovascular death, nonfatal MI, or nonfatal stroke [27].

Risk factor with positive association: A variable that implies a higher likelihood of discontinuation (i.e., odds ratio [OR] >1 and hazard ratio [HR] >1).

Risk factor with negative association: A variable that implies a lower likelihood of discontinuation (i.e., OR < 1 and HR < 1).

2.4 | Assessment of the Methodological Quality of the Included Studies

Two reviewers (S.A.A./A.A.B., S.A.A./H.E., and A.A.B./H.E.) independently assessed the quality and critically appraised

TABLE 1 | Eligibility criteria for including studies in this review.

Participants/ population	Patients with or at risk of cardiovascular events who are new statin initiators
Interventions	Patients who discontinued statin therapy
Comparisons	Patients who continued statin therapy or no comparison group
Outcomes	Cardiovascular events
Study design	RCTs, nonRCTs, cohort, case–control, cross-sectional, or quasi-experimental design

Abbreviation: RCT, randomized controlled trials.

eligible studies using the Mixed Methods Appraisal Tool (MMAT) [28], which allows the appraisal of all the study designs included in a systematic review of mixed studies. This overcomes the challenges and labor intensiveness related to using different critical appraisal tools for different study designs. Whenever a disagreement occurred between the two reviewers, a consensus was reached through discussions with the other team members (Y.B.O. and/or A.A.). For each study design, the tool has a set of five questions answered as "Yes," "No," or "Cannot tell." The MMAT user guide does not specify or assign a score to each answered criterion. Hence, calculating a single score for the quality of a study is not mandatory. Consequently, the studies included in this review were not rated (e.g., high or low) for their methodological quality.

2.5 | Data Extraction

A standardized data extraction tool was developed and pilot tested based on the study objectives and according to the PRISMA reporting guidelines. Data extraction was performed by two independent reviewers (S.A.A./A.A.B., S.A.A./H.E., or A.A.B./H.E.), with a third reviewer (A.A. or Y.B.O.) consulted in case of any disagreement. The data items extracted from each included study were authors, country of study, year of publication, study design, sample size, study population, sample characteristics, main outcomes, summary of key findings, including statistical estimates, and other relevant information.

2.6 | Data Synthesis

In this review, we used a narrative approach for data synthesis. Pooling of the quantitative findings was not feasible because of the perceived high methodological and clinical heterogeneity. Wide variations were observed in the targeted populations, study designs, data collection tools, definitions of outcome measures, and other relevant parameters. This hindered the possibility of pooling the prevalence rates using meta-analysis. Therefore, a meta-analysis of quantitative data was not performed in this review. Textual and quantitative summaries of the findings based on the extracted data are presented. This review used a narrative synthesis approach to determine the prevalence of statin discontinuation.

3 | Results

This systematic review of the literature was conducted and reported in accordance with the PRISMA guidelines [29].

3.1 | Search Results

As shown in Figure 1, 877 studies were retrieved from four electronic databases. The removal of duplicates resulted in 689 studies for screening. Title and abstract screening led to the exclusion of 552 studies owing to various reasons (Figure 1). The full texts of the remaining articles ($n = 137$) were retrieved and reviewed. Of these, 85 articles were further excluded for the following reasons: the reported prevalence of statin discontinuation was not within the first year of initiation ($n = 30$), study did not meet the review objectives ($n = 25$), study population did not fit the review population ($n = 5$), prevalence of discontinuation was not specific to statin therapy ($n = 3$), cardiovascular outcomes were surrogate markers ($n = 3$), and other reasons ($n = 19$). Overall, 52 studies met the inclusion criteria.

3.2 | Characteristics of the Included Studies

This review included 52 studies (Table 2) [18, 19, 21, 22, 30–77] published in English from 2002 to 2022. Most studies used quantitative observational designs ($n = 45$) [18, 19, 21, 22, 30, 32, 34–39, 41–46, 48–52, 54–65, 67–71, 73–77], predominantly retrospective and prospective cohort studies. Seventeen studies were conducted in the United States [18, 30, 33–35, 40, 42, 47, 48, 53, 54, 56, 62, 67, 72, 75, 76], seven in Australia [52, 57–60, 64, 68], five in Finland [21, 22, 45, 66, 71], and three in Taiwan [37, 38, 48]. Two studies were conducted in each of the following countries: the United Kingdom [19, 61], Sweden [38, 39], Canada [41, 77], New Zealand [49, 65], China [73, 74], and South Korea [50, 51]. One study was conducted in each of the following countries: France [44], Denmark [69], Spain [55], Greece [31], Thailand [32], Japan [43], and Israel [70]. The studies included 4 277 061 participants, with the number of participants ranging from 318 to 1 399 872. Most studies ($n = 44$) included participants who had newly started statin therapy. The highest mean age was 82.5 years [58], while the lowest mean age was 52.5 years [76]. Thirty-nine studies included patients who received statins for primary and secondary prevention. Three studies [42, 44, 55] included patients who received statins for only primary prevention, and 10 studies [31, 37, 41, 49, 50, 56, 61, 62, 64, 74] included patients who received statins for only secondary prevention.

3.3 | Prevalence of Statin Discontinuation

Data from 37 studies reported the prevalence of statin discontinuation within the first year of initiation, represented in Table 3 [18, 19, 21, 22, 31, 32, 34–38, 41, 43, 45, 46, 48, 51, 52, 54–56, 58–63, 65–67, 69, 70, 73–77]. In the included studies, the prevalence of statin discontinuation within the first year of initiation ranged from 0.8% [31] to 70.5% [55]. The degree of prevalence was independent of the sample size, with studies with low and high sample sizes indicating wide variability in prevalence rates. The prevalence of statin discontinuation in the study with the largest sample size was 19.6% [51] and in the study with the lowest sample size was 22.3% [32]. The prevalence of statin discontinuation in the study with the highest mean age was 36.9% [58] and in the study with the lowest mean age was 57% [76].

Four studies [58, 60, 63, 76] compared the 6-month discontinuation prevalence with the 1-year discontinuation prevalence (23.2% vs. 30.1%, 22.9% vs. 36.9%, 27.2% vs. 42.7%, and 44% vs. 57%, respectively), indicating higher discontinuation rates over time. Majority of the other studies determined the rates of discontinuation at one time point within 1 year, with a few studies projecting prevalence rates using time-to-discontinuation curves. The difference in statin discontinuation rates between individuals in the primary prevention and secondary prevention groups was reported in four

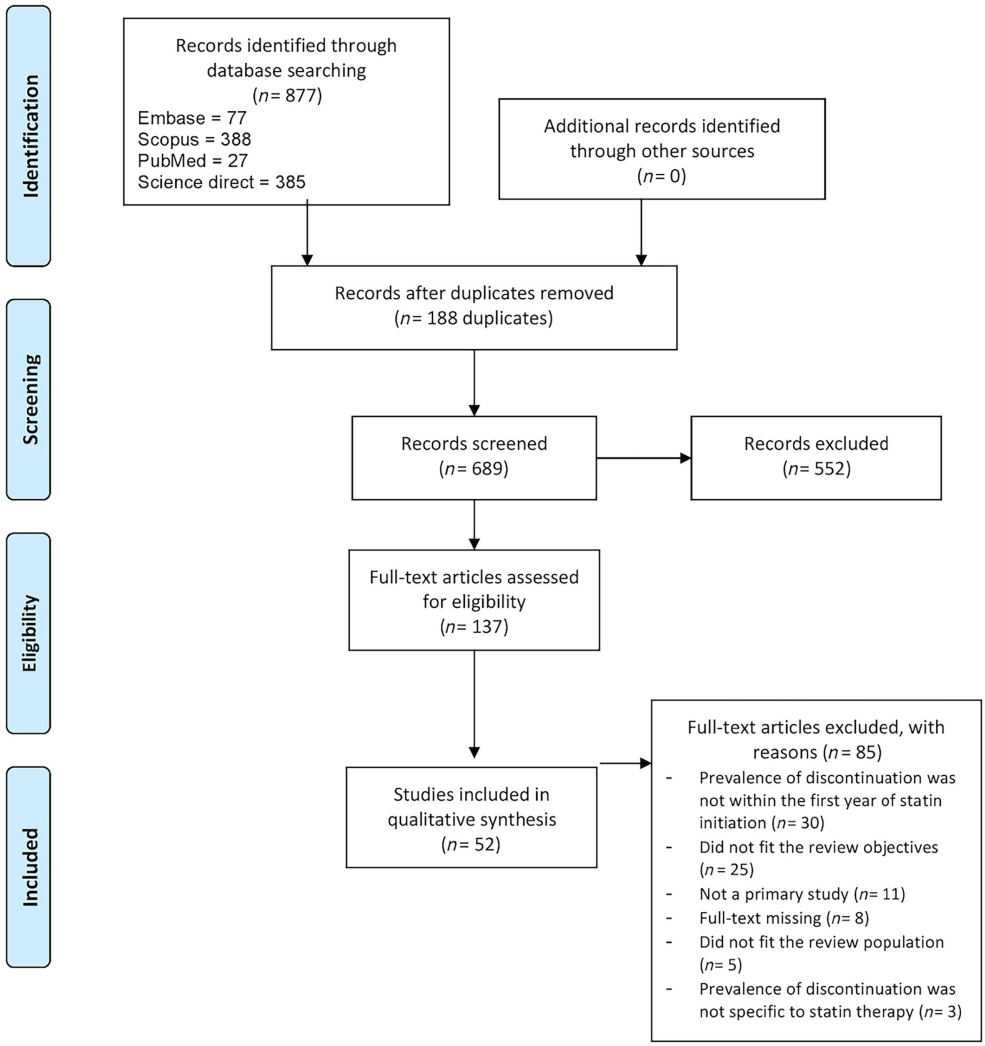

FIGURE 1 | PRISMA flow diagram.

studies [19, 39, 63, 65], with a higher discontinuation rate among individuals in the primary prevention group than among those in the secondary prevention group (29.8% vs. 19.7%, 32% vs. 18.4%, 13.3% vs. 10.5%, and 32% vs. 21%, respectively). Some studies [36, 45, 51] reported the prevalence rates based on the presence of diabetes. In one study [36], patients with diabetes without ASCVD had a discontinuation rate (36.21%) similar to that of patients with diabetes and ASCVD (36.56%). Meanwhile, the study conducted by Kim et al. found that patients with diabetes without ASCVD had a higher discontinuation rate (21.4%) than that had by patients with diabetes and ASCVD (19.6%) [51].

3.4 | Factors Associated With Statin Discontinuation

The factors identified in the included studies were classified into sociodemographic-, clinical characteristic-, medication-, patient-, and provider-related factors. Generally, these factors can be assessed on the basis of their positive or negative associations with statin discontinuation (Table 4).

3.5 | Sociodemographic-Related Factors

Several sociodemographic factors were reported to be associated with a higher likelihood of statin discontinuation, with age displaying a varied and mixed association with statin discontinuation across different age groups (i.e., <50 vs. 50–59 [35], <55 vs. ≥55 [72], ≤54 vs. 55–64 [65], ≥65 vs. < 65 [50], ≥75 vs.70–74 [69], 70–74 vs. <70 [71], and ≥85 vs. 65–74 [59]). The diverse and inconsistent relationships between the age categories and statin discontinuation are shown in Table 4. Male sex ($n = 4$ [42, 65, 68, 70]), nonWhite vs. White individuals ($n = 2$ [19, 65]), and lack of insurance coverage ($n = 2$ [72, 74]) were associated with a higher likelihood of statin discontinuation. Other sociodemographic factors that increased the likelihood of statin therapy discontinuation were divorced marital status ($n = 1$) [69], high education level of >10 years ($n = 1$ [69]) or primary education or below ($n = 1$ [32]), and being a smoker ($n = 2$) [19, 48]. Conversely, some factors associated with a lower likelihood of statin discontinuation were a higher body mass index ($n = 1$) [21], being an ex-smoker ($n = 1$) [19], and having a higher income ($n = 2$) [38, 72].

TABLE 2 | Characteristics of included studies ($n = 52$).

Authors/year	Country of study	Study design	Sample size	Study population	Sample characteristic (average age)
Vu et al. [72] (2022)	Finland	Cohort study	47 829	Statin users who got a clinically verified AD diagnosis during 2005–2011 and a matched comparison cohort without AD	79 years
Xie et al. [74] (2022)	China	Cohort follow-up study	10 337	Follow up to CPACS-2 trial including consecutive patients with ACS admitted to the participating hospitals and followed-up surviving patients till 1 year after discharge	63.2 ± 11.6 years
Alsuhibani et al. [30] (2021)	United States	Retrospective cohort study	19 332	Patients aged 19 years who were statin users at the time of bariatric surgery	Primary prevention: 51.6 years Secondary prevention: 54.1 years
Boettiger et al. [32] (2021)	Thailand	Observational cohort study	318	Patients ≥18 years with a history of statin use on ART, who attended HIV-NAT Research Collaboration Centre in Bangkok between 2001 and 2020 with written informed consent for their data to be analyzed	48.1 years
Gao, Seki, and Kawakami [43] (2021)	Japan	Retrospective cohort study	128 626	Patients aged ≥18 years who initiated treatment with a statin (pitavastatin, atorvastatin, pravastatin, simvastatin, or fluvastatin) between January 1, 2014, and December 31, 2016	53 years
Talic et al. [68] (2021)	Australia	Cohort study	141 062	Patients older than ≥18 years of age with newly dispensed prescriptions of atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin were included in the analyses	59.8 years

(Continues)

TABLE 2 | (Continued)

Authors/year	Country of study	Study design	Sample size	Study population	Sample characteristic (average age)
Hsu et al. [46] (2020)	Taiwan	A before–after cohort study	Primary prevention:610411 Secondary prevention: 40404	Patients aged ≥20 years or above who were newly diagnosed with ASCVD or newly diagnosed with CVD-related risk factors during the pre-regulation period and post-regulation period	Not reported
Kerr et al. [49] (2020)	New Zealand	Retrospective cohort study	19 867	Patients who were alive 30 days after discharge were included. Only the first presentation per person in the three-year period was included	65.3 years
Reynolds et al. [62] (2020)	United States	Retrospective cohort study	11 059	Patients aged ≥40 years with incident severe PAD, including a subset with CLI, diagnosed between October 1, 2002 and September 30, 2015. Patients having 12 months of continuous membership and a pharmacy benefit prior to the index date and 1 month after the index date to capture a change in therapy after a PAD/CLI diagnosis	68.6 years
Seaman et al. [64] (2020)	Australia	Retrospective population-based longitudinal cohort study	22 495	Individuals who were provided with sufficient supply of statin medications for tertiary prevention at the end of 2004	Continued therapy: 67.8 years. Discontinued therapy: 65.6 years
Sigglekow, Horsburgh, and Parkin [65] (2020)	New Zealand	Cohort study	289 666	Patients who were dispensed a publicly funded statin between January 1, 2005, and December 31, 2013. Patients were classified into primary and secondary prevention groups	Primary prevention: 59 years* Secondary prevention: 67 years*
Rezende Macedo do Nascimento et al. [63] (2020)	Scotland	Retrospective longitudinal cohort study	73 716	All adult patients (≥18 years old) who newly initiated statin therapy between January 2010 and December 2015	61.4 years

(Continues)

TABLE 2 | (Continued)

Authors/year	Country of study	Study design	Sample size	Study population	Sample characteristic (average age)
Ofori-Asenso et al. [59] (2019)	Australia	Retrospective cohort study	22 340	Older adults started statins. Analyses were performed separately for general beneficiaries (with a higher co-payment; $n = 4841$) and concessional beneficiaries (with a lower co-payment; $n = 17\,499$)	73.1 years
Giral et al. [44] (2019)	France	Nationwide population-based retrospective cohort study	120 173	Patients aged ≥75 in 2012–2014, previously adherent to statin therapy for at least 2 years with no history of cardiovascular disease	Not reported
Chen et al. [36] (2019)	Taiwan	A retrospective longitudinal database analysis	80 167	Patients aged ≥20 years with history of clinical ASCVD or DM (without previous clinical ASCVD) initiating statin or statin plus ezetimibe therapy during 2006–2012	65.74 years
Thompson et al. [69] (2019)	Denmark	Register-based descriptive drug utilization study	83 788	All Danish persons, aged 70 years or older, initiating statin treatment	75 years*
Bradley et al. [33] (2019)	United States	Cross-sectional survey study	5693	Participants who have been recommended for statin therapy according to the 2013 ACC/AHA guideline in the PALM registry	68 years
Noaman et al. [57] (2018)	Australia	Retrospective cohort study	363	Older adults patients admitted to a large Australian geriatric evaluation and management unit	81.4 years
Kim et al. [51] (2018)	South Korea	Retrospective cohort study	1 399 872	Patients aged ≥18 years with 41 outpatient pharmacy claim for a statin and/or ezetimibe dated from January 1, 2012, to December 31, 2014	61.6 years
Ofori-Asenso et al. [58] (2018)	Australia	Retrospective cohort study	589	Patient aged ≥65 years with dementia	82.5 years
Ofori-Asenso et al. [60] (2018)	Australia	Retrospective cohort study	7400	Older adults aged ≥65 years with DM who were dispensed medications between January 1, 2007, and December 31, 2016	74.6 years

(Continues)

TABLE 2 | (Continued)

Authors/year	Country of study	Study design	Sample size	Study population	Sample characteristic (average age)
Chung et al. [37] (2018)	Taiwan	Retrospective cohort study	2468	Patients with a principal diagnosis of ICH (ICD-9-CM: 431) on admission	66.4 years
Protty et al. [61] (2017)	South Wales (United Kingdom)	Retrospective longitudinal study	1806	Patients who were started on statins at the point of discharge from ACS tertiary centers were included in the study and followed up for 3 years	68.0 years
Silvennoinen et al. [66] (2017)	Finland	Survey	1022	Finnish adults diagnosed with CAD, DM, hypertension, or severe hereditary dyslipidemia	67.0 years
Malo et al. [55] (2017)	Spain	Prospective longitudinal study	725	Middle-aged male Mediterranean Spanish worker newly treated with statin	54.7 years
Burke et al. [34] (2016)	United States	Retrospective cohort study	92 621	Patients with evidence of either ASCVD or familial hypercholesterolemia who initiated statin or ezetimibe therapy between January 1, 2007, and December 31, 2012	64.7 years
Halava et al. [21] (2016)	Finland	Prospective cohort study	9285	Local government employees who had initiated statin medication between January 1, 1998, and December 31, 2010	55.7 years
Lin et al. [54] (2016)	United States	Retrospective cohort study	541 221	Adult patients at high cardiovascular risk, who received more than one prescription for statin monotherapy and who had not received lipid-modifying therapy during the previous 12 months were identified	57.7 years
Vinogradova et al. [19] (2016)	United Kingdom	Prospective open cohort study	431 023	Patients aged 25–84 years who started statin treatment between January 1, 2002, and September 30, 2013	61.4 years
Jacobson et al. [47] (2016)	United States	Survey	1500	Participants who have taken a statin within the past 2 years and to have had ≥1 statin-associated adverse experience in the last 6 months	58 years

(Continues)

TABLE 2 | (Continued)

Authors/year	Country of study	Study design	Sample size	Study population	Sample characteristic (average age)
Citarella et al. [39] (2015)	Sweden	Cohort study	29 389	Subjects who purchased at least one statin between July 1, 2006, and June 30, 2007	Not reported
Kim et al. [50] (2015)	South Korea	Prospective, multicenter, and observational registry	3807	Patients who survived for 1 year after AMI	64.3 years
Knott et al. [52] (2015)	Australia	Nationally representative, cluster-stratified, cross-sectional survey	1260	Patients over 55 years old and who filled prescriptions for statins within 12 months of their consultation date between April and June 2008	68 years
Kutner et al. [53] (2015)	United States	Multicenter, parallel group, unblinded, pragmatic clinical trial	381	English-speaking adults (aged ≥18 years) receiving a statin for 3 months or longer for primary or secondary prevention of cardiovascular disease	74.1 years
Muntner et al. [56] (2014)	United States	Retrospective cohort study	2695	Medicare beneficiaries who experienced an AMI, coronary artery bypass graft or PCI in 2007, 2008, or 2009	Not reported
Citarella et al. [38] (2014)	Sweden	Population-based cohort study	86 002	All subjects who purchased at least one statin between July 1, 2006, and June 30, 2007	Not reported
Daskalopoulou et al. [41] (2014)	Canada	Population-based cohort study	48 229	Patients who survived an AMI for at least 90 days	70.1 years
Simpson et al. [67] (2013)	United States	Retrospective cohort study	11 473	Patients with high risk of cardiovascular disease who newly initiated on statins between January 1, 2006, and August 31, 2009	55.3 years
Wei et al. [72] (2013)	United States	Cross-sectional, self-administered Internet-based survey	10 138	Adult participants diagnosed with high cholesterol by a physician, currently or previously on a statin	61 years
Zhang et al. [18] (2013)	United States	Retrospective cohort study	107 835	Adults who received a statin prescription between January 1, 2000, and December 31, 2008	61.1 years
Cohen et al. [40] (2012)	United States	Observational survey based	10 138	Individuals with high cholesterol, self-reported current or former use of a statin	61 years

(Continues)

TABLE 2 | (Continued)

Authors/year	Country of study	Study design	Sample size	Study population	Sample characteristic (average age)
Wong et al. [73] (2011)	China	Cohort study	5806	Adult patients of Chinese ethnicity with lipid-lowering prescription	62.2 years
Athyros et al. [31] (2010)	Greece	A post hoc analysis of GREASE, a prospective, randomized, open label study	880	Patients with established coronary heart disease, aged younger than 75 years, stratified to patients with abnormal liver tests and patients with normal liver tests	58.3 years
Helin-Salmivaara et al. [45] (2009)	Finland	A nationwide register study	562 598	Initiators of statin with or without the presence of diabetes	Not reported
Yeaw et al. [76] (2009)	United States	Retrospective cohort study	94 700	Patients initiating a prescription drug of interest in any of six drug classes (prostaglandin analogs, statins, bisphosphonates, oral antidiabetics, ARBs, and overactive bladder medications	52.5 years
Helin-Salmivaara et al. [22] (2008)	Finland	Retrospective cohort study	18 072	Persons who had started a statin between January 1, 1995, and December 31, 1995	Not reported
Foody et al. [42] (2008)	United States	Retrospective cohort study	186 653	New statin users with and without prior cardiovascular events within the 12-month pre-treatment period	52.4 years
Yu et al. [77] (2008)	Canada	Observational study of a cohort	19 038	Adult patients who newly initiated statin therapy	58.2 years
Vinker et al. [70] (2008)	Israel	Retrospective cohort study	47 680	Individuals enrolled in the Central District of Clalit Health Services HMO who filled at least one prescription for statins between January 1, 1999, and December 31, 2006	61.3 years
Kamal-Bahl et al. [48] (2007)	United States	Retrospective cohort study	161 540	Patients newly initiated on lipid-modifying drug classes	Not reported
Caspard et al. [35] (2005)	United States	Retrospective cohort study	4776	Patients with baseline LDL-C $\geq$ 130 mg/dL and who started statin treatment between January 1, 1994, and July 1, 1999	Not reported

(Continues)

TABLE 2 | (Continued)

Authors/year	Country of study	Study design	Sample size	Study population	Sample characteristic (average age)
Yang et al. [75] (2002)	United States	Retrospective cohort study	15 488	New initiator for lipid-lowering drugs due to coronary heart disease, hyperlipidemia, or other atherosclerotic diseases, and who received two or more prescriptions for LLD between January 1, 1990, and December 31, 1997	Not reported

Abbreviations: ACS: acute coronary syndrome; AD: Alzheimer's disease; AMI: acute myocardial infarction; ARBs: angiotensin II receptor blocker; ART: antiretroviral therapy; ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; CLI: critical limb ischemia; CPACS-2: clinical pathway for acute coronary syndrome phase 2; DM: diabetes mellitus; GREASE: Greek atorvastatin and coronary heart disease evaluation; HIV-NAT: human immunodeficiency virus-Netherlands, Australia, Thailand; HMO: health maintenance organization; ICH: intracerebral hemorrhage; LLD: lipid lowering drugs; PAD: peripheral artery disease; PALM: patient and provider assessment of lipid management; PCI: percutaneous coronary intervention.

[a]Median age.

3.6 | Clinical Characteristic-Related Factors

The most predominant clinical factors that showed a lower likelihood of statin therapy discontinuation included having ASCVD ($n = 9$; i.e., stroke [69], MI [69], coronary artery disease (CAD) [22, 45], angina [59], secondary prevention of CVD [30, 38, 57, 69], and congestive heart failure [19, 49, 59]) and polypharmacy [59]. Having risk factors for ASCVD ($n = 6$; i.e., diabetes [22, 42, 59] and atrial fibrillation [19, 69]) were associated with a higher likelihood of statin therapy discontinuation. Hypertension, an ASCVD risk factor, was reported in two studies to be associated with a higher likelihood of statin therapy discontinuation [42, 69], whereas it was associated with a lower likelihood of discontinuation in four studies [19, 42, 59, 74]. Other clinical characteristic-related factors that increased the likelihood of discontinuation were a Charlson comorbidity score of ≥3 ($n = 1$) [69] and health care utilization ($n = 3$) [44, 57, 77] (i.e., outpatient visits, hospital admission during follow-up, admission to a skilled nursing home, discharge to a residential care facility, initiation of enteral or oral feeding, failure of improvement assessed using the Functional Independence Measure, and lower Mini Mental State Examination score). Conversely, very high baseline (>5 mmol/L) and high (≥4.1 mmol/L) LDL-C ($n = 2$) [39, 74] and other health care utilization factors ($n = 3$; i.e., revascularization [49], coronary artery bypass grafting (CABG)/percutaneous translumenal coronary angioplasty [77], and in-hospital percutaneous coronary intervention/CABG) [74] exhibited a lower likelihood of statin discontinuation. Table 4 presents more details of the clinical factors associated with statin discontinuation.

3.7 | Medication-Related Factors

The included studies reported that several concomitant medications were associated with a lower likelihood of statin therapy discontinuation. These included antihypertensive agents ($n = 3$) [42, 72, 77], oral antihyperglycemic agents ($n = 2$) [69, 72], previous antihyperlipidemic treatment ($n = 2$) [35, 74], nonstatin lipid-lowering drugs ($n = 1$) [42], psychiatric medications ($n = 1$) [72], antidepressants ($n = 1$) [69], hormone replacement therapy ($n = 2$) [22, 45], and anticoagulation therapy ($n = 3$) [19, 59, 69]. Taking aspirin for the primary and secondary prevention of ASCVD was associated with a higher and lower likelihood of statin discontinuation, respectively ($n = 1$) [19]. Two studies showed a significantly lower likelihood of statin discontinuation when one or more of the different cardiovascular drugs were used within 365 days before statin initiation [22, 45]. Atorvastatin use compared with simvastatin was associated with a lower likelihood of discontinuation ($n = 3$) [42, 59, 77]. Concerns over adverse effects or experiencing adverse effects contributed to a significantly greater likelihood of statin therapy discontinuation ($n = 1$) [66]. In addition, the use of generic statins compared with brand statins was associated with a lower risk of statin discontinuation ($n = 1$) [43].

3.8 | Patient-Related Factors

The likelihood of discontinuation was higher when patients had more than 1 day delay of statin therapy dispensation ($n = 1$) [77],

TABLE 3 | Prevalence of statin discontinuation.

Authors/year	Sample size	Discontinuation rate (*n*, %)
Xie et al. [74] (2022)	10337	2634 (25.5)
Boettigera et al. [32] (2021)	318	71 (22.3)
Gao, Seki, and Kawakami [43] (2021)	The generic group 14313	3466 (24.2)
	The brand-name group 14313	3969 (27.7)
Hsu et al. [46] (2020)	Secondary prevention group	
	CHD 18360	9685 (52.75)
	CBVD 20277	8675 (60.38)
	PAD 1767	12243 (55.52)
	Primary prevention group	
	HTN 123179	69953 (56.79)
	DM 124743	73948 (59.28)
	DLP 362489	245731 (67.79)
Reynolds et al. [62] (2020)	5285	660 (12.5)
Sigglekow, Horsburgh, and Parkin [65] (2020)	Secondary prevention group 50811	10010 (19.7)
	Primary prevention group 238855	71179 (29.8)
Rezende Macedo do Nascimento et al. [63] (2020)	All patients at 6 months 73716	17102 (23.2)
	All patients at 12 months 73716	22189 (30.1)
	Secondary prevention at 6 months 10632	1212 (11.4)
	Secondary prevention at 12 months 10632	1956 (18.4)
	Primary prevention at 6 months 63084	15897 (25.2)
	Primary prevention at 12 months 63084	20187 (32)
Ofori-Asenso et al. [59] (2019)	Concessional and general beneficiaries 22340	9982 (44.7)
	Concessional beneficiaries 17499	7542 (43.1)
	General beneficiaries 841	2440 (50.4)
Chen et al. [36] (2019)	Overall 80167	30778 (38.4)
	ASCVD 80167	4055 (36.56)
	Diabetes without ASCVD 80167	11261 (36.21)

(Continues)

TABLE 3 | (Continued)

Authors/year	Sample size	Discontinuation rate (*n*, %)
Thompson et al. [69] (2019)	83 788	10 892 (13)
Kim et al. [51] (2018)	First lipid-lowering treatment discontinuation ASCVD 807 547	158 279 (19.6)
	Diabetes without ASCVD 592 325	126 758 (21.4)
	Second lipid-lowering treatment discontinuation ASCVD 807 547	110 634 (13.7)
	Diabetes without ASCVD 592 325	84 110 (14.2)
Ofori-Asenso et al. [58] (2018)	At 6 months 589	135 (22.9)
	At 1 year 589	217 (36.9)
Ofori-Asenso et al. [60] (2018)	Based on 45-day gap criteria[a] At 6 months 7400	3034 (41)
	At 1 year 7400	4129 (55.8)
	Based on 90-day gap criteria At 6 months 7400	2013 (27.2)
	At 1 year 7400	3160 (42.7)
	Based on 180-day gap criteria At 1 year 7400	2094 (28.3)
Chung et al. [37] (2018)	2468	813 (33)
Protty et al. [61] (2017)	1333	716 (53.7)
Silvennoinen et al. [66] (2017)	1022	45 (4.4)
Malo et al. [55] (2017)	725	511 (70.5)
Burke et al. [34] (2016)	ASCVD or FH cohorts 92 621	11 485 (12.4)
	ASCVD cohort 91 740	11 376 (12.4)
	FH cohort 937	127 (13.6)
Halava et al. [21] (2016)	9285	1142 (12.3)
Lin et al. [54] (2016)	541 221	286 847 (53.0)

(Continues)

TABLE 3 | (Continued)

Authors/year	Sample size	Discontinuation rate (*n*, %)
Vinogradova et al. [19] (2016)	Primary and secondary prevention groups 570 337	71 897 (12.6)
	Primary prevention group 431 023	57 317 (13.3)
	Secondary prevention group 139 314	14 580 (10.5)
Citarella et al. [39] (2015)	Subjects without previous CV events 18 972	6071 (32)
	Subjects with previous CV events 10 417	2188 (21)
Knott et al. [52] (2015)	1260	147 (12)
Muntner et al. [56] (2014)	2695	187 (6.9)
Daskalopoulou et al. [41] (2014)	14 120	488 (3.46)
Simpson et al. [67] (2013)	11 473	2811 (24.5)
Zhang et al. [18] (2013)	107 835	50 543 (47.9)
Wong et al. [73] (2011)	5806	1172 (20.2)
Athyros et al. [31] (2010)	880	7 (0.8)
Helin-Salmivaara et al. [45] (2009)	In patients with diabetes 84 570	19 367 (22.9)
	In patients without diabetes 478 028	125 243 (26.2)
Yeaw et al. [76] (2009)	Based on 30-days gap criteria[a] At 6 months 94 700	52 085 (55)
	Based on 60-days gap criteria At 6 months 94 700	41 668 (44)
	At 1 year 94 700	53 979 (57)
	Based on 90-days gap criteria At 6 months 94 700	35 986 (38)
Helin-Salmivaara et al. [22] (2008)	18 072	4820 (26.7)
Yu et al. [77] (2008)	Based on 31–183 days dispensation delay 19 038	2120 (11.1)
	Based on >183 days dispensation delay 19 038	1293 (6.8)
Vinker et al. [70] (2008)	47 680	29 132 (61.1)
Kamal-Bahl et al. [48] (2007)	161 540	46 847 (29)
Caspard et al. [35] (2005)	4776	1226 (26)
Yang et al. [75] (2002)	15 488	2303 (14.8)

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CBVD: cerebrovascular disease; CHD: coronary heart disease; CV: cardiovascular; DLP: dyslipidemia; DM: diabetes mellitus; FH: familial hypercholesterolemia; HTN: hypertension; PAD: peripheral artery disease.
[a]Gap criteria: interval days between medication refills.

TABLE 4 | Factors associated with statin discontinuation in patient with cardiovascular disease.

Factors	Statistically significant positive association[a], reference	Statistically significant negative association[b], reference
Sociodemographic-related		
Age		
Age <35	$n=1$ [65]	
Age 35–54	$n=1$ [65]	
Age >40		$n=1$ [30]
Age <50	$n=1$ [35]	
Age <55	$n=1$ [72]	
Age ≥45		$n=3$ [22, 38, 45]
Age ≥50		$n=1$ [70]
Age ≥60		$n=3$ [21, 55, 68]
Age ≥65	$n=1$ [50]	$n=1$ [65]
Age 70–74	$n=1$ [71]	
Age ≥75	$n=2$ [69, 71]	$n=1$ [65]
Age ≥85	$n=1$ [59]	
Age (per 10 years increase)		$n=1$ [49]
Octogenarian status	$n=1$ [57]	
Gender		
Male	$n=4$ [42, 65, 68, 70][c]	$n=5$ [30, 35, 65, 69, 71, 72][d]
Body mass index		
≥25		$n=1$ [21]
Ethnicity		
Other ethnic groups vs. white	$n=2$ [19, 65]	
Marital status		
Divorced	$n=1$ [69]	
Education		
>10 years	$n=1$ [69]	
Primary or below	$n=1$ [32]	
Smoking status		
Ex-smoker vs. nonsmoker		$n=1$ [19]
Smoker vs. nonsmoker	$n=2$ [19, 48]	
Region		
Capital vs. Northern Denmark	n = 1 [69]	
Zealand vs. Northern Denmark	$n=1$ [69]	
Outside Sweden		$n=1$ [38]
Midwest United States vs. west		$n=1$ [42]
South United States vs. west	$n=2$ [30, 42]	
Northeast United States vs. South		$n=1$ [30]

(Continues)

TABLE 4 | (Continued)

Factors	Statistically significant positive association[a], reference	Statistically significant negative association[b], reference
North central vs. South		$n=1$ [30]
Ethiopia vs. others	$n=1$ [70]	
New immigrants (to Israel)		
Immigration in 1990 and later (compared with others)	$n=1$ [70]	
Individual income		
2nd quartile and above		$n=1$ [38]
Annual household income		$n=1$ [72]
Insurance		
Uninsured	$n=2$ [72, 74][a]	
Plan type		
Point of service vs. fee for service	$n=1$ [77]	
Preferred provider (organization-large employer) vs. fee for service	$n=1$ [77]	
Payer type: medicaid vs. commercial	$n=1$ [42]	
Payer type: medicare Risk vs. commercial	$n=1$ [42]	
Payer type: self-insured/other/unknown vs. commercial	$n=1$ [42]	
Plan type: PPO vs. HMO	$n=1$ [42]	
Plan type: POS vs. HMO		$n=1$ [42]
Plan type: indemnity vs. HMO	$n=1$ [42]	
Plan type: other/unknown vs. HMO		$n=1$ [42]
Nonconcession user	$n=1$ [48]	
Clinical characteristics-related		
Indication		
Secondary prevention of CVD	$n=1$ [49]	$n=4$ [30, 38, 57, 69]
Comorbidities		
Chronic diseases		
Any chronic disease before starting statins		$n=1$ [70]
Any chronic disease after starting statins		$n=1$ [70]
Diabetes	$n=3$ [22, 42, 57]	$n=1$ [49]
Type 1 diabetes	$n=1$ [19]	
Type 2 diabetes		$n=1$ [19]
Angina		$n=1$ [59]
MI		$n=1$ [69]
Hypertension	$n=2$ [42, 69]	$n=4$ [19, 42, 59, 74]*
Congestive heart failure	$n=1$ [71]	$n=3$ [19, 49, 59]
Pain	$n=1$ [59]	

(Continues)

TABLE 4 | (Continued)

Factors	Statistically significant positive association[a], reference	Statistically significant negative association[b], reference
Stroke		$n=1$ [69]
CAD	$n=1$ [69]	$n=2$ [21, 22]
Vascular comorbidities		$n=1$ [21]
Atrial fibrillation	$n=2$ [69, 71][d]	$n=1$ [71][c]
Dementia		$n=1$ [69]
Dementia, short-term statin use		$n=1$ [19]
Dementia, long-term statin use	$n=1$ [19]	
Anxiety	$n=1$ [59]	
Steroid responsive condition	$n=1$ [59]	
Liver disease	$n=1$ [19]	
COPD	$n=1$ [19]	
Cancer	$n=1$ [19]	
Metastatic solid tumors	$n=1$ [44]	
CKD	$n=1$ [42]	$n=1$ [30]
Polypharmacy (≥5 medications)		$n=1$ [59]
Charlson comorbidity score		
≥1		$n=1$ [65]
≥3	$n=1$ [69]	
Genetic characteristics		
Familial hypercholesterolemia	$n=1$ [71][d]	$n=1$ [71][c]
Health care utilization		
Revascularization		$n=1$ [49]
CABG/PTCA		$n=1$ [77]
In-hospital PCI/CABG		$n=1$ [75][a]
Outpatient visits	$n=1$ [77]	
Hospital admission during follow-up	$n=1$ [44]	
Admission to a skilled nursing home	$n=1$ [44]	
Discharge to residential care facility	$n=1$ [57]	
Initiation of enteral or oral feeding	$n=1$ [44]	
Failure of improvement in FIM	$n=1$ [57]	
Lower MMSE	$n=1$ [57]	
Baseline LDL-C		
Very high (>5 mmol/L) vs. low ≤3 mmol/L)		$n=1$ [39]
High (≥4.1 mmol/L) vs. (<4.1 mmol/L)		$n=1$ [75][a]
2–<3 vs. <2	$n=1$ [49]	
>3 vs. <2	$n=1$ [49]	
Unmeasured	$n=1$ [75][a]	

(Continues)

TABLE 4 | (Continued)

Factors	Statistically significant positive association[a], reference	Statistically significant negative association[b], reference
Bariatric procedure types, vs. LAGB		
RYGB	$n=1$ [30]	
SG	$n=1$ [30]	
BPD-DS/WDS	$n=1$ [30]	
Clinical pathway intervention		$n=1$ [75][a]
Medication-related		
Concomitant medication use		
Antiplatelets		$n=1$ [69]
Aspirin	$n=1$ [71][c]	$n=1$ [71][d]
Anticoagulant therapy		$n=3$ [19, 59, 69]
Warfarin		$n=1$ [42]
Anti-hypertensive agents		$n=3$ [42, 72, 77]
Psychiatric medication		$n=1$ [72]
ACEIs or ARBs		$n=1$ [69]
Beta-blockers		$n=1$ [69]
Calcium channel blockers		$n=1$ [69]
Oral antihyperglycemics		$n=2$ [69, 72]
Previous anti-hyperlipidemia treatment		$n=2$ [35, 75][a]
Lipid-lowering (nonstatin) drug use		$n=1$ [42]
Fibric acid derivatives		$n=1$ [77]
Antidepressants		$n=1$ [69]
Each of other noncardiovascular treatment	$n=1$ [19]	
Hormone replacement therapy		$n=2$ [21, 22]
Discontinuation of ACEIs, ARBs, or aliskiren during follow-up	$n=1$ [44]	
Number of different cardiovascular drugs during 365 days prior to the statin initiation		
≥1		$n=2$ [21, 22]
Statin use before cohort entry		
≥1 year		$n=1$ [71]
3 months		$n=1$ [49]
Statin 3 months post discharge		
Number of cardiovascular drug substance other than statin use		
≥1		$n=1$ [71]
Number of concomitant medications		
3–4		$n=1$ [32]
>4		$n=1$ [32]

(Continues)

TABLE 4 | (Continued)

Factors	Statistically significant positive association[a], reference	Statistically significant negative association[b], reference
Statin type		
Atorvastatin vs. simvastatin	$n=1$ [65]	$n=2$ [42, 59]
Rosuvastatin vs. simvastatin	$n=1$ [19]	$n=1$ [59]
Pravastatin vs. simvastatin		$n=2$ [19, 65]
Pitavastatin vs. simvastatin	$N=1$ [30]	
Lovastatin vs. atorvastatin	$n=1$ [77]	
Simvastatin vs. atorvastatin	$n=1$ [77]	
Statin type at discharge		
Atorvastatin vs. others		$n=1$ [75][a]
Statin dose at baseline (potency units)		
Two or more vs. one		$n=1$ [19]
Defined daily dose		$n=1$ [65]
Statin dose at discharge from ACS event		
Lower dose (<10 mg atorvastatin or equivalent) vs. standard dose (10–19 mg atorvastatin)	$n=1$ [75][a]	
High dose of statin (≥20 mg atorvastatin or equivalent) vs. standard dose (10–19 mg atorvastatin)	$n=1$ [75][a]	
Low intensity vs. high intensity	$n=2$ [49, 68]	
Moderate intensity vs. high intensity	$n=2$ [49, 68]	
Switching statin plus up-titrating intensity vs. no switching		$n=1$ [68]
Cholesterol monitoring frequency		
Annually	$n=1$ [72]	
New or worsened muscle aches, cramps, or pain while taking statin	$n=1$ [72]	
Internet use to research statin	$n=1$ [72]	
Use of nonprescription products to lower cholesterol	$n=1$ [66]	
Concerns over adverse effects	$n=1$ [66]	
Experienced adverse effects	$n=1$ [66]	
Generic vs. brand-name statin use		$n=1$ [43]
Patient-related		
Satisfaction with physician explanation of treatment		
Satisfied or extremely satisfied dissatisfied, extremely dissatisfied	$n=1$ [72]	
Perception of futility	$n=1$ [66]	
Difficulties in use	$n=1$ [66]	
Concerns over costs		$n=1$ [66]

(Continues)

TABLE 4 | (Continued)

Factors	Statistically significant positive association[a], reference	Statistically significant negative association[b], reference
Dispensation delay		
≥1 days	$n=1$ [77]	
Retail vs. mail order prescription	$n=1$ [30]	
Days' supply of first statin dispensing		
≤30	$n=1$ [65]	
≥91		$n=1$ [65]
Frequency of GP visits		
≥2 vs. 1		$n=1$ [64]
Provider-related		
Index prescriber		
GP vs. specialist	$n=1$ [65]	$n=1$ [59]
Provisional general vs. specialist	$n=1$ [65][c]	$n=1$ [65][d]
Internal medicine vs. general specialist		$n=1$ [65]
Urgent care vs. general specialist	$n=1$ [65]	
Internal medicine/cardiology/neurology vs. primary care		$n=1$ [38]
Internal medicine vs. general/family practice		$n=1$ [77]
Cardiology vs. FP/GP	$n=1$ [42]	
Other specialty vs. FP/GP	$n=1$ [42]	
Unknown specialty vs. FP/GP	$n=1$ [42]	
Health care provider		
Private	$n=1$ [38]	

Abbreviations: ACEIs: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ARBs: angiotensin ii receptor blocker; BPD-DS/WDS: biliopancreatic diversion with or without duodenal switch; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: coronary kidney disease; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; FIM: functional independence measure; FM: family medicine; FP: family physician; GP: general practitioner; HMO: health maintenance organization; LAGB: laparoscopic adjustable gastric banding; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; MMSE: Mini Mental State Examination; PCI: percutaneous coronary intervention; POS: point of service; PPO: preferred provider organization; PTCA: percutaneous translumenal coronary angioplasty; RYGB: roux-en-y gastric bypass; SG: laproscopic sleeve gasterectomy.

[a]Implies higher likelihood of discontinuation (i.e., OR >1, HR >1).

[b]Implies less likelihood of discontinuation (i.e., OR <1, HR <1).

[c]For primary prevention group.

[d]For secondary prevention group.

difficulty with its use ($n=1$) [66], or had a perception of futility ($n=1$) [66]. One study [65] showed a higher and lower likelihood of statin therapy discontinuation when the first statin dispensed is for ≤30 and ≥91 days, respectively.

3.9 | Provider-Related Factors

Studies have reported a significantly lower likelihood of statin discontinuation when the healthcare provider was specialized (i.e., internal medicine/cardiology/neurology) compared with a general practitioner (i.e., primary care/general/family practice clinicians) ($n=3$) [38, 59, 77]. Conversely, another study reported a significantly higher likelihood of discontinuation when the healthcare provider was a cardiology specialist than when the provider was a general or family practice clinician ($n=1$) [42]. Moreover, one study found that receiving care in the private sector compared with the public sector was associated with a higher likelihood of statin discontinuation ($n=1$) [38].

3.10 | Measure of Cardiovascular Events/Outcomes After Statin Discontinuation

Only five of the 52 included studies reported the risk of cardiovascular events during the first year after discontinuation of statin therapy. All the five studies reported in Table 5 [37, 41, 44, 50, 53] showed an increased risk. One study reported significant increase in admission rate for cardiovascular events after 6 and 12 months of statin discontinuation

TABLE 5 | Risk of cardiovascular events/outcomes in patients who discontinued statins.

Authors/year	Cardiovascular events/outcomes		
Giral et al. [44] (2019)	Covariate	For a 6-month gap:	For a 12-month gap:
	Admission for a cardiovascular event		
	Adjusted HR	1.34 (95% CI 1.18–1.53)	1.28 (95% CI 1.08–1.51)
	Covariate	Continued	Discontinued
	Number of outcome events:		
	At 3–7 months:	934/119035 (0.78%)	34/1138 (2.98%)
	At 8–12 months	962/114212 (0.84%)	39/3456 (1.13%)
	Total	1896/233247 (0.81%)	73/3594 (1.6%)
Chung et al. [37] (2018)	Covariate	Continued	Discontinued
	All-cause mortality event number, *n* (%)	35 (4.9)	87 (12.3)
	HR (95% CI)	0.38 (95% CI 0.26–0.57)	Ref
Kim et al. [50] (2015)	Covariate	Adjusted HR (95% CI, *p*)	
	All-cause mortality	3.45 (95% CI 2.81 to 4.24, $p < 0.001$)	
	Cardiac mortality	4.65 (95% CI 3.14 to 6.87, $p < 0.001$)	
Kutner et al. [53](2015)	Covariate	Continued	Discontinued
	Mortality, *n* (%)	39 (20.3)	45 (23.8)
	90% CI, *p*	Ref	CI −3.5%–10.5%; $p = 0.36$
	Survival		
	Median time to death	190 days	229 days
	90% CI, *p*	CI, 170–257	CI, 186–332, $p = 0.60$.
	Time to first cardiovascular-related event, *n* (%), *p*	11 (6.73)	13 (6.88), $p = 0.64$
Daskalopoulou et al. [41] (2014)	Covariate	Adjusted HR (95% CI, *p*)	
	1-year all-cause mortality		
	Nonusers	Reference category	
	Statin stoppers	1.36 (95% CI 1.08–1.70, $p = 0.008$).	
	Users	0.81 (95% CI 0.74–0.88, $p < 0.0001$)	

compared with statin continuation (adjusted HR 1.34 [95% confidence interval [CI] 1.18–1.53] and 1.28 [95% CI 1.08–1.51], respectively) [44]. Chung et al. showed significantly lower event rates in terms of all-cause mortality with statin continuation than with statin discontinuation (4.9% vs. 12.3%, respectively) [37]. Similarly, the study by Kim and colleagues showed significantly higher mortality rate for the statin discontinuation group than for the continuation group: all-cause mortality (27.9% vs. 7.7%, respectively; HR 3.45; 95% CI 2.81–4.24, $p < 0.001$) and cardiac mortality (11.1% vs. 1.7%, respectively; HR 4.65; 95% CI 3.14–6.87; $p < 0.001$) [50]. In addition, another study reported that statin stoppers had significantly increased 1-year all-cause mortality compared with that had by nonusers (adjusted HR 1.36; 95% CI 1.08–1.70, $p = 0.008$) [41]. However, one study showed no significant difference in the time to first cardiovascular-related event in patients with limited life expectancy ($p = 0.64$), with cardiovascular event rates of 6.88% in the discontinuation group and 5.73% in the continuation group [53].

3.11 | Quality Assessment of Included Studies

As shown in Table 6, most of the studies that assessed quality using the MMAT quality assessment tool were quantitative nonrandomized ($n = 45$ [18, 19, 21, 22, 30, 32, 34–39, 41–46, 48–52, 54–65, 67–71, 73–77]), followed by quantitative descriptive ($n = 5$ [33, 40, 47, 66, 72]) and quantitative RCTs ($n = 2$ [31, 53]). In quantitative nonrandomized studies, the participants were generally representative of the target population and all underwent appropriate measurements regarding the outcome and exposure. However, only 16 of the 45 studies accounted

TABLE 6 | Methodological quality assessment of included studies using MMAT.

Quantitative randomized controlled trials					
Authors/year	**Is randomization appropriately performed?**	**Are the groups comparable at baseline?**	**Are there complete outcome data?**	**Are outcome assessors blinded to the intervention provided?**	**Did the participants adhere to the assigned intervention?**
Kutner et al. [53] (2015)	Y	Y	Y	Can't tell	Y
Athyros et al. [31] (2010)	Can't tell	Can't tell	Can't tell	Can't tell	Y

Quantitative nonrandomized					
Authors/year	**Are the participants representative of the target population?**	**Are measurements appropriate regarding both the outcome and intervention (or exposure)?**	**Are there complete outcome data?**	**Are the confounders accounted for in the design and analysis?**	**During the study period, is the intervention administered (or exposure occurred) as intended?**
Vu. et al. [71] (2022)	Y	Y	Y	N	Y
Xie. et al. [74] (2022)	Y	Y	N	N	Y
Alsuhibani et al. [30] (2021)	Y	Y	Y	Y	Y
Boettigera et al. [32] (2021)	Y	Y	Y	N	N
Gao, Seki, and Kawakami [43] (2021)	Y	Y	Y	N	Y
Talic et al. [68] (2021)	Y	Y	Y	N	Y
Hsu et al. [46] (2020)	Y	Y	Y	N	Y
Kerr et al. [49] (2020)	Y	Y	Can't tell	N	Y
Reynolds et al. [62] (2020)	Y	Y	Y	N	Y
Seaman et al. [64] (2020)	Y	Y	Y	Y	Y
Sigglekow, Horsburgh, and Parkin [65] (2020)	Y	Y	Y	Y	Y
Rezende Macedo do Nascimento et al. [63] (2020)	Y	Y	Y	N	Y

(Continues)

TABLE 6 | (Continued)

	Quantitative nonrandomized				
Authors/year	**Are the participants representative of the target population?**	**Are measurements appropriate regarding both the outcome and intervention (or exposure)?**	**Are there complete outcome data?**	**Are the confounders accounted for in the design and analysis?**	**During the study period, is the intervention administered (or exposure occurred) as intended?**
Ofori-Asenso et al. [59] (2019)	Y	Y	N	Y	Y
Giral et al. [44] (2019)	Y	Y	Y	Y	Y
Chen et al. [36] (2019)	Y	Y	Y	N	Y
Thompson et al. [69] (2019)	Y	Y	Y	Y	Y
Noaman et al. [57] (2018)	Y	Y	N	N	Y
Kim et al. [51] (2018)	Y	Y	Y	N	Y
Ofori-Asenso et al. [58] (2018)	Y	Y	N	N	Y
Ofori-Asenso et al. [60] (2018)	Y	Y	N	N	Y
Chung et al. [37] (2018)	Y	Y	Y	Y	Y
Protty et al. [61] (2017)	Y	Y	Y	N	Y
Malo et al. [55] (2017)	Y	Y	Y	Y	Y
Burke et al. [34] (2016)	Y	Y	Y	N	Y
Halava et al. [21] (2016)	Y	Y	Y	N	Y
Lin et al. [54] (2016)	Y	Y	Y	N	Y
Vinogradova et al. [19] (2016)	Y	Y	Y	N	Y
Citarella et al. [39] (2015)	Y	Y	Can't tell	Y	Y
Kim et al. [50] (2015)	Y	Y	Y	Y	Y
Knott et al. [52] (2015)	Y	Y	Y	Y	Y
Muntner et al. [56] (2014)	Y	Y	Y	N	Y
Citarella et al. [38] (2014)	Y	Y	Can't tell	Y	Y
Daskalopoulou et al. [41] (2014)	Y	Y	Y	Y	Y

(Continues)

TABLE 6 | (Continued)

Quantitative nonrandomized					
Authors/year	**Are the participants representative of the target population?**	**Are measurements appropriate regarding both the outcome and intervention (or exposure)?**	**Are there complete outcome data?**	**Are the confounders accounted for in the design and analysis?**	**During the study period, is the intervention administered (or exposure occurred) as intended?**
Simpson et al. [67] (2013)	Y	Y	Y	N	Y
Zhang et al. [18] (2013)	Y	Y	Y	N	Y
Wong et al. [73] (2011)	Y	Y	Y	N	Y
Helin-Salmivaara et al. [45] (2009)	Y	Y	N	N	Y
Yeaw et al. [76] (2009)	Y	Y	N	N	Y
Helin-Salmivaara et al. [22] (2008)	Y	Y	Y	N	Y
Foody et al. [42] (2008)	Y	Y	Y	Y	Y
Yu et al. [77] (2008)	Y	Y	Y	Y	Y
Vinker et al. [70] (2008)	Y	Y	Y	Y	Y
Kamal-Bahl et al. [48] (2007)	Y	Y	N	N	Y
Caspard et al. [35] (2005)	Y	Y	Y	N	Y
Yang et al. [75] (2002)	Y	Y	N	N	Y

Quantitative descriptive					
Authors/year	**Is the sampling strategy relevant to address the research question?**	**Is the sample representative of the target population?**	**Are the measurements appropriate?**	**Is the risk of nonresponse bias low?**	**Is the statistical analysis appropriate to answer the research question?**
Bradley et al. [33] (2019)	Y	Y	Y	Y	Y
Silvennoinen et al. [66] (2017)	Y	Y	Y	Can't tell	Y
Jacobson et al. [47] (2016)	Y	Y	Y	Y	Y
Wei et al. [72] (2013)	Y	Y	Y	Y	Y
Cohen et al. [40] (2012)	Y	Y	Y	Y	Y

for confounders in their design and analysis [30, 37–39, 41, 42, 44, 50, 52, 55, 59, 64, 65, 69, 70, 77]. Furthermore, exposure occurred as intended in all the 45 studies. In the quantitative descriptive studies, the sampling strategy was relevant for addressing the research questions in the five categories of MMAT, except for the nonresponse bias category, which four of the five studies were assigned low risk [33, 40, 47, 72]. Of the two RCTs included in this review, one met all the quality assessment criteria, except blinding, which could not be determined, and the other was of low quality, partly because it was a post hoc analysis of the RCT.

4 | Discussion

The major finding of this systematic review was that the rate of statin discontinuation within the first year of initiation ranged from 0.8% to 70.5%. This wide range of discontinuation could be explained by the inclusion of heterogeneous studies in different study populations (e.g., older adults and patients with human immunodeficiency virus [HIV], Alzheimer's disease, or primary prevention of ASCVD). In addition, discontinuation of statin therapy was sometimes temporary, and patients were often successfully rechallenged after the underlying reasons for discontinuation were resolved [34, 35, 51]. Furthermore, studies who obtained their results from pharmacy claims data could identify patient nonadherence because patients who had not picked their statin medications after 30 days were considered to have discontinued their statin therapy [51, 77].

Another important finding of this study was that multiple factors, including male sex, nonWhite descent, and lack of prescription insurance, led to higher rates of statin therapy discontinuation. Conversely, statin discontinuation was less likely in patients with ASCVD, MI, CAD, and angina; those taking statin therapy for the secondary prevention of CVD; or those with polypharmacy. Patients without prescription drug coverage and with inadequate prescription coverage are more likely to self-discontinue their medications or extend their monthly medications for more than 2 months to reduce their out-of-pocket costs [78–80]. Patients with multiple chronic medical conditions are often prescribed several medications (polypharmacy) [81–83]. The combination of multiple medical conditions, high out-of-pocket costs, polypharmacy burden, and associated medication side effects contribute to reduced adherence to and eventual discontinuation of medications if the patients are not closely followed/monitored by healthcare professionals. Usually, patients on complex polypharmacy are followed up regularly by a multidisciplinary team, including pharmacists and nurses. Regular follow-ups and assessment of cholesterol levels make patients feel accountable, lowering their likelihood of discontinuing their medications [84–86]. Therefore, depending on how polypharmacy is managed, it may have either a positive or negative association with statin discontinuation. Frequent interaction of patients on polypharmacy with the health system ensures that factors that may influence low adherence (e.g., transportation to the pharmacy, lack of money to cover copay, and lack of motivation) are managed, and patients can maximize the benefit of the protective effect of statin therapy. Furthermore, muscle-related side effects, the fear of side effects, and perception of side effects are among the common reasons patients often report for declining to start and for discontinuing statin therapy [33, 40]. This report was also confirmed by primary care providers, who faced challenges reinitiating statin therapy in patients who have experienced side effects [87]. Pharmacists and nurses have used various strategies to increase statin adherence and persistence, with the goal of reducing statin discontinuation. This includes phone reminders, face-to-face counseling, home visits, and cardiovascular risk assessments to inform patients about the risk of an ASCVD [88–92].

Medication-related factors that reduced the likelihood of statin therapy discontinuation included multiple medications, especially antihypertensives, oral antihyperglycemic agents, previous antihyperlipidemia treatment, nonstatin lipid-lowering agents, psychiatric medications, antidepressants, hormone replacement therapy, and anticoagulation therapy. This finding can be partly due to the effect of motivation, education, and counseling provided to patients by multiple prescribers [93] and supporting pharmacists and nurses or because taking multiple medications concomitantly makes it easier to manage the pill burden [94]. Individuals and patients on multiple medications (e.g., aspirin, statins, and blood pressure medications) to reduce their CV risk with no significant CV history, but with modifiable and nonmodifiable risk factors are more likely to discontinue their medications than that observed among those who have experienced life-threatening CV events, such as acute MI [65]. One study reported that taking aspirin for the primary prevention of ASCVD was associated with an increased likelihood of statin discontinuation and a lower likelihood of statin discontinuation in secondary prevention patients [95]. This finding may be explained by the fact that different guidelines have provided conflicting recommendations regarding aspirin use for the primary prevention of CVDs; thus, many patients may not feel the need to use multiple medications including statins [95]. In contrast, patients who use aspirin for secondary prevention are generally sicker and could have experienced severe cardiovascular events that make them more concerned about their health, so they adhere better to their medications [96].

Some patient-related factors that led to higher statin discontinuation rates included delays in dispensing medications or difficulty in receiving the medication on time. This is often multifactorial, partly related to the overall health literacy and amount of information patients receive about their health and about the importance of medication adherence [97], as well as access to medicines that could be related to underlying social factors, such as transportation issues, and the inability of patients to afford copayments for health care and medications. Until these underlying issues are resolved, some patients are forced to discontinue and restart their medications several times per year [98, 99].

We found a trend of improvement in statin therapy adherence when healthcare providers had an internal medicine, cardiology, or neurology specialty compared with primary care, general, or family care providers. A study published in 1998 found some deficiencies in healthcare provided by medical generalists compared with specialists in many health-related areas, including CVD management [100]. However, the study concluded that these deficiencies were neither striking nor clinically significant [100]. This might represent an area of improvement through the transition of care and collaboration between medical generalists and specialists to improve overall patient health and medication

adherence, including taking statin [101]. Primary care providers admitted to having difficulty getting patients to restart statin therapy after experiencing side effects from the medication [87].

Furthermore, receiving care from the private sector, compared with the public sector, was associated with a higher likelihood of statin discontinuation. Although this finding has been previously reported in many disease conditions, it was reported to be common among patients with HIV and dyslipidemia [102]. This may be partly explained by the higher cost of medications in the private sector than in the public sector, where healthcare and medication costs are often subsidized [102, 103].

Only five of the included studies reported the risk of cardiovascular events during the first year after discontinuation of statin therapy. These included a significant increase in cardiac-related admissions 6 and 12 months after statin discontinuation and in all-cause mortality rates. Observational studies reflecting real-world practices over the years have shown evidence of an increased risk of 1-year CV events and all-cause mortality in patients, who discontinued statin therapy for primary or secondary prevention [41, 44, 104]. Although this is an important area of investigation, it remains under studied, probably owing to the difficulty in the follow-up of these patients and heterogeneity of patients who mostly use statins.

The strength of this review is the inclusion of multiple studies that are comprehensive and representative of the topic. In addition, the included studies were conducted in different regions, thus increasing the generalizability of the results. All studies included in this review were assessed for quality using the MMAT quality assessment tool, which suggested that most of the studies were of high quality, and the overall rating of the included articles was relatively high. The major limitation of this review is the marked heterogeneity in the specific outcomes reported and populations included. Owing to the variability of the studies and study populations included in this review, our findings should be interpreted with caution, and more robust studies may be warranted to reaffirm the findings related to the factors associated with statin discontinuation.

In conclusion, this systematic review found a high prevalence of statin discontinuation and an increased likelihood of adverse cardiovascular outcomes within the first year of discontinuation, despite the wide variability across published studies. Furthermore, this review identified multiple risk factors that could lead to the discontinuation of statin therapy within 1 year of initiation. These factors, especially modifiable factors such as smoking and lack of insurance coverage, must be addressed, and patients at risk of discontinuation should be regularly assessed for adherence. Some consequences of statin discontinuation, such as the recurrence of major adverse cardiovascular events, are serious and require prompt intervention to improve adherence and prevent sequelae. Further studies are needed to assess the specific reasons for discontinuation and the consequences of poor adherence to individual patient health.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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