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Statin Utilization among Patients with Acute Coronary Syndrome: Systematic Review

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Abstract

BACKGROUND: The early use of statin with intensive regimen has been recommended by the recent guidelines as the prevention of acute coronary syndrome (ACS) related events among the high-risk patients. Meanwhile, the inconsistent statin utilization for targeted patient in current practice is still an issue.

AIM: This study aims to review the utilization rate of statin among patients with ACS.

METHODS: A systematic search of relevant studies published between inceptions to June 2020 was conducted in PubMed. Patients and intervention domains were used to build up the searching formula. A study was eligible for inclusion if it was an original study of patients with ACS and it examined the utilization of statin. The risk of bias was assessed using Axis and NOS checklist.

RESULTS: Among the 49 eligible studies, 38 were cohort studies while the others were cross-sectional studies. The utilization rate of statin at hospital admission ranged from 16% to 61% while 25% to 75% during the hospitalization. Of the total studies, 35 studies reported the statin rate at discharge ranging from 58% to 99%. Almost all studies revealed the reduction of statin utilization rate along the follow-up period. The number of statins prescribed was found to be lower among female and elderly patients.

CONCLUSION: Despite the established benefits of statin among patients with ACS, our study revealed that statin was underutilized for secondary prevention after ACS. To improve patients' clinical outcomes with ACS, efforts should be made to increase optimal treatment and compliance with a statin.

Introduction

The number of death and disability-adjusted life year loss due to the cardiovascular related disease has been widely reported worldwide [1]. The current guidelines recommended the use of statin as the major therapy for atherosclerotic cardiovascular disease (ASCVD) as well as the acute coronary syndrome (ACS) [2]. The primary and secondary prevention purpose of statin prescribing has been applied for patients with ACS [3]. The effect of low-density lipoprotein cholesterol (LDL-c) level reduction is closely related to the diminishing risk of cardiovascular events recurrences among ACS patients [4], [5], [6]. The guideline from American Heart Journal had given their recommendation to initiate or continue statin therapy among patients with clinical or high-risk symptoms of ASCVD since 2013 [4] and still stated in the updated version [2], [5]. Current evidence also revealed that statin could prevent major adverse cardiac events, cardiac death, and re-hospitalization among ACS patients [6], [7], [8], [9], [10]. Although the guidelines and current evidence consistently revealed the benefits of statin among the ACS patients [2], [4], [5], [10], the actual rate of statin utilization was also an issue of concerns. To date, several studies were conducted to examine the rate of statin utilization among the ACS patients in current practice. Therefore, we performed a systematic review to describe statin utilization rate among patients with ACS.

Methods

Search strategy and eligibility criteria

Relevant studies were identified from the PubMed database (from inception to June 2020). Patients (P) and Intervention (I) domains were used to build up the searching formula as follows: P- "Acute Coronary Syndrome" [Mesh]; I- "Hydroxymethylglutary-CoA Reductase Inhibitors" [Mesh], statin, atorvastatin, simvastatin, rosuvastatin, pitavastatin, pravastatin, and lovastatin. The two domains were combined with AND. Study selection was performed independently

by two reviewers. A study was eligible for inclusion if; (1) it was an original study conducted among patients with ACS, and (2) it examined the utilization of statin. A study was subsequently excluded if; (1) it was published in non-English language; (2) qualitative study; (3) interventional study; and (4) inaccessible of the full text.

Data extraction and quality assessment

The predesigned data extraction form was used by the reviewers to extract the data independently. Negotiation and consensus were done among the reviewers to resolve any disagreement. For each included full paper, the authors extracted the following data; bibliography details; setting; study design; characteristics of patients; statin utilization at hospital admission, during hospitalization, discharge and after hospital discharge; the pattern of statin utilization; and factors affecting statin utilization.

The quality assessment of all selected studies was conducted using the standard checklist to set up a good standard for the selected articles, such as the Axis checklist (for cross-sectional study) [11] and the Newcastle-Ottawa (NOS) checklist (for cohort study) [12]. The Axis checklist consisted of 20 questions, classified into the quality of introduction (Q1), study design (Q2), sample size justification (Q3), target population (Q4), sampling frame (Q5), sample selection (Q6), addressing the non-responders (Q7), measurement validity (Q8), measurement reliability (Q9), statistics (Q10), overall methods (Q11), raw data (Q12), response rate (Q13, Q14), the internally consistent result (Q15), comprehensive description of results (Q16), justified discussions and conclusions (Q17), limitations (Q18), conflicts of interest (Q19), and ethical approval (Q20) [11]. The NOS checklist covered quality assessment related to the selection process (4 questions), comparability in the analysis process (1 question), and outcome reported (3 questions) [12].

In terms of the NOS scale, the number of stars represented the quality of cohort studies with 8–9 stars representing good quality, 6–7 stars representing moderate quality, and less than 6 stars representing low-quality [12].

Data analysis

Characteristics of each included study were described. The utilization of statin was tabulated to identify patterns across the included studies. Utilization at each time point (i.e., before hospitalization, in-hospital, discharge, and follow-up period) was also reported and summarized as a trend of statin use over time.

Results

Study selection

A total of 252 studies were identified from the PubMed database. Among those studies, 100 studies were excluded after screening titles and abstracts. Thirty-seven studies were further excluded due to inaccessible of full-text. After screening full-text studies, 66 studies were excluded from the study (not examining the statin utilization-42, review articles-17, interventional studies-4, and not reporting statin utilization among ACS patients-3). Finally, 49 studies were included in this systematic review [Figure 1].

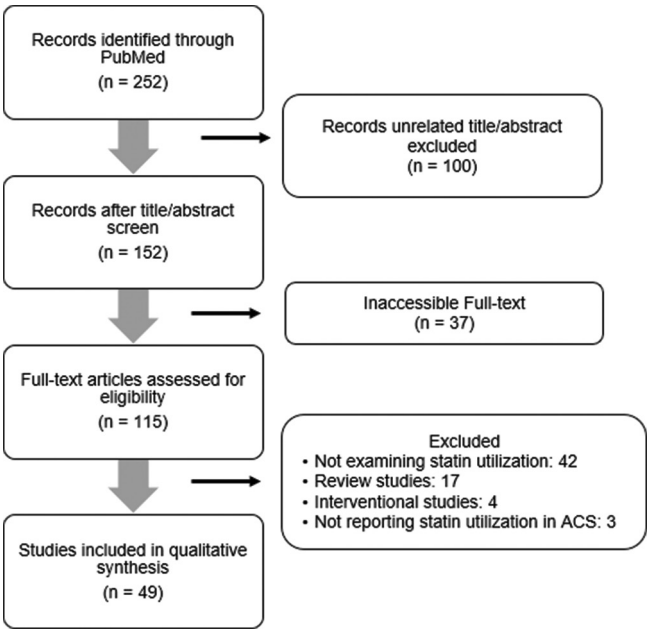

Figure 1: Flow chart for study selection

Study quality

Among the 41 cross-sectional studies assessed by the Axis checklist, all those studies had "Yes" answer for questions number 1, 2, 4, 5, 6, 9, 10, 11, 12, 15, 16, and 17 and "No" answer for question number 3 and 14. Eighteen studies did not measure and categorize the non-responders [6], [7], [9], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26]. There were nine studies [10], [18], [24], [27], [28], [29], [30], [31], [32] collecting data on statin use directly from the patients either by interview or self-reporting. By assessing the quality among the selected studies related to question number 13, missing data/loss to follow-up was higher than 20% in the three studies [28], [33], [34]. Referring to question number 18, six studies [8], [15], [21], [35], [36], [37] did not report their study limitation in the discussion part. Thirteen out of 41 studies declared their conflict of interest according to question number 19 in the checklist [9],

[10], [16], [18], [19], [24], [26], [28], [33], [34], [38], [39], [40]. Twelve studies did not receive the ethic committee approval nor the participant consent [6], [8], [14], [19], [21], [24], [25], [26], [33], [37], [38], [41]. The details of the assessment are presented in Table 1. The eight cohort studies assessed by the NOS checklist, three studies had eight stars [42], [43], [44] and the remaining four studies had nine stars [45], [46], [47], [48], [49], representing high quality. The details of the assessment are shown in Table 2.

Statin prescribing pattern

This systematic review described the pattern of statin utilization in the ten studies [9], [16], [20], [27], [30], [33], [35], [37], [41], [50], which was prescribed with another ACS medication such as antiplatelet, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), and beta-blocker as summarized by Table 3. Seven studies [9], [20], [33], [35], [37], [50] reported the use of statin together with aspirin, beta-blockers, and ACEI/ARB, which was considered as the evidence-based treatment of secondary prevention among the ACS patients. The utility rate of such evidence-based treatment varied from 25% [37] to 86.7% [50]. The use of statin along with beta-blocker and antiplatelet was reported in five studies [20], [30], [35], [37], [50], with the ranges between 10.1% [20] and 93.2% [30] at discharge. The combination therapy between statin and antiplatelet at discharge was examined in the four studies [20], [27], [35], [50] with prescribing rate ranging from 2.6% [20] to 97.6% [50].

Study characteristics

Characteristics of all 49 included studies are shown in Table 4. The 49 included studies were published from 2008 to 2020. Among the included studies, 13 studies were from Asia, 16 studies from Europe, nine studies from Australia-New Zealand, six from America, one from Africa, and four studies conducted in the selected countries from multiple continents. Of all included studies, nine studies were conducted in multiple countries. Data sources were registry, teaching hospital, specific care unit, national data linkage, and secondary and tertiary hospital. The range of sample sizes varied from 151 to 159,713. In terms of study design, 38 were cohort, while 11 were cross-sectional studies. All studies except one study [9] examined statin utilization as secondary prevention.

Statin utilization

Table 5 displays statin utilization along with factors associated with statin utilization. Among all included studies, 14 studies reported the use of statin at hospital admission. Statin utilization at admission

Table 1: Quality assessment of cross-sectional studies

Study	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20
Amar *et al*. [35]	2008	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	No	No	Yes
Lee *et al*. [41]	2008	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	No
Vermeer and Bajorek [13]	2008	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	Yes
Bi *et al*. [27]	2009	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Wong *et al*. [37]	2009	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No
Wong *et al*. [8]	2009	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No
Abdallah *et al*. [14]	2010	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	No
Melloni *et al*. [28]	2010	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Ramanath *et al*. [17]	2010	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	Yes
Aliprandi-Costa *et al*. [18]	2011	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	Yes	Yes
Bourdès *et al*. [50]	2011	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Javed *et al*. [33]	2011	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
The Access Investigators [29]	2011	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Andrikopoulos *et al*. [30]	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Ranasinghe *et al*. [19]	2012	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	Yes	No
Wai *et al*. [36]	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	No	No	Yes
Yusuf *et al*. [7]	2012	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	Yes
Andrikopoulos *et al*. [30]	2013	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Huffman *et al*. [56]	2013	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Kassab *et al*. [15]	2013	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	No	No	Yes
Shehab *et al*. [6]	2013	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	No
Gausia *et al*. [20]	2014	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	Yes
Grey *et al*. [71]	2014	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Jin *et al*. [31]	2014	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Maggioni *et al*. [38]	2014	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	Yes	No
Pereira *et al*. [54]	2014	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Shimony *et al*. [16]	2014	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	Yes	Yes
Wang *et al*. [51]	2014	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Anzai *et al*. [23]	2015	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	Yes
Ghadri *et al*. [21]	2015	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	No	No	No
Kassaian *et al*. [32]	2015	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	Yes
Medagama *et al*. [22]	2015	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	Yes
Selby *et al*. [9]	2015	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Gunnell *et al*. [39]	2016	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Boccara *et al*. [24]	2017	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	Yes	No
Eisen *et al*.	2017	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Khedri *et al*. [10]	2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Boklage *et al*. [26]	2018	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	Yes	No
Hoedemaker *et al*. [25]	2018	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	No
Hao *et al*. [34]	2019	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Desta *et al*. [52]	2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	DK	No	Yes	Yes	Yes	Yes	No	Yes

DK: Don't know.

ranged from 11.43% to 94.8%. Unfortunately, there were only two studies whose statin utilization at admission was more than 50% [6], [47]. In terms of statin utilization during hospitalization, many studies (7 out of 11 studies) reported that statin utilization was higher than 80% [22], [29], [30], [32], [34], [51], [52]. We found that most of the selected studies (39 studies) measured statin utilization rates at hospital discharge. Statin utilization at discharge varied from 20% to 99%. It should be noted that 29 studies (74%) reported that more than 80% of ACS patients received statin at hospital discharge.

Among the included studies, 18 studies reported statin use in a specified follow-up period after discharge. Most of those studies (17 of 18) reported statin use at 6 and/or 12 months as the follow-up time points. During the follow-up period, statin utilization rate ranged between 24.7% [31] and 94% [49]. The lowest rate (24.7%) of statin utilization during the follow-up period was reported among elderly patients (≥65 years old) [31].

Table 2: Quality assessment of cohort studies

Study	Year	Selection				Comparability		Outcome			Score
		1	2	3	4	A	B	1	2 (6 months)	3	
Kim *et al*. [42]	2012	*	*	*	*			*		*	8
Zeymer *et al*. [43]	2013	*	*	*	*			*	*	*	8
Gencer *et al*. [49]	2015	*	*	*	*	*		*	*	*	9
Ferreira-González *et al*. [44]	2016	*	*	*	*			*	*	*	8
Mantel *et al*. [45]	2017	*	*	*	*	*		*	*	*	9
Turner *et al*. [46]	2017	*	*	*	*	*		*	*	*	9
Al-Zakwani *et al*. [47]	2018	*	*	*	*	*		*	*	*	9
Sun *et al*. [48]	2018	*	*	*	*	*		*	*	*	9

The decreasing trends of statin utilization from discharge time point to follow-up periods were reported in the 11 studies [23], [27], [28], [31], [35], [36], [38], [43], [49], [51], [53]. Only one study conducted by Hoedemaker *et al*. [25] found that statin utilization slightly increased (85.2–88.1%) during 30 days of post-hospitalization discharge then decreased during 12 months of follow-up period (88.1–84.1%). Among the 11 studies that reported the decreasing tendency of statin utilization, the average of alteration did not exceed 25% except for one study conducted by Jin *et al*. [31].

Several studies reported the utilization rate of statin by age and gender. Of the included studies, seven studies compared statin utilization between male and female groups [6], [13], [21], [34], [39], [41], [54]. All of these studies reported that the use of statin was lower in females than males. At discharge time point, the male group was more likely to receive statin therapy compared to the female ($p < 0.001$) as reported by Lee *et al*. [41] and Vermeer and Bajorek [13] (OR 3.36; 95% CI 1.11–10.15). Ghadri *et al*. [21] reported that the female group was less likely to be prescribed with statins at hospital discharge (85.2% vs. 89.4%). Shehab *et al*. [6] reported that the proportion of male versus females receiving statin at admission was 95.1% versus 93.6%, and, at discharge, it was 92.1% versus 88.2%. Females were less likely to receive statin during the hospitalization (94.3% vs. 95.4%) and at discharge (90.7% vs. 93.2%) compared to male as reported by Hao *et al*. [34]. Among the STEMI patients, 92.4% of female participants received statin compared to 93.6% of males. Similarly, in the NSTE-ACS subgroup, 87.1% of females and 92.2% of males received statin therapy [54].

Four studies reported the use of statin utilization by age [23], [31], [41], [54]. All of these studies reported a significantly lower rate of statin utilization among the elderly. Elderly patients aged ≥80 years with NSTE-ACS were much less likely to receive statins (OR 0.35, 95% CI 0.19–0.64) at a discharge time point, as reported by Pereira *et al*. [54]. More specifically, into the age group, Lee *et al*. [41] reported that patients with ages <45, 65–79, and ≥80 years old were significantly less likely to receive statin compared to patients in the 45–64 age group ($p < 0.05$).

Table 3: Statin prescribing pattern with others acute coronary syndrome medication

Study	Year	AP+S	ACEI+S	BB+S	BB+AP+S	BB+ACEI/ARB+S	AP+ACEI/ARB+S	AP+BB+ACEI/ARB+S
Amar *et al*. [35]	2008	88.5 at discharge 83.8 at 14 months	53.5 at discharge 44.8 at 14 months		74.5 at discharge 65.9 at 14 months			46.2% at discharge 45.6% at 14 months of post-discharge
Lee *et al*. [41]	2008					29.9% at 3 months of post-discharge 37.5% at 6 months of post-discharge 42.6% at 12 months of post-discharge 46.3% at 18 months of post-discharge		
Bi *et al*. [27]	2009	78.5 at discharge 63.8 at 6 months 57.5 at 12 months						47.7% at discharge 43.6% at 6 months 40.6% at 12 months
Wong *et al*. [37]	2009				22.7% at discharge			25.1% at discharge
Javed *et al*. [33]	2011							57% at discharge 48% at 3 months of post-discharge
Bourdès *et al*. [50]	2011	97.6% at discharge			90.9% at discharge		92.4% at discharge	86.7% at discharge
Andrikopoulos *et al*. [30]	2012				93.2 at discharge 87.7 at 6-month follow-up			
Shimony *et al*. [16]	2014						58,3 at discharge	
Gausia *et al*. [20]	2014	2.6% at discharge	0.6% at discharge	0.2% at discharge	10.1% at discharge	0.6% at discharge	10.5% at discharge	50.7% at discharge
Selby *et al*. [9]	2015							41,8 at discharge 51,05 at 30 days of post-discharge

AP: Antiplatelet, S: Statin, ACEI: Angiotensin-converting enzyme inhibitor, BB: Beta-blocker, ARB: Angiotensin receptor blocker.

Table 4: The characteristics of studies

Study	Year	Country	Time points	Data Source	Patients characteristics	Design	Sample Size
Amar *et al*. [35]	2008	France	At discharge to 14-month follow-up	PREVENIR-4 study	Patients hospitalized with ACS (2005)	Cross-Sectional	1700
Lee *et al*. [41]	2008	US (Mid Atlantic state)	3, 6, 12, and 18-months follow-up	Medical claim from Managed Care Organization	Patients with ACS at discharge	Cohort	1135
Vermeer and Bajorek [13]	2008	Australia	At discharge	1 Major public teaching hospital	Patients diagnosed as primary or secondary ACS (January-April 2007)	Cross-Sectional	169
Bi *et al*. [27]	2009	China	At discharge, 6 and 12-months follow-up	51 Hospitals (Secondary and Tertiary Hospital)	Patients admitted to hospitals with a diagnosis of STEMI, NSEMI, or UA during Sept 2004-May 2006	Cohort	2901
Wong *et al*. [37]	2009	New Zealand	At discharge	2 Coronary Care Units	Hospital survivors with ACS discharged during 2000–2002	Cohort	1057
Wong *et al*. [8]	2009	New Zealand	At discharge to 5-year follow-up	2 Coronary Care Units	Hospital survivors with ACS discharged during 2000–2002 prescribed with aspirin	Cohort	1025
Abdallah *et al*. [14]	2010	Lebanon	In hospital and at discharge	Tertiary referral university hospital	Patients hospitalized and diagnosed with ACS (2002–2005)	Cross-Sectional	1025
Melloni *et al*. [28]	2010	USA	At admission, at discharge, and 12-month follow-up	MAINTAIN Registry	ACS patients (January 2006-September 2007)	Cohort	788
Ramanath *et al*. [17]	2010	USA	In a hospital, at discharge and 6-month follow-up	University of Michigan Health System's ACS registry	Patients hospitalized due to ACS and underwent coronary angiography	Cohort	2264
Aliprandi-Costa *et al*. [18]	2011	Australia New Zealand	In-hospital and 6-month follow-up	GRACE registry	17,263 STEMI and 3892 NSTE-ACS	Cohort	5615
Bourdès *et al*. [50]	2011	France	At discharge	PREVENIR-5 study	Patients hospitalized for the 1st episode of ACS	Cross-Sectional	4850
Javed *et al*. [33]	2011	USA	At discharge	GWTG program	ACS related hospitalization from 2005–2009	Cohort	159713
The Access Investigators [29]	2011	Africa Latin America Middle Eastern Countries	At admission, at discharge, 6 and 12-months follow-up	ACCESS registry	Patients hospitalized with ACS (2007–2008) 46.1%STEMI and 54% NSTE-ACS	Cohort	11731
Andrikopoulos *et al*. [30]	2012	Greece	At discharge and 6-month follow-up	TARGET study (17 centers)	Patients admitted with ACS (2012): 44.7% STEMI, 34.2% NSTEMI, 21.1% UA	Cohort	418
Kim *et al*. [42]	2012	Korea	In-hospital and 30-day follow-up	MUSTANG Registry	Patients presented with ACS and underwent PCI	Cohort	3362
Ranasinghe *et al*. [19]	2012	Australia New Zealand	In a hospital, at discharge, and 6-month follow-up	GRACE registry	Patients hospitalized and diagnosed with ACS at admission and discharge time points	Cohort	5556
Wai *et al*. [36]	2012	Australia	At discharge, 14-day and 3-month follow-up	DMACS project (49 hospitals)	Patients discharged with ACS (June-Sep 2008) 22%STEMI, 38% NSTEMI, 20% UA, 20% Un-specified	Cross Sectional	1545
Yusuf *et al*. [7]	2012	USA	At discharge and 12-month follow-up	1 University hospital	Patients discharged with acute MI (2000–2006)	Cohort	456
Andrikopoulos *et al*. [30]	2013	Greece	At discharge and 6-month follow-up	TARGET study	Patients with ACS admitted to the selected 17 hospitals	Cohort	366
Huffman *et al*. [55]	2013	India	In hospital and at discharge	Kerala ACS registry	ACS patients admitted to 125 hospitals (2007–2009)	Cross-Sectional	25718
Kassab *et al*. [15]	2013	Malaysia	At admission and discharge	1 Tertiary hospital	Patients with a primary diagnosis with ACS	Cross-Sectional	380
Shehab *et al*. [6]	2013	6 Middle Eastern Countries Bahrain Saudi Arabia Qatar Oman United Arab Emirates Yemen	At admission, at discharge, and 12 months follow up	Gulf RACE-2 Registry	Patients hospitalized with ACS as final diagnostic from 65 hospitals (2008–2009)	Cohort	7930
Zeymer *et al*. [72]	2013	Spain UK France Czech rep Germany Greece Norway Austria Hungary Belgium Netherland Sweden Denmark Finland	At admission, in hospital, at discharge, 3-month, 6-month, and 12-month follow-up	APTOR registry	Patients presented with ACS and underwent PCI	Cohort	4546
Gausia *et al*. [20]	2014	Australia	At admission and discharge	WA hospital morbidity Data Linkage System	ACS patients discharged alive (2002–2004)	Cohort	1717
Grey *et al*. [71]	2014	New Zealand	At discharge, 7-day, 30-day, 90-day, 12-month, 2-year, and 3-year follow-up	National datasets linkage of Public Hospital	ACS patients discharged from hospital over the year in 2007	Cohort	11348
Jin *et al*. [31]	2014	China	At discharge and 12-month follow-up	Cardiac center unit at a university hospital	Hospitalized patients with ACS (2009–2011)	Cohort	469
Maggioni *et al*. [38]	2014	Italy	At discharge	ARNO Observatory record linkage (7 local Italian health authorities)	Patients discharged with ACS	Cross-Sectional	3078
Pereira *et al*. [54]	2014	Portugal	At discharge	10 Public Hospitals	Patients discharged with ACS (744 STEMI and 1364 NSTE-ACS)	Cohort	2111

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Table 4: (*Continued*)

Study	Year	Country	Time points	Data Source	Patients characteristics	Design	Sample Size
Shimony *et al*. [16]	2014	High-income (Canada and United States) and Low/ middle-income (India, Iran, Pakistan, and Tunisia)	At discharge	ZESCA study (38 Centers from 6 countries)	Current smoker (smoked ≥ 10 cigarettes/day) ACS patients admitted to the ICCU or similar type of cardiology ward	Cross-Sectional	392 (265 from HIC, 127 from LMIC)
Wang *et al*. [51]	2014	Brazil	In a hospital, at discharge, and 6-month follow-up	ACCEPT registry	ACS patients (2011–2012)	Cohort	2453
Anzai *et al*. [23]	2015	Japan	In a hospital, at discharge, and 2-year follow-up	1 Teaching hospital	Patients underwent PCI for ACS with stenting (2005–2009)	Cohort	405
Gencer *et al*. [49]	2015	Switzerland	At discharge and 12-month follow-up	4 Teaching hospitals	ACS patients hospitalized during 2009–2012	Cohort	1602
Ghadri *et al*. [21]	2015	Switzerland	In-hospital and 30-day follow-up	Z-ACS registry (1 university hospital)	ACS patients underwent coronary angiography during 2007–2012	Cohort	2612
Kassaian *et al*. [32]	2015	Iran	1 month and 12-month follow-up post-discharge	11 Tertiary hospitals	Patients discharged alive with confirmed ACS	Cohort	1799
Medagama *et al*. [22]	2015	Sri Lanka	In hospital and at discharge	1 Tertiary teaching hospital	Patients presented with ACS (November 2011-March 2012)	Cohort	256
Selby *et al*. [9]	2015	Switzerland	At admission	Teaching hospital	Patients admitted with ACS without previous CVD	Cross-Sectional	3172
Ferreira-González *et al*. [44]	2016	Spain	At discharge and 2-year follow-up	ACDC registry (22 hospitals)	Patients admitted with ACS + PCI (Jan-April 2008)	Cohort	917
Gunnell *et al*. [39]	2016	Western Australia	At discharge and 20 years follow-up	Western Australia Data Linkage System	Patients alive after ACS (2008)	Cohort	23642
Boccara *et al*. [24]	2017	France	1 month, 6-month, 12-month, 18-month, 2-year, and 3-year follow-up	PACS-HIV study	Post-hospital discharged patients with ACS and received statin prescription (2003–2006)	Cohort	282
Eisen *et al*. [10]	2017	36 countries from North America, South America, Western Europe, Eastern Europe, Asia Pacific)	3-month and 6-month follow-up post-discharge	SOLID-TIMI 52 study	Patients after ACS (2009–2011)	Cohort	12446
Khedri *et al*. [40]	2017	Sweden	At admission, at discharge, and 3-month follow-up	SWEDEHEART registry (72 hospitals)	Patients admitted with first ACS (2005–2010)	Cohort	77432
Mantel *et al*. [45]	2017	Sweden	12-month follow-up post-discharge	National Population-based data linkage	Patients experienced first MI or UA (2007–2010)	Cohort	4319
Turner *et al*. [46]	2017	UK	At discharge, 1 month and 12-month follow-up	PhACS study, NSTE-ACS cohort	ACS patients discharged on high potency statin	Cohort	1005
Al-Zakwani *et al*. [47]	2018	4 Middle Eastern Countries	At admission, in hospital, at discharge, 1 month, 6-month, and 12-month follow up	Gulf COAST registry (24 hospitals)	Patients diagnosed with ACS admitted to the hospital (2012–2013)	Cohort	3681
Boklage *et al*. [26]	2018	USA	At admission, in-hospital and 12-month follow-up	MarketScan Research Databases	Patients who experienced at least 1 inpatient admission with ACS as primary diagnose (2002–2014)_	Cohort	7802
Hoedemaker *et al*. [25]	2018	Netherland	In a hospital, 30-day and 12-month follow-up	1 Tertiary hospital (Single center registry)	STEMI and NSTEMI patients admitted to a hospital (2006–2014)	Cohort	9202
Sun *et al*. [48]	2018	China	6-month and 12-month follow-up post-discharge	CAPSC-2 and CAPSC-3 registry	ACS + LDL-c <70 mg/dl	Cohort	3374
Hao *et al*. [34]	2019	China	In hospital and at discharge	CCC-ACS registry	Patients with STEMI or NSTE-ACS at hospital discharge (2014–2018)	Cohort	82196
Desta *et al*. [52]	2020	Ethiopia	In hospital and at discharge	1 Specialized Hospital	ACS patients admitted during 2013-2018 (72.8% STEMI, 15.2% NSTEMI, 12%UA)	Cross-Sectional	151

ICCU: Intensive cardiac care unit, NSTEMI: Non–ST-elevation myocardial infarction, NSTE-ACS: Non–ST-elevation acute coronary syndrome, STEMI: ST-elevation myocardial infarction, UA: Unstable angina.

Discussion

The present systematic review included data regarding statin utilization from the 49 studies over the world. Our review found that the rate of statin utilization at discharge varied from 20% to 99%. It should be noted that one-third (ten studies) of the included studies, which reported the use of statin at discharge, found that less than 80% of ACS patients received statin at hospital discharge. It should be noted that almost all those studies [7], [8], [14], [20], [23], [24], [33], [37], [55] collected the data before 2013 except Boccara *et al*. [24], who collected the data from 2002 to 2014 when the recommendation of using statin as primary prevention and secondary prevention for ACS was just published in 2014 [4].

About 64% of the studies found that statin utilization rate during hospitalization was higher than 80%. Of the four studies, which reported statin utilization rate during less than 80% hospitalization, two studies were conducted in low and middle-income countries, including Lebanon [14] and Ethiopia [52]. The affordability and limited access to the essential medicines were reported among the low- and middle-income countries [56]. The others were conducted in high-income countries, but they used retrospective data in 1999–2007 [19] and 2002–2014 [26].

Although existing evidence indicated that adherence to statin treatment was associated with the reduction in cardiovascular related events and all-cause mortality [57], [58], [59], a previous systematic review found a low adherence rate of statin treatment [60]. Similarly, almost all included studies in our review, which examined the statin utilization trend along the follow-up time points, found that the level of statin use was diminished since the discharge time point. It could probably be due to several reasons, including the

Table 5: Statin utilization and pattern of staying usage

Study	Statin utilizationxc				Pattern of statin use	Factor predicting statin use
	At Admission (%)	In Hospital (%)	At Discharge (%)	Post Discharge (%)		
Amar *et al*. [35]			89.2	85.6 (14 mos)	46.2%, 45.6% use combination of 4 treatments (Beta blocker, antiplatelet, stain, ACE) at discharge and 14 mos follow-up	
Lee *et al*. [41]				62.6 (3 mos) 60.3 (6 mos) 73.5 (12 mos) 76.6 (18 mos)		Older patients were less likely to receive statin ($p < 0.001$) Women were less likely than men to receive statin (<0.001)
Vermeer and Bajorek [13]	40		85			Men were likely to be discharged with a statin; OR = 3.36 (1.11, 10.15)
Bi *et al*. [27]			80.4	65.8 (6 mos) 59.4 (12 mos)		
Wong *et al*. [37]			58.8 (47% for patients without revascularization; 73% among patients with revascularization)			
Wong *et al*. [8]			59.5			
Abdallah *et al*. [14]		59 (62% in STEMI, 53% in NSTEMI, 62% in UA, p = 0.03)	60 (64% for STEMI, 51% for NSTEMI, 64% for UA, p < 0.01)			
Melloni *et al*. [28]	40		89.5	66.7 (12 mos)		
Ramanath *et al*. [17]			80.6 (69.1% among non-obstructive CAD, 81.1% among obstructive CAD)			
Aliprandi-Costa *et al*. [18]			64.5, 65.4 for STEMI, NSTEACS (2000–2001) 80, 80.6 for STEMI, NSTEACS (2004–2005) 88.5, 84.4 for STEMI, NSTEACS (2006–2007)			
Bourdès *et al*. [50]				Of 2131 patients who received EBCM at discharge, 98.1% still used statin at 24 months after discharge		
Javed *et al*. [33]			The use of intensive statin monotherapy: 26.9 at 2005 29.1 at 2006 30.2 at 2007 30.4 at 2008 32.2 at 2009			
The Access of Investigators (29)		90.7 (90% in NSTE-ACS; 91% in STEMI)	89.2 (88% in NSTE-ACS; 91% in STEMI)			
Andrikopoulos *et al*. [30]	40	96	93			
Kim *et al*. [42]	49.8		83.7			
Ranasinghe *et al*. [19]		76				
Wai *et al*. [36]			92	89 (3 mos)		
Yusuf *et al*. [7]			20.6			
Andrikopoulos *et al*. [53]			93.2	87.7 (6 mos)		
Huffman *et al*. [55]	11.43		78.9			In hospital: 40% received optimal treatment (Aspirin, clopidogrel, Beta-blocker, statin, and heparin) At discharge: 46% received optimal treatment (Aspirin, clopidogrel, Beta-blocker, statin)
Kassab *et al*. [15]			95.9			
Shehab *et al*. [6]	94.8 (Male 95.1% female 93.6%, p = 0.019)		91 (Male = 92.1%, female = 88.2%, p < 0.001)			Female are less likely than male to received statin during hospitalization and at discharge
Zeymer *et al*. [72]	34		89	88.5 (6 mos) 87 (12 mos)		
Gausia *et al*. [20]			75.4% (aboriginal 73.5%, non-aboriginal 76.2%, p = 0.25)			
Grey *et al*. [71]	44			59 (7 days) 71 (30 days) 83 (3 mos) 69 (12 mos) 67 (36 mos)		
Jin *et al*. [31]			88.8 (85.1 in elderly vs. 90.6 in non-elderly, p = 0.067)	24.7 (12 mos) (21.8 in elderly vs. 29.6 in non-elderly, 9 = 0.005)		Underused at follow-up occurred in elderly > non-elderly
Maggioni *et al*. [38]			80.3	67.2 (12 mos)	At discharge: 55% received atorvastatin, 26.6%-simvastatin, 14.8%-rosuvastatin, 10.1%-pravastatin, 4.8%-Fluvastatin, 8.5%-Simvastain+Ezetimibe 0.6%-Lovastatin	

(*Contd*...)

Table 5: (*Continued*)

Study	Statin utilizationxc				Pattern of statin use	Factor predicting statin use
	At Admission (%)	In Hospital (%)	At Discharge (%)	Post Discharge (%)		
Pereira *et al*. [54]			93% among STEMI, 90% among NSTE-ACS			Patients aged≥80 years with NSTE-ACS were much less likely to be discharged with statins (OR 0.35, 95% CI 0.19–0.64)
Shimony *et al*. [16]			90.3% in HIC 76.8% in LIC (OR =2.8,95% CI: 1.6–5.0)			
Wang *et al*. [51]		90.6	93	85.4 (6 mos)		
Anzai *et al*. [23]		87 (age< 80 yrs) 69 (age≥ 80 yrs)	87 (age < 80 yrs) 69 (age ≥ 80 yrs)	86 (age< 80 yrs) 65 (age≥ 80 yrs)		The elderly were less likely to receive statin
Gencer *et al*. [49]			99 (of this 70 were at high-intensity statin)	94 (12 mos)		
Ghadri *et al*. [21]	31.3 (31.8 in male vs. 29.4 in female, p = 0.26)		88.5 (89.4 in male vs. 85.2 in female, p =0.004)			Females were less likely to receive a statin at discharge as compared to males
Kassaian *et al*. [32]		94.3				
Medagama *et al*. [22]		96.1	96.1			
Selby *et al*. [9]	16 compared to 27 eligible for statin					
Ferreira-González *et al*. [44]			89.4			
Gunnell *et al*. [39]			79.6 (82% in male, 75.5% in female)			Female were less likely to dispense with a statin (OR = 0.82; 95%CI 0.76–0.88)
Boccara *et al*. [24]			12,4			
Eisen *et al*. [10]			95.2		Of those received statin, 41.9% got high intensity statin. Of these patients, 82% were still on high potency statin after 2.3 years	
Khedri *et al*. [40]	21		84.4			Patients with eGFR 30-59 were more likely to statin treatment cessation (OR = 1.35, 1.29–1.41)
Mantel *et al*. [45]				73.5 (3 mos) 63.5 (6–12 mos)		
Turner *et al*. [46]				84.4 (12 mos)		
Al-Zakwani *et al*. [47]	61		97			
Boklage *et al*. [26]	30.5	70.9		63.5 (12 mos)		
Hoedemaker *et al*. [25]			85.2	88.1 (30 days) 84.1 (12 mos)		43.7, 46.6, 25.5 received optimal treatment at discharge, 30 days, and 12 mos, respectively.
Sun *et al*. [48]			85			
Hao *et al*. [34]	17.5	95.1 (95.4 in male, 94.3 in female)	92.6 (93.2 in male, 90.7 in female)			Female were less likely to receive statin at discharge (OR = 0.86. 0.81–0.92)
Desta *et al*. [52]		84.1	94.7			

NSTEMI: Non–ST-elevation myocardial infarction, NSTE-ACS: Non–ST-elevation acute coronary syndrome, STEMI: ST-elevation myocardial infarction, UA: Unstable angina, Mos: Months.

side-effect of stain [61], [62], poor prescriber-patient relationship [60], and the quantity of received drugs at discharge [31]. The previous studies also found that under-used of statin among ACS was also associated with low education (OR 3.39; 95% CI 1.65–9.32), the greater number of comorbidities (OR 1.64; 95%CI 1.12–2.39), the quantity of received drugs at discharge (OR 1.31; 95%CI 1.11–1.55), low income (OR 3.97; 95%CI 1.47–10.75), and depression (OR 2.62; 95%CI 2.03–3.38) [31]. As the rate of statin utilization during follow-up was decreasing, effective intervention by a multi-disciplinary team, which included physician/cardiologist, pharmacist as well as patient's family support to improve statin utilization among ACS should be implemented. Health system and policy support were also required to improve ACS evidence-based medicine adherence, including statin.

Our studies also revealed that statin utilization rate was lower among females, as compared to males. It could lead to higher mortality among female patients with ACS [63], [64], [65]. On the other hand, it could probably be due to the fact that males experienced more invasive procedures than females; thus, they were supposed to receive more statin prescriptions [6], [39]. Furthermore, statin utilization was also found to be lower among the elderly. A prior study reported that the number of concurrent medication and the comorbid diseases owned by the elderly could impact their adherence [31]. Therefore, more efforts should be made to improve the utilization rate among these patients.

This review is not without any limitations. First, only one database (PubMed) was used to identify studies. Second, our study mainly focused on statin utilization by putting aside other evidence-based treatment for ACS. However, recent guidelines recommended using statin among the ACS patients and recommended that high-risk statin be used among high-risk populations without considering their LDL-c level [2], [5], [66], [67]. It should be noted that our

study did not mainly focus on the intensity of statin as well as other evidence-based treatment for secondary prevention among ACS. Nevertheless, our study could imply that the rate of evidence-based treatment among ACS patients would be even lower than the rate of statin utilization. Finally, it should be noted that the utilization rate of statin among ACS also depends on the characteristics of ACS patients, such as renal function [40], [68], liver function [69], and Parkinson's disease [70].

Conclusion

Although the benefits of statin in ACS patients have been established [6], [7], [8], [9], [10], our study revealed the under-utilization rate of statin for secondary prevention among ACS patients, especially during follow-up. This review highlighted the suboptimal adherence to the guideline recommendation in real-world practice. To improve patients' clinical outcomes with ACS, substantial efforts should be made to increase optimal treatment prescription among physicians and increase adherence of statin among ACS patients [5].

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