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- “Hydroxymethylglutaryl-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].

![Flow chart for study selection](image)

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],
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...
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 |
|---------------|------|-----------|---------------|---------|-------|
| Kim et al. [42]| 2012 | 9         | 9             | 8       |       |
| Zeymer et al. [43]| 2013 | 9         | 9             | 8       |       |
| Gencer et al. [44]| 2015 | 9         | 9             | 8       |       |
| Ferreira-Gonzalez et al. [44]| 2016 | 9         | 9             | 8       |       |
| Mantel et al. [45]| 2017 | 9         | 9             | 8       |       |
| Turner et al. [46]| 2017 | 9         | 9             | 8       |       |
| Al-Zakwani et al. [47]| 2018 | 9         | 9             | 8       |       |
| Sun et al. [48]| 2018 | 9         | 9             | 8       |       |

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. [38]| 2008 | 83.4 | 54.1 | 54.1 | 54.1 | 47.5 at discharge | 54.1 | 47.5 at discharge |
| Lee et al. [41]| 2008 | 83.4 | 54.1 | 54.1 | 54.1 | 47.5 at discharge | 54.1 | 47.5 at discharge |
| Bi et al. [27]| 2009 | 83.4 | 54.1 | 54.1 | 54.1 | 47.5 at discharge | 54.1 | 47.5 at discharge |
| Wong et al. [27]| 2009 | 83.4 | 54.1 | 54.1 | 54.1 | 47.5 at discharge | 54.1 | 47.5 at discharge |
| Boudet et al. [50]| 2011 | 83.4 | 54.1 | 54.1 | 54.1 | 47.5 at discharge | 54.1 | 47.5 at discharge |
| Andrikopoulos et al. [53]| 2012 | 83.4 | 54.1 | 54.1 | 54.1 | 47.5 at discharge | 54.1 | 47.5 at discharge |
| Shimi et al. [16]| 2014 | 83.4 | 54.1 | 54.1 | 54.1 | 47.5 at discharge | 54.1 | 47.5 at discharge |
| Gausia et al. [20]| 2014 | 83.4 | 54.1 | 54.1 | 54.1 | 47.5 at discharge | 54.1 | 47.5 at 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) | At discharge to 14-month 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, NSTEMI, 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 prescribed with aspirin | 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 | University of Michigan Health System’s ACS registry | ACS patients (January 2006-September 2007) | Cohort | 788 |
| Ramanath et al. [17] | 2010 | USA | In hospital and 6-month follow-up | University of Michigan Health System’s ACS registry | Patients hospitalized due to ACS and underwent coronary angiography | Cohort | 2264 |
| Aijandi-Costa et al. [18] | 2011 | Australia | In hospital and 6-month follow-up | PREVENIR-5 study | Patients hospitalized for the first episode of ACS | Cross-Sectional | 4850 |
| Bourdes et al. [50] | 2011 | France | At discharge | GWTG program | ACS related hospitalization from 2005–2009 | Cohort | 159713 |
| Javed et al. [33] | 2011 | USA | At discharge | ACCESS registry | Patients hospitalized with ACS (2007–2008) 46.1%STEMI and 54% NSTEMI-ACS | Cohort | 11731 |
| The Access Investigators [29] | 2011 | Latin America Middle Eastern Countries | At admission, at discharge, 6 and 12-months follow-up | TARGET study (17 centers) | Patients admitted with ACS (2012): 44.7% STEM1, 34.2% NSTEMI, 21.1% UA | Cohort | 418 |
| Andrikopoulos et al. [30] | 2012 | Greece | At discharge and 6-month follow-up | MUSTANG Registry | Patients presented with ACS and underwent PCI | Cohort | 3362 |
| Kim et al. [42] | 2012 | Korea | In hospital and 30-day follow-up | GRACE registry | Patients hospitalized and diagnosed with ACS at admission and discharge time points | Cohort | 5556 |
| Ranasinghe et al. [19] | 2012 | Australia New Zealand | In a hospital, at discharge, and 6-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 |
| Wai et al. [36] | 2012 | Australia | At discharge, 14-day and 3-month follow-up | 1 University hospital | Patients discharged with acute MI (2000–2006) | Cohort | 456 |
| Yusuf et al. [7] | 2012 | USA | At discharge and 12-month follow-up | TARGET study | Patients with ACS admitted to the selected 17 hospitals | Cohort | 366 |
| Andrikopoulos et al. [30] | 2013 | Greece | At discharge and 6-month follow-up | Kerala ACS registry | Patients admitted to 125 hospitals (2007–2009) | Cross-Sectional | 25718 |
| Huffman et al. [55] | 2013 | India | At hospital and at discharge | 1 Tertiary hospital | Patients with a primary diagnosis of ACS | Cross-Sectional | 380 |
| Kassab et al. [15] | 2013 | Malaysia | At admission and discharge | Gulf RACE-2 Registry | Patients hospitalized with ACS as final diagnostic from 65 hospitals (2008–2009) | Cohort | 7930 |
| Shehab et al. [8] | 2013 | 6 Middle Eastern Countries | At admission, at discharge, and 12 months follow-up | APTOR registry | Patients presented with ACS and underwent PCI | Cohort | 4546 |
| Zeymer et al. [72] | 2013 | Spain UK France Czech rep Germany Greece Norway Austria Hungary Belgium Netherlands Sweden Denmark Finland Australia Yemen | At admission, in hospital, at discharge, 3-month, 6-month, and 12-month follow-up | WA hospital morbidity datasets and National datasets linkage of Public Hospital | Patients with ACS discharged alive (2002–2004) | Cohort | 1717 |
| Gausia et al. [20] | 2014 | Australia | At admission and discharge | WA hospital morbidity datasets and National datasets linkage of Public Hospital | Patients with ACS discharged from hospital over the year in 2007 | Cohort | 11384 |
| Grey et al. [71] | 2014 | New Zealand | At discharge, 7-day, 30-day, 90-day, 12-month, 2-year, and 3-year follow-up | Data Linkage System | Patients with ACS admitted to hospitals | Cohort | 469 |
| 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 | 3078 |
| Maggioni et al. [38] | 2014 | Italy | At discharge | ARNO Observatory record linkage (7 local Italian health authorities) | Patients discharged with ACS | Cross-Sectional | 2111 |
| Pereira et al. [54] | 2014 | Portugal | At discharge | 10 Public Hospitals | Patients discharged with ACS (744 STEMI and 1364 NSTEM-ACS) | Cohort | 2111 |

(Contd...)
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 (36 Centers from 6 countries) | Current smoker (smoked ≥ 10 cigarettes/day) ACS patients admitted to the ICU 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 | Teaching hospital | Patients underwent PCI for ACS with stenting (2005–2009) | Cohort | 405 |
| Gencer et al. [49] | 2015 | Switzerland | In hospital and 12-month follow-up | Teaching hospitals | ACS patients hospitalized during 2009–2012 | Cohort | 1602 |
| Ghiatri 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 | 11 Tertiary hospitals | Patients discharged alive with confirmed ACS | Cohort | 1799 |
| Medagama et al. [22] | 2015 | Sri Lanka | In hospital and at discharge | 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-Gonzalez et al. [44] | 2016 | Spain | At discharge and 2-year follow-up | ACC 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 PACS-HIV study | Patients alive after ACS (2008) | Cohort | 23642 |
| Bocca et al. [24] | 2017 | France | 3-month and 6-month follow-up | SOLID-TIMI 52 study | Patients after ACS (2009–2011) | Cohort | 12446 |
| 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 | 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 | SWEDHEART registry (72 hospitals) | Patients admitted with first ACS (2005–2010) | Cohort | 77432 |
| Mantel et al. [45] | 2017 | Sweden | 12-month follow-up | 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 | PhAACS 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 and 12-month follow-up | Gulf COAST registry (24 hospitals) | Patients diagnosed with ACS admitted to the hospital (2012–2013) | Cohort | 3681 |
| Boldt 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 diagnosis (2002–2014), STEMI and NSTEMI patients admitted to a hospital (2006–2014) | Cohort | 7802 |
| Hoedemaker et al. [25] | 2018 | Netherlands | In a hospital, 30-day and 12-month follow-up | 1 Tertiary hospital (Single center registry) | Patients with STEMI or NSTEMI admitted to hospital (2013–2018) | Cross-Sectional | 151 |
| Sun et al. [49] | 2018 | China | In-hospital and 6-month follow-up | 12-month follow-up | Patients with STEMI or NSTEMI admitted to hospital (2013–2018) | Cross-Sectional | 151 |
| Hao et al. [34] | 2019 | China | In hospital and at discharge | CAC-ACS registry | Patients with STEMI or NSTEMI admitted to hospital (2013–2018) | Cross-Sectional | 82196 |
| Desta et al. [52] | 2020 | Ethiopia | In hospital and at discharge | 1 Specialized Hospital | Patients with STEMI or NSTEMI admitted to hospital (2013–2018) | Cross-Sectional | 151 |

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 Boccaro 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...
| Study | Statin utilizationx | Pattern of statin use | Factor predicting statin use |
|-------|---------------------|-----------------------|-----------------------------|
|       | At Admission (%)   | In Hospital (%)       | At Discharge (%)  | Post Discharge (%) | 46.2%, 45.6% use combination of 4 treatments (Beta blocker, antiplatelet, stain, ACE) at discharge and 14 mos follow-up |
|       |                     |                       | Older patients were less likely to receive statin (p < 0.001) | Women were less likely than men to receive statin (<0.001) |
|       |                     |                       | Men were likely to be discharged with a statin; OR = 3.36 (1.11, 10.15) |
|       |                     |                       | Female are less likely than male to received statin during hospitalization and at discharge |
|       |                     |                       | In hospital: 40% received optimal treatment (Aspirin, clopidogrel, Beta-blocker, stain, and heparin) At discharge: 46% received optimal treatment (Aspirin, clopidogrel, Beta-blocker, stain) |
|       |                     |                       | Female is less likely than male to receive statin during hospitalization and at discharge |
|       |                     |                       | Undersused at follow-up occurred in elderly > nonelderly |
|       |                     |                       | At discharge: 55% received atorvastatin, 26.6%-simvastatin, 14.8%-rosuvastatin, 10.1%-pravastatin, 8.5%-Simvastain+Ezetimibe 0.6%-Lovastatin |
|       |                     |                       |                          |

| Study            | Statin utilizationx | Pattern of statin use | Factor predicting statin use |
|------------------|--------------------|-----------------------|-----------------------------|
| Amar et al. [35] | 89.2               | 85.6 (14 mos)         |                            |
| Lee et al. [41]  | 62.6 (3 mos)       | 60.3 (6 mos)          | 73.5 (12 mos)               | 76.6 (18 mos) |
| Vermeer and Bajorek [13] | 85              |                       |                            |
| Bi et al. [27]   | 62.6 (3 mos)       | 60.3 (6 mos)          | 73.5 (12 mos)               | 76.6 (18 mos) |
| Lee et al. [41]  | 58.8 (47% for patients without revascularization; 73% among patients with revascularization) | 59.4 (12 mos) |                            |
| Vermeer and Bajorek [13] | 85              |                       |                            |
| Lee et al. [41]  | 40                 | 85                    | 89 (69.1% among non-obstructive CAD, 81.1% among obstructive CAD) 64.5, 65.4 for STEMI, NSTEMACS (2000–2001) 80, 80.6 for STEMI, NSTEMACS (2004–2005) 88.5, 84.4 for STEMI, NSTEMACS (2006–2007) | Of 2131 patients who received EBCM at discharge, 98.1% still used statin at 24 months after discharge |
| Aliprandi-Costa et al. [18] | 40 | 93 | 93.7 | 87.7 (6 mos) |
| Bourdès et al. [50] | 40 | 93 | 93.7 | 87.7 (6 mos) |
| Javed et al. [33] | 90.7 (90% in NSTEMI; 91% in STEMI) | 89.2 (88% in NSTEMI; 91% in STEMI) | 83 (12 mos) | 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 89.2 (88% in NSTEMI; 91% in STEMI) |
| The Access of Investigators [29] | 90.7 (90% in NSTEMI; 91% in STEMI) | 89.2 (88% in NSTEMI; 91% in STEMI) | 83 (12 mos) | Of 2131 patients who received EBCM at discharge, 98.1% still used statin at 24 months after discharge |
| Andrikopoulos et al. [30] | 40 | 93 | 93.7 | 87.7 (6 mos) |
| Kim et al. [42]  | 49.8               | 76                    | 92 (3 mos)  |                                        |
| Wai et al. [38]  | 20.6               | 93.2                  | 87.7 (6 mos) |                                        |
| Yusuf et al. [37] | 11.43             | 78.9                  | 87.7 (6 mos) |                                        |
| Kassab et al. [15] | 94.8 (Male 95.1%, female 93.6%, p = 0.019) | 95.9 (Male = 92.1%, female = 88.2%, p < 0.001) | 87 (12 mos) | Female is less likely than male to receive statin during hospitalization and at discharge |
| Shehab et al. [8] | 94.8 (Male 95.1%, female 93.6%, p = 0.019) | 95.9 (Male = 92.1%, female = 88.2%, p < 0.001) | 87 (12 mos) |                                        |
| Zeymer et al. [72] | 34               | 89                    | 88.5 (6 mos) |                                        |
| Gausia et al. [20] | 75.4% (aboriginal 73.5%, non-aboriginal 76.2%, p = 0.25) | 59 (7 days) | 77 (12 mos) |                                        |
| Grey et al. [71]  | 44                 |                       | 83 (3 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) | 67.2 (12 mos) |                                        |
| Maggioni et al. [38] | 80.3             |                       | 67.2 (12 mos) | At discharge: 55% received atorvastatin, 26.6%-simvastatin, 14.8%-rosuvastatin, 10.1%-pravastatin, 8.5%-Simvastain+Ezetimibe 0.6%-Lovastatin |

(Contd...)
side-effect of statin [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                          | Statin utilization (%) | Pattern of statin use | Factor predicting statin use             |
|-------------------------------|-----------------------|-----------------------|-----------------------------------------|
| 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) | The elderly were less likely to receive statin |
| Wang et al. [51]               | 90.6 vs. 87 (age< 80 yrs) | Females were less likely to receive a statin at discharge as compared to males |
| Anza et al. [23]               | 87 (age ≥ 80 yrs) vs. 69 (age < 80 yrs) |                                |
| Gencer et al. [49]             | 99 (of this 70 were at high-intensity statin) vs. 94 (12 mos) |                                |
| Ghadri et al. [21]             | 31.3 (31.8 in male vs. 29.4 in female, p = 0.26) |                                |
| Kassaia et al. [32]            | 94.3 vs. 96.1 vs. 96.1 |                                |
| Medagama et al. [22]           | 94.3 vs. 96.1 vs. 96.1 |                                |
| Selby et al. [8]               | 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) |                                |
| Boccara et al. [24]            | 12.4 vs. 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 |
| Eisen et al. [10]              | 95.2 |                                |
| Khedri et al. [40]             | 21 vs. 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) vs. 63.5 (6-12 mos) vs. 84.4 (12 mos) |                                |
| Turner et al. [46]             | 61 vs. 97 vs. 84.4 (12 mos) |                                |
| Al-Zaikani et al. [47]         | 70.9 vs. 85.2 vs. 84.1 (12 mos) | 43.7, 46.6, 25.5 received optimal treatment at discharge, 30 days, and 12 mos, respectively. |
| Hoedemaker et al. [25]         | 30.5 vs. 30.5 vs. 30.5 (12 mos) |                                |
| Sun et al. [48]                | 17.5 vs. 95.1 (95.4 in male, 94.3 in female) vs. 85 vs. 92.6 (93.2 in male, 87.0 in female) | Female were less likely to receive statin at discharge (OR = 0.86, 0.81–0.92) |
| Desta et al. [52]              | 84.1 vs. 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.
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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