



Review Article

Prior statin use and the incidence of in-hospital arrhythmia in acute coronary syndrome: A systematic review and meta-analysis



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ABSTRACT

Background: The benefit of prior statin use to reduce the incidence of arrhythmia in acute coronary syndrome (ACS) is still a matter of debate. Statins have multiple pleiotropic effects, which may reduce the incidence of in-hospital arrhythmia. A systematic review and meta-analysis were performed to evaluate prior statin use and the incidence of in-hospital arrhythmia in ACS.

Methods: This systematic review was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). We performed a literature search through Pubmed, Proquest, EBSCOhost, and Clinicaltrial.gov. A random-effect model was used due to moderate heterogeneity. Quality assessment was performed using Newcastle Ottawa Scale. Sensitivity analysis was performed by using leave one or two out method. PROSPERO registration number: CRD42022336402.

Results: Nine eligible studies consisting of 86,795 patients were included. A total of 22,130 (25.5%) patients were in statin use before the index ACS event. The prevalence of old myocardial infarction, heart failure, hypertension, diabetes mellitus, and chronic renal failure and concomitant treatment with aspirin, clopidogrel, and beta blocker was higher in the prior statin group compared to no previous statin. Overall, prior statin use was associated with a significantly lower incidence of in-hospital arrhythmia during ACS compared to no previous statin (OR 0.60; 95% CI 0.49–0.72; $P < 0.00001$; $I^2 = 54%$, P -heterogeneity = 0.03). In subgroup analysis, previous statin use reduced the incidence of atrial fibrillation or atrial flutter (OR 0.64; 95% CI 0.43–0.95; $P = 0.03$; $I^2 = 73%$, P -heterogeneity = 0.01) and ventricular tachycardia or ventricular fibrillation (OR 0.57; 95% CI 0.49–0.65; $P < 0.00001$; $I^2 = 8%$, P -heterogeneity = 0.35).

Conclusions: Based on aggregate patient data, prior statin use may reduce the incidence of in-hospital arrhythmia during ACS, particularly atrial fibrillation or atrial flutter and ventricular tachycardia or ventricular fibrillation.

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1. Background

Acute coronary syndrome (ACS) is one of the most common diseases in the world,¹ affecting 7 million people worldwide.² One complication of ACS is arrhythmia which is associated with poor outcomes.^{3,4} Sustained ventricular tachycardia, ventricular fibrillation, atrioventricular block, and atrial fibrillation are commonly reported during ACS.^{5–9} Other arrhythmias such as non-sustained ventricular tachycardia (NSVT), asystole, premature ventricular

complex (PVC), and supraventricular tachycardia are also reported in ACS during the period of hospitalization.⁴

Statin or 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) has been used to prevent coronary artery disease for 30 years.¹⁰ According to the guidelines, statin is recommended as secondary prevention in ACS.^{11–14} Besides lipid-lowering effect, statin also possesses pleiotropic effects such as reducing inflammatory cells in atherosclerotic plaques and increasing plaque stability.¹⁵ The incidence of atrial fibrillation (AF), PVC, and NSVT also decrease with early intensive statin treatment during the ACS hospitalization period.^{16,17} The hypothesis was that statin's pleiotropic effects might improve autonomic control and increase the stability of the myocardium.^{16,17} Also, statin can stabilize plaque and may reduce ischemia-related ventricular arrhythmia.¹⁸ Other than secondary

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prevention, prior statin therapy before ACS was associated with milder ACS presentation and lower in-hospital major adverse cardiovascular events (MACE).¹⁹ However, the data regarding previous statin or pre-hospital statin treatment and arrhythmia in ACS are scarce. Also, the benefit of previous statin use in reducing arrhythmia events during ACS hospitalization period is still conflicting.^{20–22} Therefore we aim to evaluate the role of previous statin use and in-hospital arrhythmia during acute coronary syndrome.

2. Methods

2.1. Protocol and registration

This study is registered in the International Prospective Register of Systematic Reviews (PROSPERO) by the following number: CRD42022336402.

2.2. Search strategy

We conducted a structured search to identify research on prior statin use and in-hospital arrhythmia in acute coronary syndrome according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guideline, with a pre-determined search strategy. The structured search process can be seen in Fig. 1. We systematically searched Pubmed, Proquest, EBSCOhost, and Clinicaltrial.gov databases from inception to June 2022. We combined the search strategy using MeSH terms and [Title/Abstract] with the following keywords: “prior statin”, “previous statin”, “pre-hospital statin”, “arrhythmia”, “arrhythmic”, “supraventricular arrhythmia”, “ventricular arrhythmia”, “atrial fibrillation”, “atrial flutter”, “ventricular tachycardia”, “ventricular fibrillation”, “atrioventricular block”, “myocardial infarction”, and “acute coronary syndrome”.

2.3. Eligibility criteria and outcome of interest

After searching, all retrieved studies were exported into Zotero. Duplicate studies were removed. Our inclusion criteria were: (1)

acute coronary syndrome patients >18 years old; (2) comparing patients with prior statin use and patients without prior statin use. Studies were excluded if they met the following criteria: (1) non-English article; (2) article with study designs such as the letter to the editor, literature review, systematic review, meta-analysis, case report, case series, or correspondence. If there was two or more published article from one trial with the same outcome of interest, the longer study duration was chosen. The outcome of interest was the incidence of arrhythmia.

2.4. Study selection and data collection

Two independent investigators conducted the literature search (KW and RD). We also manually screened for additional eligible studies from the related articles and the references in the relevant studies. Any differences were solved through a discussion. If there is a disagreement between two investigators, the third investigator (KSN) will be asked to make the final decision.

Articles were reviewed based on title, abstract, and full text. After identifying the included studies, data extraction was performed. The following data were extracted from the included studies: first author, publication year, comorbidities (angina, old myocardial infarction, heart failure, hypertension, diabetes mellitus, chronic renal failure, current smoker), left ventricular ejection fraction, final diagnosis (unstable angina [UA], non-ST segment elevation myocardial infarction [NSTEMI], ST-segment elevation myocardial infarction [STEMI]), the minimum duration of statin treatment before admission, type of arrhythmia, study design, baseline lipid parameter (low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglyceride, total cholesterol), concomitant medications before admission (aspirin, clopidogrel, beta blocker, angiotensin-converting enzyme [ACE] inhibitor, angiotensin receptor blocker [ARB], spironolactone), and the type of statin. The corresponding author of the studies was contacted via email to request access to missing data with a maximum of two attempts.

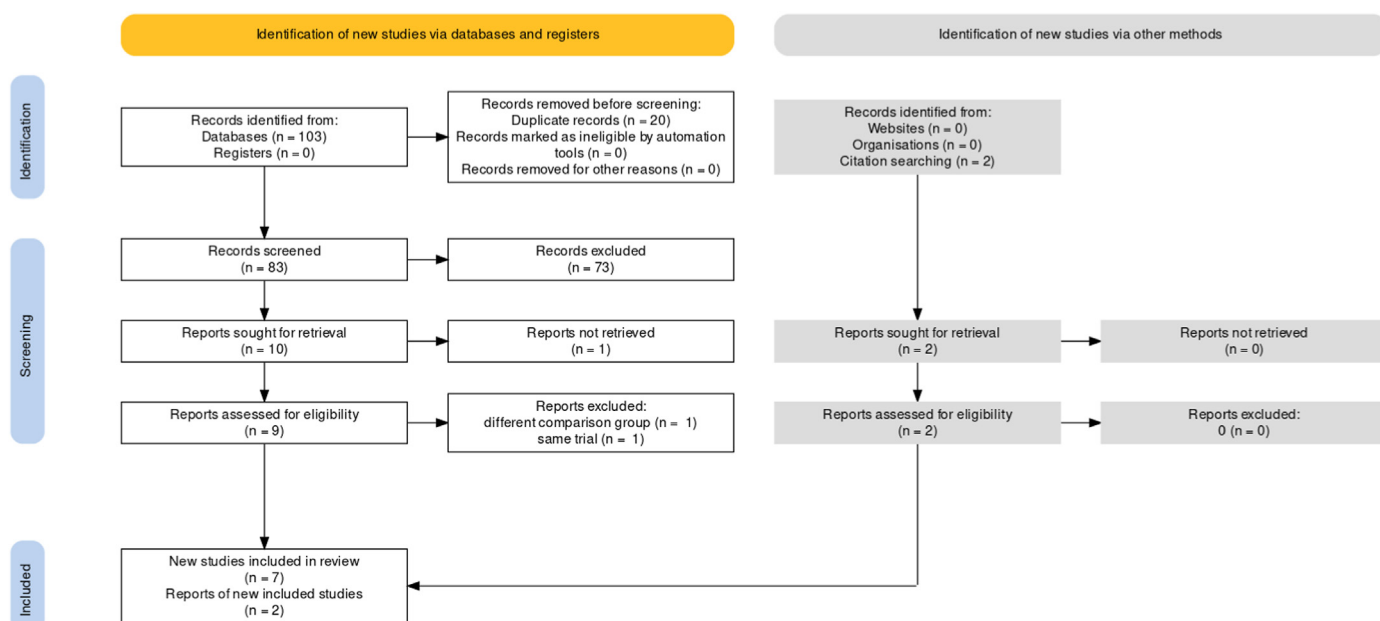


Fig. 1. PRISMA flow diagram.

2.5. Risk of bias assessment

The Newcastle Ottawa Scale (NOS) was used to assess the risk of bias for cross-sectional, case–control, and cohort studies.²³ KW and RD performed this critical appraisal. Any difference was resolved through a discussion. If the agreement was not reached, the opinion of a third reviewer (KSN) was consulted. The articles' assessment can be seen in Table 1. The NOS consists of 3 evaluation criteria: selection (0–4 points); comparability (0–2); and outcomes assessment (0–3 points). The maximum score from NOS is 9.

2.6. Statistical analysis

For each included study, the data regarding incidence of arrhythmia were expressed as odds ratio (OR) and 95% confidence intervals (95% CI). A random-effect model was used assuming there will be a significant heterogeneity. The heterogeneity between studies was measured by the I² value and the I² value is interpreted as: 0–25% (heterogeneity might not be important); 25–75% (moderate heterogeneity); and 75–100% (considerable heterogeneity).²⁴ Subgroup analysis according to the type of arrhythmia will be performed with sufficient studies. Text and tables were used to provide a descriptive summary and explanation of the findings of the included studies. If there is a minimum 10 included studies, the funnel plot will be used and a meta-regression will be performed. The meta-analysis was performed using Review Manager (Revman) version 5.4. Sensitivity analysis was conducted to study the robustness and to detect the source heterogeneity by using leave one or two out methods.^{25,26} Eight out of nine included studies used chi-square test or fisher exact test as appropriate to analyze categorical outcome variables.^{20–22,27–30,32} One included study did

not specifically mention the statistical method to analyze categorical outcome variables.³¹

3. Results

Nine eligible studies with a total of 86,795 patients with the acute coronary syndrome were included and only one study reported patients with suspected ACS.^{20–22,27–32} A total of 22,130 (25.5%) patients had consumed statin before the index ACS event. The included studies were published between 2006 and 2018. The characteristics of the included studies are summarized in Table 1. Overall, comorbidities such as old myocardial infarction (MI), heart failure (HF), hypertension, diabetes mellitus (DM), and chronic renal failure were more common in ACS patients with prior statin use compared to ACS patients without prior statin, as seen in Table 2. Left ventricular ejection fraction (LVEF) was comparable between both groups, except from 2 studies.^{29,30} For final diagnosis during hospitalization, STEMI was more frequent in patients without prior statin use compared to patients with prior statin use. Quality assessment of the included studies can also be seen in Table 1. The reported in-hospital arrhythmias were new-onset AF, new-onset atrial flutter, in-hospital AF or atrial flutter, sustained ventricular tachycardia (VT), ventricular fibrillation (VF), and 2nd or 3rd degree AV block.

The minimum duration between statin initiation and index ACS event can be seen in Table 2, which varies from ≥7 days to >6 months. The reported statins were rosuvastatin, atorvastatin, pravastatin, fluvastatin, and simvastatin. However, only 1 study reported the average statin dose which was 22 ± 10 mg/day.²¹ No studies reported a specific dose for each statin. The duration between statin initiation and index ACS event was reported in 3 studies.^{21,29,30} In new-onset AF and sustained VT or VF, the duration

Table 1
Characteristics of the included studies.

First Author (Year)	Study type	Population	Type of arrhythmia	Outcome	NOS
Ishii et al (2006)	Retrospective, single center	AMI (STEMI) patients undergoing reperfusion therapy with emergency PCI	VF in ≤48 h after reperfusion and VT	Resolution on ST-segment elevation on ECG; achievement of TIMI 6 grade 3 flow; corrected TIMI frame count; maximum serum CK level; and the type and frequency of ventricular arrhythmias	6
Ramani et al (2007)	Single center, observational	Patients with suspected ACS/NSTEMI	New-onset AF or atrial flutter	The occurrence of new-onset AF and atrial flutter	8
Vedre et al (2009)	Prospective, multicenter, observational cohort	ACS (UA, NSTEMI, STEMI) patients ≥18 years old	CA or VF, sustained VT, AF or atrial flutter	Primary outcomes were in-hospital AF and the composite end point of VT, VF, and/or cardiac arrest	9
Ozaydin et al (2010)	Observational	ACS (UA, NSTEMI, STEMI) patients admitted to coronary care unit	New-onset AF	The occurrence of in-hospital AF in patients with and without previous paroxysmal AF	6
Ozaydin et al (2011)	Observational, case-controlled retrospective	ACS (UA, NSTEMI, STEMI) patients admitted to coronary care unit	Sustained VT or VF	The occurrence of sustained VT or VF	7
Apiyasawat et al (2013)	Prospective, multicenter, observational cohort	ACS (UA, NSTEMI, STEMI) patients ≥18 years old	Sustained VT or VF	Primary outcome was the occurrence of VA Secondary outcome was a composite endpoint of VA or cardiac death	8
Marenzi et al (2015)	Prospective, single center	STEMI patients who underwent primary PCI	VT or VF, high-degree conduction disturbances requiring pacemaker	Primary outcomes were infarct size and myocardial salvage index Secondary endpoint was troponin I peak value	5
Li et al (2016)	Prospective, multicenter	ACS (NSTEMI and STEMI) patients ≥18 years old	In-hospital persistent VT or VT or Mobitz type II or III AV block	ACS severity at presentation, major arrhythmia, MACE (all-cause mortality, non-fatal or reoccurred MI, non-fatal stroke)	9
Park et al (2018)	Prospective, multicenter, observational	ACS (NSTEMI and STEMI) patients ≥18 years old with successful PCI	VT, VF, and AV block	Primary outcome was the incidence and rate of ventricular tachyarrhythmia and mortality during the index period Secondary endpoint were cardiovascular death and MACEs (all-cause death, recurrent MI, and any revascularization during follow-up)	9

ACS = acute coronary syndrome; AF = atrial fibrillation; AMI = acute myocardial infarction; AV = atrioventricular; CA = cardiac arrest; MACE = major adverse cardiovascular event; MI = myocardial infarction; NOS = newcastle Ottawa scale; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; VF = ventricular fibrillation, VT = ventricular tachycardia.

Table 2
Basic demographic of the included studies.

First Author (Year)	Ishii et al (2006)		Ramani et al (2007)		Vedre et al (2009)		Ozaydin et al (2010)		Ozaydin et al (2011)	
Group (n)	Prior statin (40)	No statin (346)	Prior statin (601)	No statin (925)	Prior statin (17,636)	No statin (47,043)	Prior statin (241)	No statin (759)	Prior statin (241)	No statin (759)
Age (years)	65 ± 10	63 ± 10	NA	NA	67 (58–76) ^a	64 (55–76)	61 ± 11	61 ± 11	62 ± 11	62 ± 12
Male, n (%)	29 (72.5)	282 (81.5)	NA	NA	11,811 (67)	31,528 (67)	158 (65.6) ^a	597 (78.7)	158 (65.6) ^a	597 (78.7)
Angina, n (%)	NA	NA	NA	NA	12,137 (69) ^a	21,562 (46)	NA	NA	NA	NA
Old MI, n (%)	NA	NA	NA	NA	NA	NA	1 (0.4)	5 (0.7)	1 (0.4)	5 (0.7)
Heart failure, n (%)	NA	NA	NA	NA	2629 (15) ^a	3931 (8.4)	14 (5.8)	45 (5.9)	14 (5.8)	45 (5.9)
Hypertension, n (%)	14 (35)	104 (30.1)	NA	NA	12,988 (74) ^a	26,893 (58)	173 (71.8) ^a	377 (49.7)	173 (71.8) ^a	377 (49.7)
Diabetes mellitus, n (%)	15 (37.5)	111 (32.1)	NA	NA	5838 (34) ^a	10,268 (22)	77 (32) ^a	159 (20.9)	77 (32) ^a	159 (20.9)
Chronic renal failure, n (%)	NA	NA	NA	NA	1925 (11) ^a	2957 (6.3)	1 (1.7)	4 (0.5)	1 (1.7)	4 (0.5)
Current smoker, n (%)	12 (30)	136 (39.3)	NA	NA	NA	NA	120 (49.8)	423 (55.7)	120 (49.8)	423 (55.7)
LVEF (%)	NA	NA	NA	NA	NA	NA	46 ± 13 (20–75) ^a	41 ± 11 (20–70)	46 ± 13 (20–75) ^a	41 ± 11 (20–70)
Final diagnosis										
Unstable angina, n (%)	NA	NA	NA	NA	7588 (43) ^a	12,272 (26)	180 (74.7) ^{b,a}	369 (48.6)	180 (74.7) ^{b,a}	369 (48.6)
NSTEMI, n (%)	NA	NA	NA	NA	6304 (36) ^a	14,938 (32)				
STEMI, n (%)	40 (100)	346 (100)	NA	NA	3744 (21) ^a	19,833 (42)	61 (25.3) ^a	390 (51.4)	61 (25.3) ^a	390 (51.4)
Minimum duration of statin treatment before admission	≥ 1 month	–	NA	–	≥ 7 days	–	NA	–	NA	–

Table 2 (continued). Baseline characteristics

First Author (Year)	Apiyasawat et al (2013)		Marenzi et al (2015)		Li et al (2016)		Park et al (2018)	
Group (n)	Prior statin (525)	No statin (1482)	Prior statin (50)	No statin (148)	Prior statin (1973)	No statin (12,817)	Prior statin (823)	No statin (354)
Age (years)	66.7 ± 10.8 ^a	62.4 ± 13.3	63 ± 10	60 ± 11	64.4 ± 11.2 ^a	63.8 ± 11.9	63 (55–72) ^a	55.5 (48–66)
Male, n (%)	309 (58) ^a	1048 (70.6)	42 (84)	141 (78)	1371 (69.5)	8908 (69.5)	588 (71.5) ^a	297 (83.9)
Angina, n (%)	NA	NA	NA	NA	1294 (65.6) ^a	4819 (37.6)	165 (20.1) ^a	23 (6.5)
Old MI, n (%)	202 (38.5) ^a	111 (7.5)	19 (38) ^a	7 (4)	616 (31.2) ^a	1192 (9.3)	165 (20.1) ^a	23 (6.5)
Heart failure, n (%)	164 (31.2) ^a	100 (6.7)	NA	NA	213 (10.8) ^a	705 (5.5)	24 (2.9)	2 (0.6)
Hypertension, n (%)	436 (83) ^a	759 (51.2)	29 (58)	77 (43)	1273 (64.5) ^a	7216 (56.3)	570 (69.3) ^a	93 (26.3)
Diabetes mellitus, n (%)	322 (61.3) ^a	696 (47)	11 (22) ^a	15 (8)	527 (26.7) ^a	2499 (19.5)	350 (42.5) ^a	86 (24.3)
Chronic renal failure, n (%)	115 (21.9) ^a	78 (5.3)	NA	NA	NA	NA	NA	NA
Current smoker, n (%)	72 (13.7) ^a	572 (38.6)	32 (64)	111 (62)	442 (22.4) ^a	4153 (32.4)	273 (33.2) ^a	189 (53.4)
LVEF (%)	49.2 ± 15	48.7 ± 14	50 ± 11	49 ± 12	NA	NA	54 (46–60)	55 (47–61.5)
Final diagnosis								
Unstable angina, n (%)	116 (22.1) ^a	125 (8.4)	0	0	NA	NA	NA	NA
NSTEMI, n (%)	258 (49.1) ^a	406 (27.4)	0	0	1572 (79.7)	7370 (57.5)	436 (53.1) ^a	147 (41.6)
STEMI, n (%)	151 (28.8) ^a	951 (64.2)	50	180	401 (20.3) ^c	5447 (42.5)	374 (45.6) ^a	200 (56.7)
Minimum duration of statin treatment before admission (days)	≥ 7 days	–	> 6 months	–	≥ 28 days	–	NA	–

LVEF = left ventricular ejection fraction; MI = old myocardial infarction; NA = not available; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

^a = $P \leq 0.05$ for the differences according to the respective study.

^b = unstable angina or NSTEMI.

^c = $P \leq 0.05$ compared to NSTEMI.

between statin initiation and index ACS event was 258 ± 256 days.^{29,30} In VT or VF and high-degree conduction disturbances requiring a pacemaker, the duration between statin initiation and index ACS event was 5 ± 3.5 years.²¹

The baseline lipid parameter can be seen in Table 3. Overall, patients with prior statin use presented with lower LDL and total cholesterol level compared to patients without prior statin. This difference might explain patients' compliance regarding statin use which resulted in lower LDL and total cholesterol level. The number of ACS patients who had concomitant medication use such as aspirin, clopidogrel, beta blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and spironolactone were more frequent in patients with prior statin use compared to patients without prior statin.

The forest plot for the incidence of overall arrhythmia can be seen in Fig. 2A. Only 8 studies with a total 85,618 patients were involved in the meta-analysis. The random-effects model was used since there was a moderate heterogeneity ($P = 0.03$; $I^2 = 54\%$). The pooled analysis showed that the incidence of in-hospital

arrhythmia during ACS was significantly lower in patients with prior statin use compared to patients without prior statin use (OR 0.60; 95% CI 0.49–0.72; $P < 0.00001$).

The subgroup analysis was performed in AF or atrial flutter and ventricular arrhythmia (VA). The VA consists of ventricular tachycardia or ventricular fibrillation. In AF or atrial flutter, the pooled analysis found that the incidence of AF or atrial flutter in ACS was significantly lower in patients with prior statin use compared to patients without prior statin use (OR 0.64; 95% CI 0.43–0.95; $P = 0.03$). Moderate heterogeneity was also observed in ACS patients with AF or atrial flutter ($P = 0.01$; $I^2 = 73\%$) and can be seen in Fig. 2B. In VA, the pooled analysis found that the incidence of VA in ACS was significantly lower in patients with prior statin use compared to patients without prior statin use (OR 0.57; 95% CI 0.49–0.65; $P < 0.00001$). Low heterogeneity was observed in a subgroup of ACS patients with VA ($P = 0.35$; $I^2 = 8\%$) and can be seen in Fig. 2C.

Moderate heterogeneity was observed in the incidence of overall arrhythmia and AF or atrial flutter. In the incidence of

Table 3
Baseline lipid parameter and concomitant medications before admission.

First Author (Year)	Ishii et al (2006)		Ramani et al (2007)		Vedre et al (2009)		Ozaydin et al (2010)		Ozaydin et al (2011)	
Group (n)	Prior statin (40)	No statin (346)	Prior statin	No statin	Prior statin	No statin	Prior statin (241)	No statin (759)	Prior statin (241)	No statin (759)
Baseline lipid parameter										
LDL cholesterol (mg/dL)	NA	NA	NA	NA	NA	NA	NA	NA	94 ± 41 ^a	111 ± 49
HDL cholesterol (mg/dL)	48 ± 11	44 ± 12	NA	NA	NA	NA	NA	NA	40 ± 9	30 ± 10
Triglyceride (mg/dL)	165 ± 137	127 ± 152	NA	NA	NA	NA	NA	NA	147 ± 65	147 ± 68
Total cholesterol (mg/dL)	208 ± 33	199 ± 57	NA	NA	164 ± 46 ^a	199 ± 49	NA	NA	172 ± 46 ^a	186 ± 41
Concomitant medications before admission										
Aspirin, n (%)	11 (27.5) ^a	33 (9.5)	NA	NA	NA	NA	198 (82.2) ^a	281 (37)	198 (82.2) ^a	281 (37)
Clopidogrel, n (%)	NA	NA	NA	NA	NA	NA	NA	NA	23 (9.5)	28 (3.6)
Beta blocker, n (%)	3 (7.5) ^a	4 (1.2)	NA	NA	NA	NA	127 (52.7) ^a	137 (18.1)	127 (52.7) ^a	137 (18.1)
ACE Inhibitor or ARB, n (%)	6 (15) ^a	16 (4.6)	NA	NA	NA	NA	121 (50.2) ^a	170 (22.4)	121 (50.2) ^a	170 (22.4)
Spironolactone, n (%)	NA	NA	NA	NA	NA	NA	NA	NA	14 (5.8)	28 (3.6)
Rosuvastatin, n (%)	–	–	NA	–	NA	–	9 (3.7)	–	9 (3.7)	–
Atorvastatin, n (%)	2 (5)	–	NA	–	NA	–	154 (63.9)	–	154 (63.9)	–
Pravastatin, n (%)	25 (62.5)	–	NA	–	NA	–	10 (4.2)	–	10 (4.2)	–
Fluvastatin, n (%)	3 (7.5)	–	NA	–	NA	–	27 (11.2)	–	27 (11.2)	–
Simvastatin, n (%)	2 (5)	–	NA	–	NA	–	41 (17)	–	41 (17)	–

Table 3 (continued). Baseline lipid parameter and concomitant medications before admission

First Author (Year)	Apiyasawat et al (2013)		Marenzi et al (2015)		Li et al (2016)		Park et al (2018)	
Group (n)	Prior statin (525)	No statin (1482)	Prior statin (50)	No statin (148)	Prior statin (1973)	No statin (12,817)	Prior statin (823)	No statin (354)
Baseline lipid parameter								
LDL cholesterol (mg/dL)	NA	NA	106 (78–123) ^a	127 (102–149)	NA	NA	91 (69–116) ^a	129 (104–162)
HDL cholesterol (mg/dL)	NA	NA	43 (36–51)	40 (34–46)	NA	NA	42 (36–50)	41 (35–48)
Triglyceride (mg/dL)	NA	NA	107 (77–149)	110 (74–154)	NA	NA	114 (76–168) ^a	131 (85–213)
Total cholesterol (mg/dL)	NA	NA	170 (145–193) ^a	193 (168–220)	NA	NA	NA	NA
Concomitant medications before admission								
Aspirin, n (%)	386 (73.5) ^a	170 (11.5)	32 (64) ^a	66 (37)	NA	NA	NA	NA
Clopidogrel, n (%)	122 (23.2) ^a	29 (2)	NA	NA	NA	NA	NA	NA
Beta blocker, n (%)	264 (50.3) ^a	138 (9.3)	18 (36) ^a	19 (11)	NA	NA	NA	NA
ACE Inhibitor or ARB, n (%)	191 (36.4) ^a	114 (7.7)	20 (40)	47 (23)	NA	NA	NA	NA
Spironolactone, n (%)	NA	NA	NA	NA	NA	NA	NA	NA
Rosuvastatin, n (%)	NA	–	11 (22)	–	NA	–	NA	–
Atorvastatin, n (%)	NA	–	23 (46)	–	NA	–	NA	–
Pravastatin, n (%)	NA	–	1 (2)	–	NA	–	NA	–
Fluvastatin, n (%)	NA	–	NA	–	NA	–	NA	–
Simvastatin, n (%)	NA	–	15 (30)	–	NA	–	NA	–

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; HDL = high density lipoprotein; LDL = low density lipoprotein; NA = not available.

^a = P ≤ 0.05 for the differences according to the respective study.

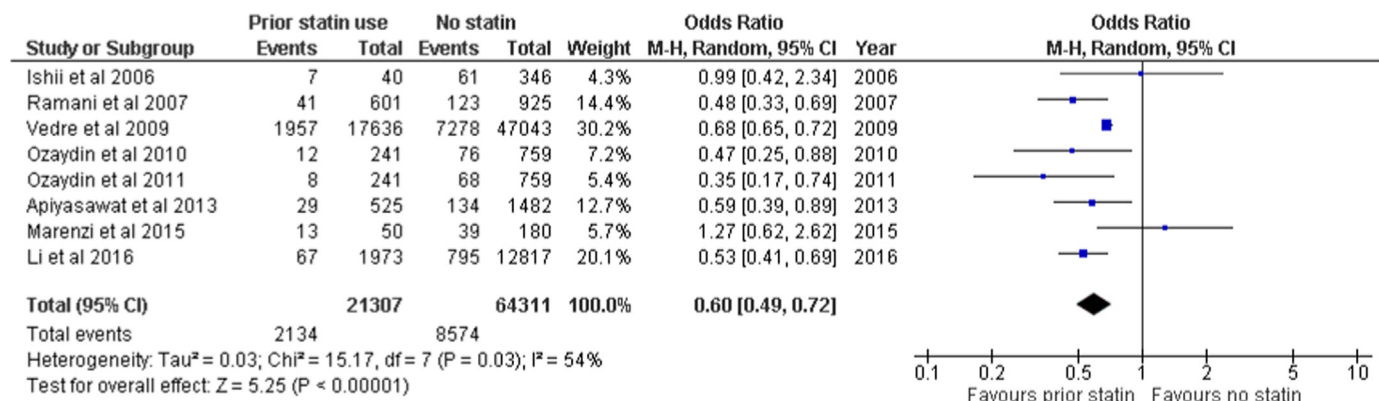


Fig. 2. Arrhythmia in acute coronary syndrome.

arrhythmia, sensitivity analysis was performed by excluding Vedre et al study. The heterogeneity reduced to 36% and the association remained significant (OR 0.57; 95% CI 0.45–0.71; P < 0.00001) (Supplementary Fig. 1). By further excluding Marenzi et al, the heterogeneity of overall arrhythmia reduced to 0% and the association remained significant (OR 0.53; 95% CI 0.44–0.62;

P < 0.00001) (Supplementary Fig. 2). For AF or atrial flutter, sensitivity analysis was conducted by excluding Vedre et al study. The heterogeneity of AF or atrial flutter reduced to 0% and the association remained significant (OR 0.50; 95% CI 0.37–0.68; P < 0.00001) (Supplementary Fig. 3).

4. Discussion

From this meta-analysis, prior statin use was significantly associated with a lower incidence of in-hospital arrhythmia during ACS. The benefit of statin in reducing the incidence of AF or atrial flutter and VT or VF was supported by the subgroup analysis, as seen in Figs. 3 and 4. The spectrum of AF ranged from new-onset AF in 2 studies^{27,29} and in-hospital AF from patients with a history of AF in 1 study.²⁸ One study did not define the type of AF.²¹ Two studies reported no difference in the incidence of arrhythmia.^{20,21} However, the incidence of arrhythmia was not the primary endpoint of both studies.^{20,21}

The reduction of high-degree AV block varies between the two studies. In one study, the incidence of high-degree AV block was comparable between prior statin use and without prior statin use.²¹ Another study reported a significantly lower incidence of high-degree AV block in ACS patients with prior statin use compared to ACS patients without prior statin use. However, this study defined the outcome of major arrhythmia as persistent VT or VF or Mobitz type II or III AV Block.³¹ Therefore, we can not conclude that previous statin can reduce the incidence of II or III-degree AV block in patients with ACS.

Only one previous meta-analysis reported the benefits of the previous statin and the incidence of AF in ACS,³³ and our subgroup analysis in AF or atrial flutter was in line with a previous meta-analysis. A 35% reduction in the risk of new-onset or recurrence AF was reported in ACS patients with prior statin use.³³ We noticed that the previous meta-analysis also included several same studies. From our inclusion criteria, another study was included. However, the included study did not assess AF or atrial flutter as its primary endpoint. Also, two randomized controlled trials (RCTs) from the early 2000s comparing statin and placebo in patients with previous MI and UA or non-Q wave MI did not assess previous statin use and the incidence of arrhythmia during ACS.^{34,35}

The benefit of statins beyond the lipid-lowering effect is well known.^{10,15} Statin possesses anti-inflammatory, anti-thrombotic, anti-proliferative, and anti-oxidant effect.^{18,36–38} These pleiotropic

effects may directly or indirectly reduce the incidence of ventricular arrhythmia (VA).¹⁸ Statin can lower the incidence of VA in ACS by reducing sarcoplasmic injury, intracellular calcium overload, and late ventricular potential in diseased myocardium.^{36,39}

Other than VA, statin can also reduce the incidence of AF in patients with concomitant coronary artery disease (CAD).⁴⁰ Pravastatin, atorvastatin, and simvastatin can reduce the incidence of AF in stabilized ACS patients and the reduction was not dose-dependent.⁴⁰ The possible mechanisms of new-onset AF in ACS are neurohormonal and autonomic nervous changes and/or changes in the atrial substrate due to atrial ischemia.^{41,42} Other than the anti-inflammatory effect, statin can increase the bioavailability of nitric oxide (NO), which can protect the atrial myocardium during atrial ischemia.³⁸ This effect can further slow or reverse structural remodeling in AF patients.³⁸

Other than a statin, LVEF and concomitant drugs may impact the incidence of arrhythmia. Concomitant treatment with aspirin, clopidogrel, beta blocker, and ACE Inhibitor or ARB was higher in ACS patients with prior statin use compared to ACS patients without statin. Beta-blockers can reduce the incidence of AF and VA during ACS, while the benefit of ACE inhibitors or ARB in reducing the incidence of AF or VA during ACS is unclear.^{18,43–45} Of note, the concomitant use of beta blocker and Renin-Angiotensin-Aldosterone (RAAS) Blocker in previous statin group from included studies varied from 7.5 to 52.7% and 15–50.2%, respectively (Table 3). The possibilities of interaction among statin, beta blocker, and ACE Inhibitor or ARB still remain, and the benefit of arrhythmia reduction in prior statin use may not solely be due to statin. Two studies reported a significant difference in LVEF between statin and non-statin groups.^{29,30} The LVEF was significantly higher in ACS patients with prior statin use than those without prior statin use and may be a confounding factor in the incidence of arrhythmia.

Moderate heterogeneity was observed from Vedre et al and Marenzi et al.^{21,28} The potential source of heterogeneity may be due to the concomitant routine medication and the type of statin, which was not reported from Vedre et al study. Also, the primary endpoint of Marenzi et al was not the incidence of arrhythmia, which may

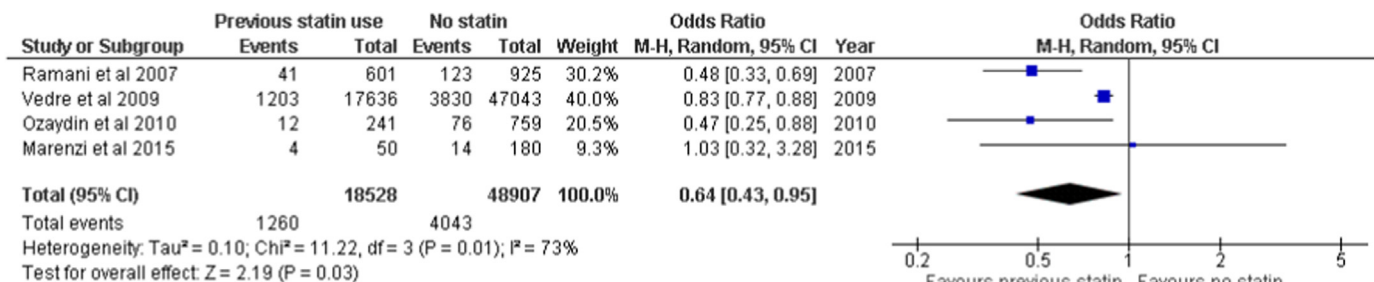


Fig. 3. Atrial fibrillation or atrial flutter.

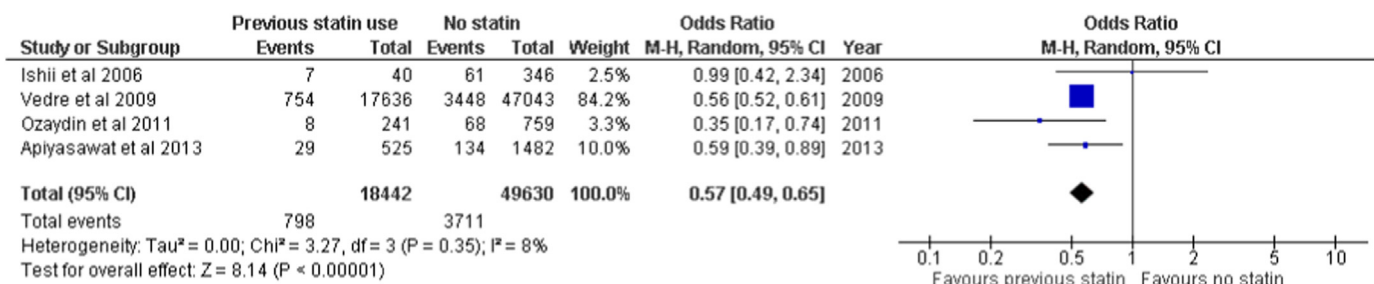


Fig. 4. Ventricular tachycardia or fibrillation.

become a potential source of heterogeneity. Other than that, the comorbidities may impact the heterogeneity.

There are several limitations in our meta-analysis. Not all studies assess the incidence of arrhythmia as a primary endpoint. We could not assess the type of statin (lipophilic or hydrophilic), dose, and duration of statin treatment due to minimum data. Moreover, our meta-analysis only reported the incidence of in-hospital arrhythmia. Whether prior statin use can reduce the long-term incidence of arrhythmia is still unknown. Also, we only included the article in English, which may not represent the whole population. Several covariates, such as age, LVEF, and concomitant medication with antiarrhythmic potential (beta blocker and ACE-inhibitor), may confound the incidence of arrhythmia. However, we could not perform a meta-regression analysis to investigate the effect of the covariates. In addition, the meta-analysis was only performed based on aggregate-patient data and we weren't able to obtain individual-patient data from all included studies. Thus, we weren't able to perform meta-analysis based on individual-patient data.

5. Conclusions

Based on aggregate-patient data, prior statin use may reduce the incidence of in-hospital arrhythmia during acute coronary syndrome, particularly in new-onset atrial fibrillation or atrial flutter and ventricular tachycardia or ventricular fibrillation. Statin may not solely reduce the incidence of in-hospital arrhythmia during acute coronary syndrome due to concomitant use of beta-blocker and RAAS Blocker. Further studies are needed to confirm this finding and assess the association between statin type, dose, and duration with the incidence of in-hospital arrhythmia during acute coronary syndrome.

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Authors' contributions

KW conceived and designed the study. KW and RD performed study selection. KW performed data extraction and interpreted the data. KW, RD, and KSN performed extensive search of relevant topics. KW performed statistical analysis. PAS, SS, and YA performed review and extensive editing of the manuscript. All authors contributed significantly to the writing of the manuscript. All authors approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2023.01.004>.

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