Atherosclerosis 286 (2019) 14–19

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Statin therapy among chronic kidney disease patients presenting with acute coronary syndrome

Sharon Shalom Natanzon[a,b,*], Shlomi Matetzky[a,b], Roy Beigel[a,b], Zaza Iakobishvili[b,c], Ilan Goldenberg[a,b], Michael Shechter[a,b], on behalf of the Acute Coronary Syndrome Israel Survey (ACSIS) investigators

[a] Leviev Heart Center, Chaim Sheba Medical Center, Tel Hashomer, Tel Aviv University, Israel
[b] Sackler Faculty of Medicine, Tel Aviv University, Israel
[c] Cardiology Department, Rabin Medical CenterTel Aviv University, Israel

HIGHLIGHTS

- Despite current guidelines, statins are still underused among chronic kidney disease patients.
- Chronic kidney disease patients presenting with acute coronary syndrome have both short- and long-term adverse outcomes.
- Statins beneficial effect is maintained among chronic kidney disease patients presenting with acute coronary syndrome regardless of renal function.

Keywords:
Chronic kidney disease
Acute coronary syndrome
Statins
Prognosis

ABSTRACT

Background and aims: The beneficial effect of statin therapy has been well established for both primary and secondary prevention of cardiovascular disease. Nevertheless, it remains under-used among patients with chronic kidney disease (CKD).

We aimed to investigate the impact of statin therapy across a wide spectrum of CKD patients presenting with acute coronary syndrome (ACS).

Methods: We included all patients with ACS enrolled in the Acute Coronary Syndrome Israel Survey (ACSIS) between the years 2006 and 2016, and allocated them to 3 groups according to their renal function based on an estimated glomerular filtration rate (eGFR) calculation on admission (MDRD formula): eGFR < 30 ml/min/1.73 m^2 (n = 525, 6%), eGFR 30–59 ml/min/1.73 m^2 (n = 1919, 21%), and eGFR > 60 ml/min/1.73 m^2 (n = 6501, 73%). Primary outcome included in-hospital, 30-day, and 1-year major adverse cardiovascular events (MACE), and the independent prognostic effect of statins among CKD patients with ACS, by Cox regression analysis.

Results: All 8945 consecutive ACS patients were included in our analysis. On hospital discharge, statin prescriptions were negatively associated with eGFR]eGFR > 60 ml/min/1.73 m^2 -95%, eGFR 30–59 ml/min/1.73 m^2 -90%, eGFR < 30 ml/min/1.73 m^2 -78% ($p < 0.001$ for trend). Kaplan-Meier curves demonstrated both short and long-term higher mortality rates in those prescribed compared with those not prescribed statins ($p < 0.001$), regardless of renal function. Cox regression analysis revealed the protective effect of discharge statins (HR-0.25, 95% C.I 0.2–0.3, $p < 0.001$).

Conclusions: In our study, the beneficial effect of statins was maintained among CKD patients presenting with ACS. Therefore, these patients should be treated with statins regardless of their eGFR.

Abbreviations: ACS, acute coronary syndrome; ACSIS, acute coronary syndrome Israeli survey; CKD, chronic kidney disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; ICCU, intensive coronary care unit; MACE, major adverse cardiovascular events; NSTEMI, non ST-elevation myocardial infarction

* Corresponding author. Leviev Heart Center, Chaim Sheba Medical Center, Tel Hashomer, Israel
E-mail address: Sharonnatanzon@gmail.com (S.S. Natanzon).

https://doi.org/10.1016/j.atherosclerosis.2019.05.002
Received 5 January 2019; Received in revised form 4 April 2019; Accepted 3 May 2019
Available online 04 May 2019
0021-9150/

1. Introduction

Chronic kidney disease (CKD) is associated with increased risk of death and cardiovascular (CV) events, with a pathophysiology of shared traditional CV risk factors (hypertension, diabetes, dyslipidemia), as well as metabolic and inflammatory mediators promoting vascular calcification [1,2].

There is a nonlinear relationship between glomerular filtration rate (GFR) and CV events, which increases even with mild renal insufficiency [estimated GFR (eGFR) in ml/min per 1.73 m^2 below 60] and continues to rise sharply below eGFR of 45. In addition, dialysis patients have a 10- to 30-fold higher risk of CV mortality [3,4].

Statins have become a cornerstone treatment for both primary and secondary prevention of CV disease (CVD), with a beneficial effect regardless of renal function in patients with eGFR > 60 ml/min per 1.73 m^2 [5].

The role of statin therapy in patients with renal dysfunction is less conclusive. Several trials have found a non-significant reduction in major adverse CV and cerebrovascular events among dialysis patients [6,7]. The prospective, randomized, placebo-controlled Study of Heart and Renal Protection (SHARP) [8] trial, which examined the combination therapy of simvastatin 20 mg daily with ezetimibe10 mg daily compared to placebo in 9270 patients with CKD (3023 on dialysis and 6247 not), with no known history of myocardial infarction (MI) or coronary revascularization, revealed a significant 17% reduction in the incidence of major atherosclerotic events during a median follow-up of 4.9 years. Furthermore, Tonelli et al. found a significant reduction in all-cause mortality, CV death and MI among patients with moderate CKD [9].

While most trials have focused on stable CVD patients or even on primary prevention therapy [7,9], much less is known about statin therapy in the setting of acute coronary syndrome (ACS).

Despite guideline recommendations, a substantial proportion of ACS patients with renal dysfunction are not prescribed statins at hospital discharge [10]. An observational study from Sweden [11] examined 42,000 MI survivors and found a lower rate of statin prescriptions at hospital discharge among renal failure patients, with a direct relationship to their eGFR. This study also highlighted the beneficial effect of statins among patients with eGFR of 30–59 following an ACS event.

We therefore hypothesized that patients with lower eGFR are prescribed statins less frequently and have worse clinical outcomes than those patients prescribed statins.

Our objective was to investigate the in-hospital, 30-day and 1-year clinical outcomes in ACS patients, classified according to their admission eGFR, and the impact of statin therapy on outcome in these patients in Israel between the years 2006 and 2016.

2. Materials and methods

The ACS Israel Survey (ACSIS) registry is a biannual prospective national survey of all ACS patients hospitalized in 25 coronary care units and cardiology wards in all general hospitals in Israel over a 2-month period (March-April) [12,13]. Demographic, historic, and clinical data were recorded on pre-specified forms for all admitted patients diagnosed with ACS. Admission and discharge diagnoses were recorded by the attending physicians based on clinical, electrocardiographic, and biochemical criteria. Patient management was at the discretion of the attending physicians. All patients signed informed consent for the ACSIS trial participation in each medical center and each institution received a priori Helsinki Board approval.

The current retrospective study is based on the data of 8945 ACS patients who were enrolled in the ACSIS trial during the years 2006–2016.

In-hospital, 30-day, and 1-year outcome data were ascertained by hospital chart review, telephone contact, and clinical follow-up data. Patient management was at the discretion of the attending physicians.

Mortality data during hospitalization, at 30 days and at 1-year post hospitalization are determined for all patients from hospital charts and by the Register. All parameters obtained from the registry are defined by the protocol.

Our ACS patients were divided into 3 groups according to their renal function based upon eGFR calculation at admission (MDRD formula): eGFR < 30 ml/min/1.73 m^2, eGFR 30–59 ml/min/1.73 m^2 and eGFR > 60 ml/min/1.73 m^2.

Primary outcomes included in-hospital, 30-day, and 1-year major adverse cardiovascular events (MACE) including all-cause mortality, hospitalization for unstable angina, recurrent MI, cerebrovascular accident (CVA), stent thrombosis and urgent revascularization.

2.1. Statistical analysis

The 3 study groups were tested with Chi-squared test for categorical variables and with.

ANOVA or Kruskal-Wallis test as appropriate for normal/non-normal distributed continuous variables. To compare 2 groups, the groups were tested with Chi-squared test for categorical variables and with *t*-test or Mann-Whitney-Wilcoxon test as appropriate for normal/non-normal distributed continuous variables. The probability of all-cause mortality during 1-year interval was graphically displayed using the Kaplan-Meier method. Cox proportional hazards multivariate-adjusted survival models were used to evaluate the independent effects of renal failure and discharge statins on 1-year all-cause mortality. In order to assess the specific contribution of discharge statins on all-cause mortality, we created several Cox proportional hazard models. Cox regression models were performed on the 3 tertiles of the renal function groups. Covariates were chosen according to the statistically significant variables found in the baseline characteristics of the groups. Further adjustments were made according to stepwise AIC selection.

The following factors were pre-specified as covariates in the multivariate survival models: sex; age; history of premature familial CVD; prior CV comorbidities and procedures: dyslipidemia, hypertension, diabetes mellitus, MI, angina pectoris, percutaneous coronary intervention, coronary artery bypass grafting, congestive heart failure, chronic renal failure, CVA/transient ischemic attack and peripheral vascular disease. R software (R core team 2018; version 3.5.1) was used for all analyses. A p-value of < 0.05 was considered statistically significant for all tests.

3. Results

Baseline characteristics of ACS patients are shown in Table 1.

Overall, 8945 consecutive patients were evaluated in our cohort. Patients were allocated according to their admission eGFR: < 30 ml/min/1.73 m^2 (n = 525,6%), 30–59 ml/min/1.73 m^2 (n = 1919, 21%), ≥60 (n = 6501, 73%) with male predominance (78%).

Patients with lower eGFR (< 60 ml/min/1.73 m^2) were significantly older, and presented with a higher incidence of CV risk factors, established coronary artery disease and non-ST elevation MI (NSTEMI). While the incidence of primary percutaneous coronary intervention in STEMI patients did not differ between the groups, the overall coronary angiography was significantly lower in the lower eGFR group: (GFR < 30–40.9%, GFR 31-59-60.8%, GFR ≥ 60–64.4%, respectively; $p < 0.001$).

Supplementary Table 1 shows the difference between the two lower eGFR groups (eGFR < 30 ml/min/1.73 m^2 *vs.* eGFR 30–59 ml/min/1.73 m^2). Patients with eGFR < 30 ml/min/1.73 m^2 had a higher incidence of CV risk factors, previous cerebrovascular and peripheral vascular disease, as well as a lower rate of coronary angiography.

Chronic kidney disease patients had a significantly higher incidence of in-hospital complications, including cardiogenic shock (17.5%, 5.4%, 1.3%, $p < 0.001$; respectively), sustained ventricular tachycardia and secondary ventricular fibrillation (4.6%, 2.3%, 1.0%, $p < 0.001$;

Table 1
Baseline characteristics.

	GFR < 30 N = 525 (5.9%)	GFR 30–59 N = 1919 (21.5%)	GFR ≥60 N = 6501 (72.6%)	*p* value
Age (mean ± SD)	73.5 ± 11.6	72.4 ± 10.9	60.4 ± 12.0	< 0.001
Male gender (n,%)	329 (63)	1279 (66)	5390 (83)	< 0.001
Hypertension (%)	453 (86.3)	1555 (81.4)	3610 (55.7)	< 0.001
Past smoker (n,%)	138 (26.6)	535 (28.1)	1303 (20.2)	< 0.001
Diabetes (n,%)	331 (63.3)	931 (48.8)	2100 (32.3)	< 0.001
Dyslipidemia (n,%)	403 (77.8)	1482 (77.6)	4588 (70.8)	< 0.001
Previous ACS (n,%)	254 (48.7)	789 (41.3)	1830 (28.2)	< 0.001
New atrial fibrillation (n,%)	77 (14.7)	171 (8.9)	194 (3.0)	< 0.001
Prior PCI (n,%)	200 (38.3)	742 (38.9)	1947 (30)	< 0.001
Prior CABG (n,%)	98 (18.7)	318 (16.6)	462 (7.1)	< 0.001
Prior CVA/TIA (n,%)	94 (18)	254 (13.3)	373 (5.7)	< 0.001
Prior PVD (n,%)	119 (22.8)	262 (13.7)	341 (5.3)	< 0.001
Prior COPD (n,%)	38 (11.3)	81 (7.6)	202 (5.4)	< 0.001
STEMI (n,%)	186 (35.5)	686 (35.7)	2942 (45.3)	< 0.001
NSTEMI (n,%)	289 (55.2)	989 (51.5)	2547 (39.2)	< 0.001
Primary PCI in STEMI(n,%)	105 (93.8)	411 (87.6)	1929 (87.5)	0.142
Coronary angiography (n,%)	212 (40.9)	1154 (60.8)	4131 (64.4)	< 0.001

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; GFR, glomerular filtration rate in ml/min/1.73 m^2; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischemic attack; NSTEMI, non ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction.

3.1%,1%. 0.6%, $p < 0.001$; respectively), higher admission Killip class (Killip 2, 19.4%, 14.6%, 5.3%, $p < 0.001$; Killip 3, 19.7%, 12.3%, 2.8% $p < 0.001$) and bleeding (Supplementary Table 2).

Higher rate of in-hospital mortality, MACE, and 1-year mortality were observed in the lower eGFR group (Supplementary Table 3).

Statin prescriptions at hospital discharge were negatively associated with eGFR. While those with eGFR > 60 ml/min/1.73 m^2 had a 95% statin prescription at discharge, those with eGFR 30–59 ml/min/1.73 m^2 had 90%, and those with eGFR < 30 ml/min/1.73 m^2 had 78% ($p < 0.001$ for trend). No significant differences were observed between the years 2006 and 2013, while an increase in statin use in the low eGFR group of patients was observed during the years 2013 and 2016 (Fig. 1).

Patients in the highest risk group (eGFR < 30 ml/min/1.73 m^2), who were not prescribed statins, tended to be older (76 ± 11 *vs.* 73 ± 11 years, $p = 0.051$) with a lower prevalence of coronary angiography, both in the intensive coronary care unit (ICCU) and throughout their hospitalization (Table 2A). Furthermore, these patients had a higher incidence of MACE (58.1% *vs.* 17.2%, $p < 0.001$), as well as higher 7-day, 30-day and 1-year mortality (25.6% *vs.* 2.6%, $p < 0.001$; 51.2% *vs.* 8.0%, $p < 0.001$; 65.1% *vs.* 29.5%, $p < 0.001$) (Table 2B).

A subgroup analysis of clinical outcomes among ACS patients with eGFR < 30 between the years 2006–2008 and 2010–2016 revealed a higher incidence of short- and long-term mortality in those who were not prescribed statins at discharge (Supplementary Table 4).

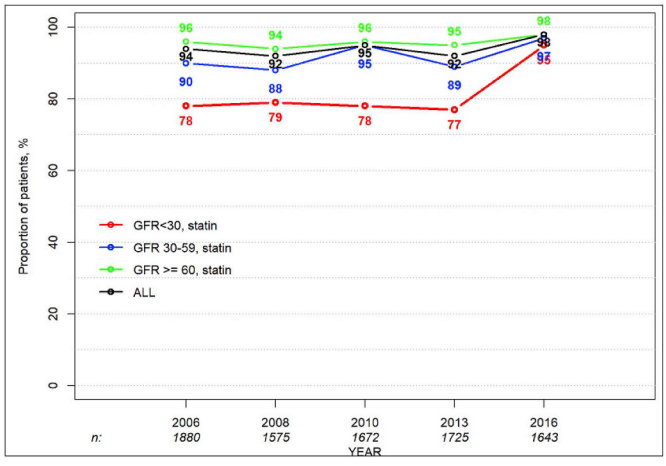


Fig. 1. Statin use among chronic kidney disease (CKD) patients presenting with acute coronary syndrome (ACS) between the years 2006 and 2016.

Table 2A
Baseline characteristics among GFR < 30 patients with/without statins.

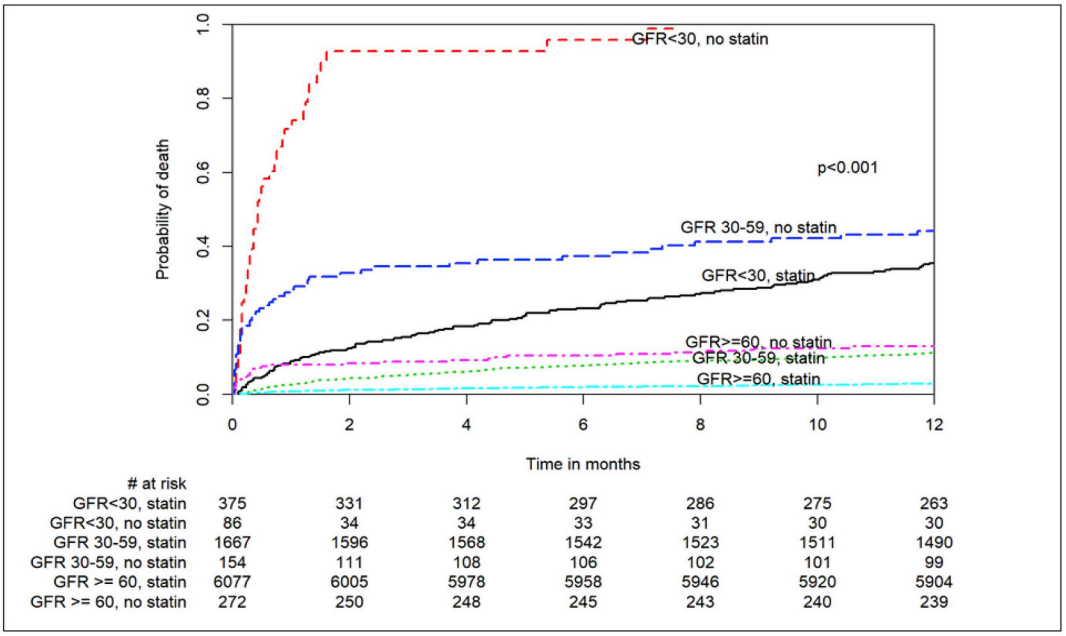
	No statins N = 86	Statins N = 380	*p* value
Age (mean ± SD)	75.6 ± 11.1	72.9 ± 11.4	0.051
Male gender (n,%)	53 (61.6)	244 (64.2)	0.745
Hypertension (n,%)	75 (87.2)	333 (87.6)	1.000
Past smoker (n,%)	19 (22.9)	104 (27.6)	0.461
Diabetes (n,%)	50 (58.1)	243 (64.3)	0.346
Dyslipidemia (n,%)	58 (69.9)	307 (81.4)	0.028
Previous ACS (n,%)	32 (37.2)	199 (52.6)	0.014
Prior PCI (n,%)	21 (24.4)	164 (43.5)	0.002
Prior CABG (n,%)	15 (17.4)	4 (19.5)	0.779
Prior CVA/TIA (n,%)	18 (20.9)	71 (18.7)	0.707
Prior PVD (n,%)	18 (20.9)	89 (23.5)	0.714
Prior COPD (n,%)	9 (17.6)	23 (9.2)	0.125
STEMI (n,%)	36 (42.4)	118 (31.1)	0.061
NSTEMI (n,%)	45 (52.9)	221 (58.2)	0.449
Primary reperfusion (n,%)	20 (23.3)	74 (19.5)	0.522
Coronary angiography (n,%)	20 (23.3)	176 (46.9)	< 0.001
New atrial fibrillation (n,%)	19 (22.1)	48 (12.6)	0.037
Pulmonary edema (n,%)	24 (27.9)	66 (17.4)	0.038

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; GFR, glomerular filtration rate in ml/min/1.73 m^2; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischemic attack; NSTEMI, non ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction.

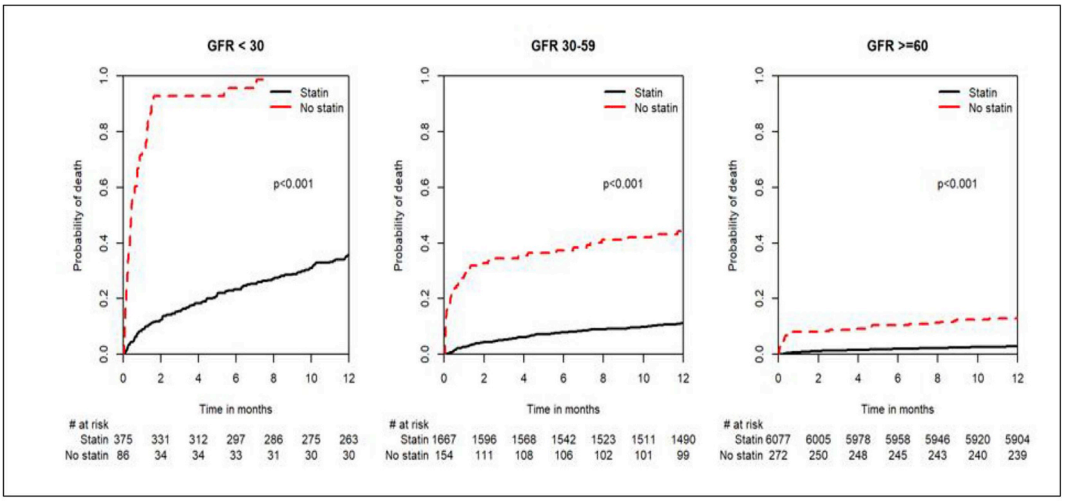
Table 2B
Clinical outcomes among patients with GFR < 30 with and without statins at discharge.

	No statins N = 86	Statins N = 380	*p* value
Any MACE* (n,%)	50 (58.1)	65 (17.2)	< 0.001
7-day mortality (n,%)	22 (25.6)	10 (2.6)	< 0.001
30-day mortality (n,%)	44 (51.2)	30 (8.0)	< 0.001
1-year mortality (n,%)	56 (65.1)	110 (29.5)	< 0.001

* MACE, major adverse cardiovascular events including all-cause mortality, hospitalization for unstable angina, recurrent MI, cerebrovascular accident, stent thrombosis and urgent revascularization; GFR, glomerular filtration rate in ml/min/1.73 m^2, CVA, stent thrombosis and urgent revascularization.



A



B

Fig. 2. Kaplan-Meier curves.
(A) Higher 1-year mortality in non-statin patients across all eGFR spectrums. (B) Higher 1-year mortality in non-statin patients with eGFR < 30 ml/min/1.73 m^2 (left panel), eGFR 30–59 ml/min/1.73 m^2 (middle panel), and eGFR > 60 ml/min/1.73 m^2 (right panel).

Kaplan-Meier curves demonstrated both short- and long-term higher mortality rates within all 3 eGFR groups in those patients who were not, compared with those who were prescribed statins at discharge (Fig. 2A and B).

Cox regression analysis demonstrated that statin therapy at discharge was an independent predictor of 1-year survival with a protective effect across all eGFR tertiles as shown in Table 3A–C.

Factors associated with a higher 1-year mortality included: age > 75 years (HR-2.20, $p < 0.001$), prior MI (HR-1.91, $p < 0.001$), hypertension (HR-1.34, p-0.02), diabetes (HR-1.55, $p < 0.001$) and STEMI (HR-1.40, $p < 0.001$).

4. Discussion

ACS management has progressed significantly since the establishment of ICCUs. Anti-aggregants, anti-diabetic and lipid-lowering drugs, as well as coronary interventions have had a major positive effect on patient prognosis.

Despite the current era medical therapy, CKD is still associated with both short- and long-term adverse outcomes among patients with ACS. While shared risk factors and a sustained inflammatory state may explain this undesired association, one recurring factor is the under-usage of guideline-recommended therapies [14] in this high-risk population.

Statins is a mainstay therapy in both primary and secondary prevention of CVD. However, large scale trials with inconclusive results, the “U shape” mortality curve among dialysis patients (increased mortality with both low and high cholesterol levels among dialysis patients [15]), the different mechanisms, in addition to atherosclerosis (including arterial stiffness and structural heart disease) [16] have resulted in lower prescription rates.

Our trial examined a large cohort of CKD patients with a wide spectrum of severities based on eGFR levels (KDIGO classification [17]),

Table 3A
Cox regression model (hazard ratio for 1-year morality, CI-95%) eGFR < 30.

	HR (C.I-95%)	*p* value
Discharge statins	0.26 (0.19–0.36)	< 0.001
Prior MI	1.60 (1.12–2.27)	0.01
Past PCI	0.58 (0.40–0.84)	0.005

Table 3B
Cox regression model (Hazard ratio for 1-year morality, CI-95%) eGFR 30-59.

	HR (C.I-95%)	*p* value
Discharge statins	0.35 (0.25–0.48)	< 0.001
Dyslipidemia	0.65 (0.49–0.87)	0.004
Heart Rate	1.01 (1.00–1.01)	0.02
Creatinine in admission	1.74 (1.15–2.64)	0.01
Coronary angiography	0.70 (0.49–0.99)	0.05
Pulmonary edema	1.62 (1.16–2.26)	0.005
PCI	0.64 (0.46–0.90)	0.01

Table 3C
Cox regression model (Hazard ratio for 1-year morality, CI-95%) eGFR > 60.

	HR (C.I-95%)	*p* value
Discharge statins	0.36 (0.24–0.55)	< 0.001
Dyslipidemia	0.72 (0.53–0.97)	0.04
Gender (male)	0.70 (0.50–0.98)	0.04
Family history of CAD	0.69 (0.49–0.99)	0.05
Coronary angiography	0.49 (0.33–0.73)	0.001
PCI	0.49 (0.35–0.69)	< 0.001
Pulmonary edema (Killip 3)	2.81 (1.89–4.19)	< 0.001

who presented with ACS and had several clinical implications.

First, CKD was associated with a higher rate of in-hospital complications, including a higher incidence of cardiac arrhythmias, a higher incidence of heart failure (associated with higher Killip class on ICCU admission), and bleeding events. These findings highlight the challenges involved in treating these ACS patients who are prone to more ischemic/thrombotic events, as well as a tendency towards bleeding, which makes them even more prone to adverse clinical events.

Second, despite previous trials, which have reported very low usage of statins among CKD patients with CVD, our study population had a significantly higher prescription rate of statins, which was probably related to the unstable nature of atherosclerotic plaque in the clinical setting of ACS. Statin use dropped significantly as eGFR decreased, which may be related to the uncertain benefit of statins among patients with end-stage renal disease with multi-factorial cardiac abnormalities, which may be unrelated to atherosclerosis *per se* [18].

Third, despite the inverse relationship between statin prescription at hospital discharge and eGFR, statins have been proven beneficial across a wide spectrum of renal functions.

Our study has shown the independent effect of both short- and long-term prognosis of statin therapy in the clinical scenario of ACS regardless of renal function.

Cox regression analysis revealed an inverse relationship between a statin protective effect and renal function. The lowest eGFR group of patients (eGFR < 30 ml/min/1.73 m^2) benefit the most from statin use. This subgroup of patients is at the highest risk of CV events and, as shown in the Kaplan-Meier analysis in the current study (Fig. 2A and B), statin therapy can significantly change a patient's prognosis. The beneficial effect of statins on outcomes has remained whether ACS patients were treated a decade ago or according to current guidelines recommendations.

Our findings concur with previous clinical trials and meta-analyses, which proved statins to be both safe and beneficial even in advanced CKD. We assume that the equivocal effect of statin therapy among stable CAD patients with renal failure is related to chronic metabolic abnormalities and cardiac remodeling processes in the setup of stable atherosclerotic plaque. On the contrary, in the setting of ACS with ruptured, unstable plaque, a high inflammatory state as well as a prothrombotic environment, statin therapy should be mandatory, with positive prognostic implications across all spectra of eGFR.

Our study has some limitations: (1) this is a retrospective observational study and despite adjustment for confounders, selection bias may have over-estimated the benefit of therapy; (2) as this is not a randomized study, the precise effect of statin therapy may not be estimated accurately; (3) there is a lack of data related to statin treatment doses, the type of statins used, and the number of crossovers with patients changing statin treatment during follow-up.

In conclusion, our study demonstrates that statin therapy is underused in CKD patients presenting with ACS. These patients are at increased risk of both mortality and CV events. CKD patients presenting with ACS should be treated with statins regardless of their eGFR.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

S. S. Natanzon contributed toward the design and performance of the study, analysis of data, and preparation of the manuscript. S. Matetzky contributed toward the design and performance of the study, analysis of data, and preparation of the manuscript. R. Beigel contributed toward the design and performance of the study, analysis of data, and preparation of the manuscript. Z. Iakobishvili contributed toward analysis of data, and preparation of the manuscript. I. Goldenberg contributed toward the design and performance of the study, analysis of data, and preparation of the manuscript. M. Shechter contributed toward the design and performance of the study, analysis of data, and preparation of the manuscript. All authors were involved in interpretation of data and the final approval of the report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.05.002.

References

[1] R.T. Gansevoort, et al., Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention, Lancet Lond. Engl. 382 (9889) (Jul. 2013) 339–352.
[2] A.L. Catapano, et al., ESC/EAS guidelines for the management of dyslipidaemias, Eur. Heart J. 37 (39) (2016) 2999–3058 Oct. 2016.
[3] A.S. Go, G.M. Chertow, D. Fan, C.E. McCulloch, C. Hsu, Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization, N. Engl. J. Med. 351 (13) (2004) 1296–1305 23.
[4] R.N. Foley, P.S. Parfrey, M.J. Sarnak, Clinical epidemiology of cardiovascular disease in chronic renal disease, Am. J. Kidney Dis. 32 (5 Suppl 3) (Nov. 1998) S112–S119.
[5] Cholesterol Treatment Trialists' (CTT) Collaboration, et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, Lancet Lond. Engl. 376 (9753) (Nov. 2010) 1670–1681.
[6] C. Wanner, et al., Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): demographic and baseline characteristics, Kidney Blood Press. Res. 27 (4) (2004) 259–266.
[7] B.C. Fellström, et al., Rosuvastatin and cardiovascular events in patients undergoing hemodialysis, N. Engl. J. Med. 360 (14) (Apr. 2009) 1395–1407.
[8] C. Baigent, et al., The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial, Lancet Lond. Engl. 377 (9784) (Jun. 2011) 2181–2192.
[9] M. Tonelli, et al., Effect of pravastatin on cardiovascular events in people with chronic kidney disease, Circulation 110 (12) (Sep. 2004) 1557–1563.
[10] J.M. Foody, et al., Lipid management in patients with unstable angina pectoris and

non-ST-segment elevation acute myocardial infarction (from CRUSADE), Am. J. Cardiol. 95 (4) (Feb. 2005) 483–485.
[11] K. Szummer, et al., Association between statin treatment and outcome in relation to renal function in survivors of myocardial infarction, Kidney Int. 79 (9) (May 2011) 997–1004.
[12] R. Kornowski, The ACSIS Registry and primary angioplasty following coronary bypass surgery, Cathet. Cardiovasc. Interv. 78 (4) (Oct. 2011) 537–539.
[13] A. Segev, et al., Contemporary use and outcome of percutaneous coronary interventions in patients with acute coronary syndromes: insights from the 2010 ACSIS and ACSIS-PCI surveys, EuroIntervention 8 (4) (Aug. 2012) 465–469.
[14] M. Tonelli, C. Bohm, S. Pandeya, J. Gill, A. Levin, B.A. Kiberd, Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency, Am. J. Kidney Dis. 37 (3) (Mar. 2001) 484–489.
[15] P. Degoulet, et al., Mortality risk factors in patients treated by chronic hemodialysis. Report of the Diaphane collaborative study, Nephron 31 (2) (1982) 103–110.
[16] W. Hou, et al., Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis, Eur. Heart J. 34 (24) (Jun. 2013) 1807–1817.
[17] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), Kidney Int. Suppl. 113 (Aug. 2009) S1–S130.
[18] M.G. Wong, C. Wanner, J. Knight, V. Perkovic, Lowering cholesterol in chronic kidney disease: is it safe and effective? Eur. Heart J. 36 (43) (Nov. 2015) 2988–2995.