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Mortality associated with stopping statins in the oldest-old – with and without ischemic heart disease

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Abstract

The association between stopping statins and 1-year mortality in the general population of the oldest-old – with or without ischemic heart disease (IHD) – has been studied herein for the first time.

This was a retrospective study. Included were all consecutive patients (n = 369) aged 80 years or more (mean age 87.8 years) hospitalized in a single Geriatrics department during 1 year. The study group included 140 patients in whom statins were stopped upon admission (statin stoppers). The control group included 229 patients who did not use statins in the first place (statin non-users). All-cause 1-year mortality rates were studied in both groups following propensity score matching and in IHD patients separately.

Overall, 110 (29.8%) patients died during the year following admission: 38 (27.1%) statin stoppers and 72 (31.4%) statin non-users ($P = .498$). Cox regression analysis showed no association between stopping statins and 1-year mortality in the crude analysis (hazard ratio [HR] 0.976, 95% confidence interval [CI] 0.651–1.463, $P = .907$) and following propensity score matching (HR 1.067, 95%CI 0.674–1.689, $P = .782$). Among 108 IHD patients, 38 (35.2%) patients died during the year following admission: 18 (27.7%) statin stoppers and 20 (46.5%) statin non-users ($P = .059$). Cox regression analysis showed a nearly significant association between stopping statins (rather than not using statins) in IHD patients and lower 1-year mortality (HR 0.524, 95%CI 0.259–1.060, $P = .072$).

Hence, stopping statins in the general population of the oldest-old – with or without IHD – is possibly safe. Future studies including the oldest-old statin continuers are warranted to confirm this observation.

Abbreviations: CI = confidence interval, HR = hazard ratio, IHD = ischemic heart disease.

Keywords: ischemic heart disease, mortality, older adults, statins

1. Introduction

Reducing drug treatment, that is, deprescribing is intended to reduce side effects, improve quality of life, increase compliance with other essential drugs, reduce financial costs, and even improve prognosis by eliminating a drug therapy whose effectiveness or necessity is questionable.[1] Deprescribing in nursing-home older adults is associated with a decline in the number of hospitalizations and a reduction in mortality during the following year.[2] Deprescribing in community-dwelling older adults is associated with an improved quality of life and is not associated with increased mortality.[3]

The use of statins among the oldest-old is very widespread; it ranges between 17% and 39% in nursing-home residents, 12% to 59% in community-dwelling patients, and 18% to 45% in combined populations.[4] According to Johansen et al, older adults aged 80 years are 2 to 3 times more likely to use statins in 2012 than they have been in 1999.[5] This is surprising since the oldest-old are often excluded from major clinical trials, and accordingly there are no clear guidelines to use statins in the oldest-old for primary or secondary cardiovascular prevention[6]; there are only 3 randomized-control trials concerning starting statins in the oldest-old, and they show that using statins is not associated with mortality reduction.[7–9] Furthermore, the use of statins involves possible side effects such as myopathy and hepatitis – particularly in older adults.[10] To date only 1 prospective study has been published on stopping statins in older adults: Kutner et al have shown that stopping (rather than continuing) statins in dying older adults (mean age 74.1 years) is associated with a better quality of life and is not associated with increased mortality rates 60 days later; moreover, there has been a trend of lower 1-year survival among statins continuers.[11]

The prognosis of stopping statins in the oldest-old has never been studied, to the best of our knowledge. Nevertheless, physicians are sometimes reluctant to stop statins in this population – especially in the oldest-old with ischemic heart disease (IHD).

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The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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Table 1

Clinical characteristics of the whole cohort, statin non-users, statin stoppers, and statin continuers.

			Unmatched			Unmatched		
		Whole cohort (n = 369)	Statin non-users (n = 229)	Statin stoppers (n = 140)	*P* value	Statin continuers (n = 43)	Statin stoppers (n = 140)	*P* value
Demographics	Age, years, mean (stan. deviation)	87.8 (5.1)	88.2 (5.3)	87.1 (4.5)	.044	83.6 (3.0)	87.1 (4.5)	<.001
	Female, n (%)	228 (61.8)	149 (65.1)	79 (56.4)	.100	30 (69.8)	79 (56.4)	.155
Co-morbidities	Hypertension, n (%)	284 (77.0)	173 (75.5)	111 (79.3)	.446	43 (100.0)	111 (79.3)	<.001
	Dementia, n (%)	177 (48.0)	118 (51.5)	59 (42.1)	.086	3 (7.0)	59 (42.1)	<.001
	Past stroke, n (%)	127 (34.4)	72 (31.4)	55 (39.3)	.142	14 (32.6)	55 (39.3)	.475
	Diabetes mellitus, n (%)	120 (32.5)	71 (31.0)	49 (35.0)	.426	19 (44.2)	49 (35.0)	.285
	Ischemic heart disease, n (%)	108 (29.3)	43 (18.8)	65 (46.4)	<.001	17 (39.5)	65 (46.4)	.485
	Atrial fibrillation, n (%)	104 (28.2)	63 (27.5)	41 (29.3)	.722	12 (27.9)	41 (29.3)	>.999
	Congestive heart failure, n (%)	81 (22.0)	45 (19.7)	36 (25.7)	.195	14 (32.6)	36 (25.7)	.435
	Chronic renal failure, n (%)	68 (18.4)	40 (17.5)	28 (20.0)	.581	14 (32.6)	28 (20.0)	.099
	Depression, n (%)	58 (15.7)	39 (17.0)	19 (13.6)	.461	7 (16.3)	19 (13.6)	.625
	Chronic lung disease, n (%)	51 (13.8)	34 (14.8)	17 (12.1)	.535	4 (9.3)	17 (12.1)	.787
	Cancer, n (%)	35 (9.5)	27 (11.8)	8 (5.7)	.066	3 (7.0)	8 (5.7)	.722
	Parkinson disease, n (%)	31 (8.4)	22 (9.6)	9 (6.4)	.337	2 (4.7)	9 (6.4)	>.999
	Peripheral vascular disease, n (%)	20 (5.4)	9 (3.9)	11 (7.9)	.153	3 (7.0)	11 (7.9)	>.999
	Collagen vascular disease, n (%)	18 (4.9)	13 (5.7)	5 (3.6)	.459	3 (7.0)	5 (3.6)	.394
	Smoking, n (%)	11 (3.0)	5 (2.2)	6 (4.3)	.345	1 (2.3)	6 (4.3)	>.999
Geriatric aspects	Nasogastric tube or gastrostomy, n (%)	12 (3.3)	9 (3.9)	3 (2.1)	.547	0 (0.0)	3 (2.1)	>.999
	Permanent urinary catheter, n (%)	16 (4.3)	12 (5.2)	4 (2.9)	.430	0 (0.0)	4 (2.9)	.574
	Pressure ulcers, n (%)	12 (3.3)	11 (4.8)	1 (0.7)	.035	1 (2.3)	1 (0.7)	.416
	Function: Severely dependent, n (%)	212 (57.5)	139 (60.7)	73 (52.1)	.288	12 (27.9)	73 (52.1)	.024
	Mildly dependent n (%)	107 (29.0)	64 (27.9)	43 (30.7)		16 (37.2)	43 (30.7)	
	Independent, n (%)	50 (13.6)	26 (11.4)	24 (17.1)		15 (34.9)	24 (17.1)	
	Nursing-home residents, n (%)	53 (14.4)	45 (19.7)	8 (5.7)	<.001	1 (2.3)	8 (5.7)	.688
Laboratory	Albumin <3.5 g/dL, n (%)	156 (42.9)	130 (57.8)	50 (36.0)	<.001	6 (14.0)	50 (36.0)	.008

2. Aims

To study the association between stopping statins and 1-year mortality in the general population of the oldest-old with or without IHD.

3. Methods

3.1. The study design

This was a retrospective study approved by the ethics Helsinki committee of Sheba Medical Center – the largest tertiary medical center in Israel.

Included were all consecutive patients aged 80 years or more hospitalized in a single acute Geriatrics department (Geriatrics and Internal Medicine D) between April 2014 and April 2015. In the case of multiple admissions, only the first admission was included in the analysis. Informed consent was not obtained from the patients since this was a retrospective study. Patient anonymity was strictly kept.

Excluded were patients who carried on with statin therapy on the day of discharge from the hospital, patients who died during hospitalization, and patients with missing data.

3.2. Data collected

Age, gender, chronic co-morbidities, functional status, residence place, use of enteral feeding tubes, use of urinary catheters, cause of stopping statins, admission albumin serum levels, and all-cause mortality rates during the year following admission (using the database of the Israeli general register office) were recorded in all patients.

3.3. Statistical analysis

Age was expressed as mean ± standard deviation. The Student *t* test was used to compare between the groups' mean ages (parametric distribution). The Chi-square test was used to compare between the prevalence of categorical variables. The Kaplan–Meier curves were used to describe cumulative survival over time, and the log-rank test was used to compare between the groups.

A multivariate Cox regression analysis was used to evaluate the association between stopping statins (rather than not using statins) and 1-year mortality. It included 3 blocks: the first block included the crude association; the second block included the association adjusted for age and gender; and the third block included all other variables in Table 1 that were selected using the backward stepwise method and the likelihood ratio as criteria. The analyses were repeated separately in patients with and without IHD.

A propensity score matching was performed since there were statistically significant differences in the baseline characteristics between the study group and the control group. A propensity score was calculated as the probability of stopping statin using multivariate logistic regression analysis. All variables in Table 1 were included in the analysis. An absolute difference of up to 5% was considered acceptable for matching. Following matching, the groups were compared using the Student *t* test or the Wilcoxon

signed test for continuous variables, and the McNemar test for categorical variables. A stratified Cox regression analysis was used to compare mortality rates between the matched groups. Finally, the whole cohort was divided into 5 equal-sized groups according to the propensity score, and a stratified Cox regression analysis was performed again.

All tests were two-sided and considered significant at $P < .05$. Data were analyzed using the SPSS statistical software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp 2016).

4. Results

The initial cohort included 466 patients. Excluded were 43 (9.2%) patients who carried on with statin therapy on the day of discharge from the hospital (statin continuers), 40 (8.6%) patients who died during hospitalization, and 14 (3.0%) patients with missing data. The final cohort included 369 patients: 228 (61.8%) women and 141 (38.2%) men. The mean age of the whole cohort was 87.8 ± 5.1 years. The 3 most common chronic co-morbidities were: hypertension, dementia, and history of stroke. The majority of patients were severely dependent (Table 1).

The study group included 140 (37.9%) patients for whom statin therapy was discontinued (statin stoppers) for various reasons – most (n = 86; 61.4%) of the times due to a combination of advanced age, and/or low total cholesterol serum levels, and/or poor functional status, and/or polypharmacy, and/or advanced malignancy, and/or adverse effects of statins; statin therapy was stopped in other patients due to a single reason – advanced age (n = 44; 31.4%), low total cholesterol serum levels (n = 9; 6.4%), and advanced malignancy (n = 1; 0.7%). The mean age of statin stoppers was 87.1 ± 4.5 years. Seventy-three (52.1%) statin stoppers were severely dependent, 59 (42.1%) patients had dementia, and 50 (36.0%) patients had hypoalbuminemia. Almost half (n = 65, 46.4%) of the statin stoppers had IHD. The control group included 229 (62.1%) patients who did not take statins on admission and at the time of discharge (statin non-users). When compared with the statin stoppers, statin non-users were significantly older, had a higher prevalence of pressure ulcers and hypoalbuminemia, and lived more often in nursing homes. On the other hand, statin continuers were significantly younger and more independent, had a higher prevalence of hypertension, and lower prevalence of dementia and hypoalbuminemia (Table 1).

Among the whole cohort, 110 (29.8%) patients died during the year following admission: 38 (27.1%) statin stoppers and 72 (31.4%) statin non-users ($P = .498$). There were no significant differences in the cumulative survival between the groups (Fig. 1A). Cox regression analysis (including all variables in Table 1) showed no association between stopping statins (rather than not using) and 1-year mortality (hazard ratio [HR] 0.976, 95% confidence interval [CI] 0.651–1.463, $P = .90$).

Overall, 3 (6.9%) statins continuers died during the year following admission (Figure 1A). Cox regression analysis (including the following variables: statin stopping/continuing, age, independency, hypertension, dementia, and hypoalbuminemia) showed that only hypoalbuminemia was associated with

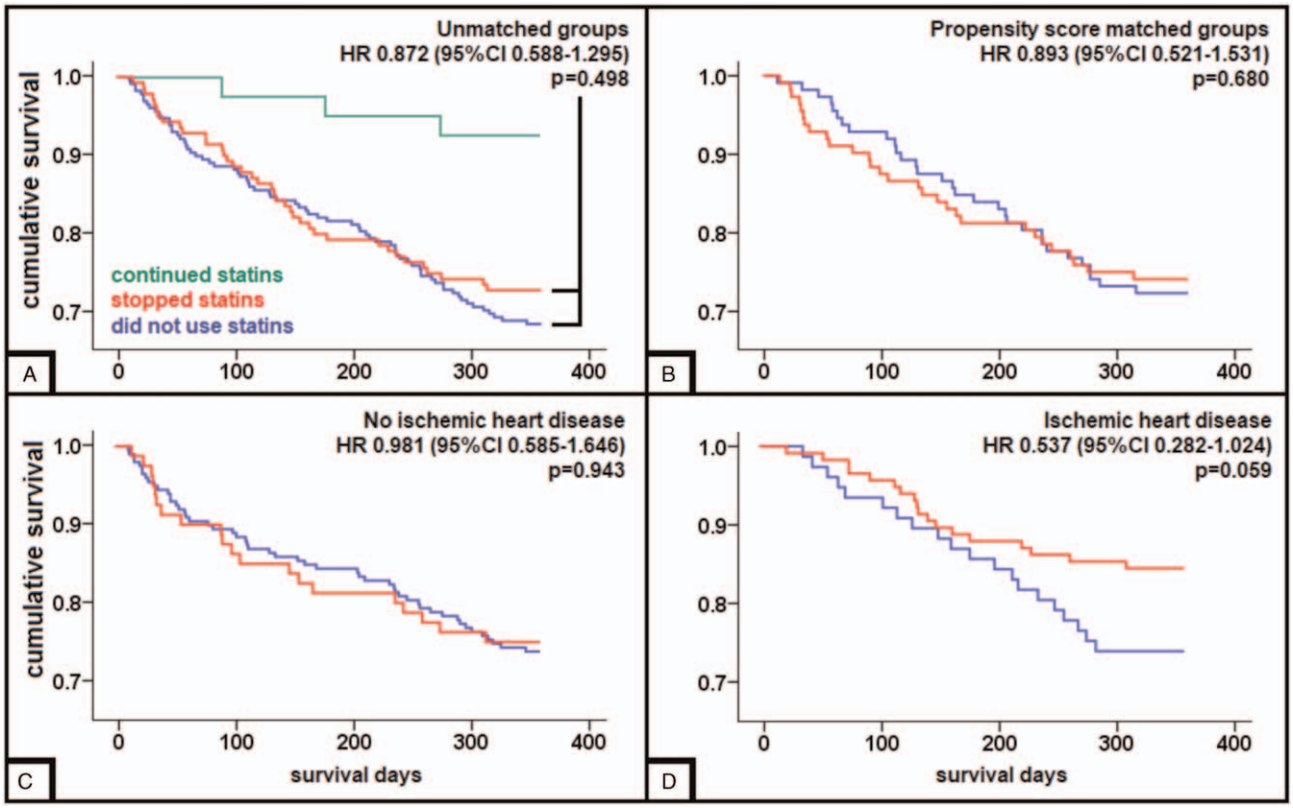

Figure 1. Cumulative survival in statins stoppers and in statins non-users: crude analysis (A); following a propensity-score matching (B); in patients without ischemic heart disease (C); and in patients with ischemic heart disease (D).

Table 2

Clinical characteristics of the whole cohort following propensity-score matching, patients with ischemic heart disease, and patients without ischemic heart disease.

		Propensity score matched			Ischemic heart disease			No ischemic heart disease		
		Statin non-users (n=112)	Statin stoppers (n=112)	*P* value	Statin non-users (n=43)	Statin stoppers (n=65)	*P* value	Statin non-users (n=186)	Statin stoppers (n=75)	*P* value
Demographics	Age, years, mean (stan. deviation)	87.9 (5.5)	87.4 (4.6)	.470	88.6 (5.8)	86.9 (4.2)	.076	88.1 (5.2)	87.3 (4.8)	.246
	Female, n (%)	69 (61.6)	66 (58.9)	.766	20 (46.5)	27 (41.5)	.693	129 (69.4)	52 (69.3)	>.999
Co-morbidities	Hypertension, n (%)	87 (77.7)	88 (78.6)	>.999	36 (83.7)	52 (80.0)	.801	137 (73.7)	59 (78.7)	.433
	Dementia, n (%)	48 (42.9)	49 (42.0)	>.999	19 (44.2)	24 (36.9)	.548	99 (53.2)	35 (46.7)	.343
	Past stroke, n (%)	35 (31.3)	41 (36.6)	.405	15 (34.9)	30 (46.2)	.319	57 (30.6)	25 (33.3)	.662
	Diabetes mellitus, n (%)	39 (34.8)	35 (31.3)	.652	16 (37.2)	24 (36.9)	>.999	55 (29.6)	25 (33.3)	.556
	Ischemic heart disease, n (%)	36 (32.1)	37 (33.0)	>.999	43 (100.0)	65 (100.0)	>.999	0 (0.0)	0 (0.0)	>.999
	Atrial fibrillation, n (%)	31 (27.7)	34 (30.4)	.749	21 (48.8)	25 (38.5)	.324	42 (22.6)	16 (21.3)	.871
	Congestive heart failure, n (%)	25 (22.3)	25 (22.3)	>.999	16 (37.2)	23 (35.4)	>.999	29 (15.6)	13 (17.3)	.713
	Chronic renal failure, n (%)	21 (18.8)	21 (18.8)	>.999	10 (23.3)	17 (26.2)	.822	30 (16.1)	11 (14.7)	.852
	Depression, n (%)	21 (18.8)	17 (15.2)	.585	3 (7.0)	3 (4.6)	.681	36 (19.4)	16 (21.3)	.734
	Chronic lung disease, n (%)	13 (11.6)	13 (11.6)	.999	7 (16.3)	9 (13.8)	.786	27 (14.5)	8 (10.7)	.547
	Cancer, n (%)	5 (4.5)	7 (6.3)	.774	4 (9.3)	6 (9.2)	>.999	23 (12.4)	2 (2.7)	.018
	Parkinson disease, n (%)	10 (8.9)	9 (8.0)	>.999	5 (11.6)	2 (3.1)	.112	17 (9.1)	7 (9.3)	>.999
	Peripheral vascular disease, n (%)	6 (5.4)	6 (5.4)	>.999	1 (2.3)	7 (10.8)	.142	8 (4.3)	4 (5.3)	.748
	Collagen vascular disease, n (%)	6 (5.4)	5 (4.5)	>.999	2 (4.7)	4 (6.2)	>.999	11 (5.9)	1 (1.3)	.189
	Smoking, n (%)	4 (3.6)	3 (2.7)	>.999	0 (0.0)	3 (4.6)	.274	5 (2.7)	3 (4.0)	.693
Geriatric aspects	Nasogastric tube or gastrostomy, n (%)	4 (3.6)	3 (2.7)	>.999	0 (0.0)	1 (1.5)	>.999	9 (4.8)	2 (2.7)	.734
	Permanent urinary catheter, n (%)	5 (4.5)	3 (2.7)	.727	3 (7.0)	1 (1.5)	.299	9 (4.8)	3 (4.0)	>.999
	Pressure ulcers, n (%)	3 (2.7)	1 (0.9)	.625	2 (4.7)	0 (0.0)	.156	9 (4.8)	1 (1.3)	.290
	Function: Severely dependent, n (%)	60 (53.6)	56 (50.0)	.514	27 (62.8)	35 (53.8)	.232	112 (60.2)	38 (50.7)	.475
	Mildly dependent n (%)	34 (30.4)	39 (34.8)		13 (30.2)	16 (24.6)		51 (27.4)	27 (36.0)	
	Independent, n (%)	18 (16.1)	17 (15.2)		3 (7.0)	14 (21.5)		23 (12.4)	10 (13.3)	
	Nursing-home residents, n (%)	13 (11.6)	8 (7.1)	.332	6 (14.0)	2 (3.1)	.057	39 (21.0)	6 (8.0)	.011
Laboratory	Albumin <3.5 g/dL, n (%)	46 (41.1)	49 (43.8)	.749	28 (66.7)	25 (38.5)	.003	102 (54.8)	25 (33.3)	.002

1-year mortality (HR 1.987, 95%CI 1.063–3.714, $P=.031$), while statin continuers had only a trend of lower 1-year mortality (HR 0.337, 95%CI 0.097–1.178, $P=.089$).

Following propensity score matching, the study group included 112 statin stoppers and the control group included 112 matched statin non-users (Table 2). Overall, 60 (26.8%) patients died during the year following admission: 29 (25.9%) statin stoppers and 31 (27.7%) statin non-users ($P=.680$). There were no significant differences in the cumulative survival between the groups (Fig. 1B). After dividing the whole cohort into 5 equal-sized groups according to the propensity score, a stratified Cox regression analysis (including all variables in Table 1) showed no association between stopping statins (rather than not using) and 1-year mortality (HR 1.067, 95%CI 0.674–1.689, $P=.782$).

Among the 261 patients without IHD, 72 (27.6%) patients died during the year following admission: 20 (26.7%) statin stoppers and 52 (28.0%) statin non-users ($P=.923$). There were no significant differences in the cumulative survival between the groups (Fig. 1C). Cox regression analysis (including all variables in Table 2) showed no association between stopping statins (rather than not using) and 1-year mortality (HR 1.427, 95%CI 0.816–2.497, $P=.212$).

Among the 108 IHD patients, 38 (35.2%) patients died during the year following admission: 18 (27.7%) statin stoppers and 20 (46.5%) statin non-users ($P=.059$). There was a trend of a better cumulative survival among statin stoppers (Fig. 1D). Cox regression analysis (including all variables in Table 2) showed a nearly significant association between stopping statins (rather than not using) and lower 1-year mortality (HR 0.524, 95%CI 0.259–1.060, $P=.072$).

5. Discussion

The favorable prognosis of using statins in older adults aged 75 to 82 years is well established in the medical literature[6]; in the current analysis, it has been shown again in a small group of statin continuers which have been relatively young, independent, and with a low prevalence of dementia and hypoalbuminemia. However, in the current analysis we have sought to focus for the first time ever on the prognosis of stopping statins in much older patients – the oldest-old aged 85 years or more – many of them

with dementia, severe dependency, and malnutrition, and particularly in the oldest-old with IHD. According to the current analysis, there are no significant differences in 1-year mortality and cumulative survival between statin stoppers and statin non-users among the oldest-old. Moreover, among the oldest-old with IHD, there is a trend of a higher cumulative survival among statin stoppers relative to statins non-users. Hence, we believe that stopping statins in the general population of the oldest-old – with or without IHD – is possibly safe.

In the current analysis, more than a third (37.9%) of the oldest-old have been taking statins upon admission. This finding is consistent with previous reports in the general population of the oldest-old.[4] Regarding stopping statins in the general population of the oldest-old, the current findings are not surprising at all. Even prior to the propensity score matching, the study group (statin stoppers) and the control group (statin non-users) have had a very high mean age (87.1 and 88.2 years, respectively), very high prevalence of severe dependency (52.1% and 60.7%, respectively), and very high prevalence of dementia (42.1% and 51.5%, respectively). One year following admission mortality rates has been very high and nearly similar in both groups (27.1% and 31.4%, respectively) – regardless of stopping statins. We believe that continuing statins in the study group being so old and fragile would have not affected the prognosis either; therefore, stopping statins in this group is again possibly safe.

The role of stopping statins in the oldest-old with IHD is the true novelty of the current analysis. In the current analysis more than half (60.2%) of the oldest-old with IHD have been taking statins upon admission – almost 2 times more than in the general population of the oldest-old. This finding is consistent with previous reports in the oldest-old with IHD.[4] It is possible that the high use of statins in this population is attributed to the lack of confidence of primary physicians and cardiologists to discontinue statins in the oldest-old with a history of IHD. Indeed, 29.3% of the patients in the current analysis have had IHD and have been taking statins upon admission despite their advanced age (mean age 86.9 years), being severely dependent (53.8%), having hypoalbuminemia (38.5%), and dementia (36.9%). Until now, only 1 study has shown that the use of statins in the oldest-old with IHD is not associated with a favorable prognosis, to the best of our knowledge; Rothschild et al have shown that statin therapy is not associated with reduced all-cause mortality in IHD patients aged 80 to 84 and 85 years or more over a median follow-up of 3.1 years.[12] At the same time, researchers begin to question the use of statins in frail malnourished older adults with IHD.[13] According to the current findings, we join their call; we believe that stopping statins (rather than not using) in the oldest-old with IHD is possibly safe. Since the cohort has been small, it is too early to conclude that stopping statins may be associated with a favorable prognosis in the oldest-old with IHD; moreover, 1 may argue if stopping statins in the oldest-old with IHD may be associated with a favorable prognosis so soon afterward; still, it is clear that stopping statins (rather than not using) in the oldest-old with IHD is possibly safe since it is not associated with increased 1-year mortality.

The present study has several limitations. It is an observational retrospective study; thus, it has been impossible to further divide the 140 patients in the study group into 70 statin stoppers and 70 statin continuers following hospital discharge; the 43 patients who have actually carried on with statin therapy on the day of hospital discharge have not been comparable to the 140 statin stoppers – they have been significantly younger and more independent, have had a higher prevalence of hypertension, and lower prevalence of dementia and hypoalbuminemia. Furthermore, although the trend of no difference in mortality between statin non-users and statin stoppers has been already obvious after 1 year, the duration of patients' follow-up has been relatively short and included all-cause mortality; in future studies, longer follow-up of 5 years or more and cardiovascular mortality rates should be examined. Finally, we do not have unequivocal information concerning adherence to our recommendations of stopping statins, but we assume that in most cases statin therapy has not been renewed in the community; the literature shows that 97% of older adults whose statins have been stopped during hospitalization are not treated with statins 4 months later in the community.[14]

Based on the current findings it is too early to recommend stopping statins in all hospitalized oldest-old patients. However, we believe that physicians should consider stopping statins in the general population of the oldest-old – particularly in very old severely dependent and cognitively impaired patients – even if they have IHD. Future prospective interventional studies in this population should include clear criteria for statin discontinuation with reference to age, activities of daily livings, cognition, and nutritional status. These studies should also report cardiovascular mortality and "softer" outcomes that are relevant to this population, such as functional decline over time and transfer to institutions. Moreover, prospective studies of statin continuation and discontinuation at any age should include relevant clinical and laboratory data concerning adverse effects of statins, such as muscle pain, muscle weakness, elevated liver enzymes serum levels, and elevated creatine phosphokinase serum levels.[10,15]

The awareness of stopping statins in older adults has increased in recent years. Physicians are debating whether to prescribe statins for the oldest-old with IHD and multi-morbidity.[13,16] Many older adults are also uncertain whether to take statins and are willing to discontinue statins if so instructed by their physician.[17] The current study may further increase the knowledge on this issue to improve physicians' decision-making.

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