Relation of Statin Use and Mortality in Community-Dwelling Frail Older Patients With Coronary Artery Disease

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Clinical decision-making for statin treatment in older patients with coronary artery disease (CAD) is under debate, particularly in community-dwelling frail patients at high risk of death. In this retrospective observational study on 2,597 community-dwelling patients aged ≥65 years with a previous hospitalization for CAD, we estimated mortality risk assessed with the Multidimensional Prognostic Index (MPI), based on the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (SVaMA), used to determine accessibility to homecare services/nursing home admission in 2005 to 2013 in the Padua Health District, Veneto, Italy. Participants were categorized as having mild (MPI-SVaMA-1), moderate (MPI-SVaMA-2), and high (MPI-SVaMA-3) baseline mortality risk, and propensity score−adjusted hazard ratios (HRs) of 3-year mortality rate were calculated according to statin treatment in these subgroups. Greater MPI-SVaMA scores were associated with lower rates of statin treatment and higher 3-year mortality rate (MPI-SVaMA-1 = 23.4%; MPI-SVaMA-2 = 39.1%; MPI-SVaMA-3 = 76.2%). After adjusting for propensity score quintiles, statin treatment was associated with lower 3-year mortality risk irrespective of MPI-SVaMA group (HRs [95% confidence intervals] 0.45 [0.37 to 0.55], 0.44 [0.36 to 0.53], and 0.28 [0.21 to 0.39] in MPI-SVaMA-1, -2, and -3 groups, respectively [interaction test p = 0.202]). Subgroup analyses showed that statin treatment was also beneficial irrespective of age (HRs [95% confidence intervals] 0.38 [0.27 to 0.53], 0.45 [0.38 to 0.54], and 0.44 [0.37 to 0.54] in 65 to 74, 75 to 84, and ≥85 year age groups, respectively [interaction test p = 0.597]). In conclusion, in community-dwelling frail older patients with CAD, statin treatment was significantly associated with reduced 3-year mortality rate irrespective of age and multidimensional impairment, although the frailest patients were less likely to be treated with statins. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;118:1624−1630)

There are limited data in relation to treatment with 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) and mortality and other clinical outcomes in representative populations of community-dwelling frail older people with coronary artery disease (CAD).[1,2] Frailty, a biologic syndrome reflecting a multidimensional state of decreased physiological reserve and increased vulnerability to stressors, has become a high-priority topic in cardiovascular medicine.[3]

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Furthermore, recent guidelines have shown that the clinical decision-making on statin prescription in older patients only rarely is based on mortality risk stratification,[4,5] resulting in many hospitalized or community-dwelling older patients with CAD not receiving statins. In older age, mortality risk stratification should be based on information on co-morbidity and functional status,[6] and it is best performed using instruments based on multidimensional Comprehensive Geriatric Assessment (CGA), integrating information of several domains of health and function.[7] Recently, a Multidimensional Prognostic Index (MPI) derived from a standardized CGA has been developed and validated for mortality risk assessment in several independent cohorts of hospitalized[8] and community-dwelling older subjects[9] with acute or chronic diseases. In a large sample of community-dwelling frail older patients with diabetes mellitus, statin treatment was associated with a reduced 3-year mortality rate, suggesting that a severely compromised health and functional status, or a very old age, did not affect the association between statin treatment and reduced mortality.[10] The objective of the present study was to test the hypothesis that effectiveness of statin treatment in community-dwelling frail older patients with CAD may vary across strata of mortality risk in a 3-year follow-up period.

Methods

This was a retrospective observational study conducted according to the guidelines for Good Clinical Practice and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11] All consecutive community-dwelling older subjects aged ≥65 years in whom a CGA-based multidimensional assessment using the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (SVaMA) was performed from January 1, 2005, to December 31, 2013, were screened for inclusion in the study. Patients were included in the analysis if they had been discharged from hospital with a main diagnosis of CAD according to *International Classification of Diseases, Ninth Revision*, 410 to 414 codes and subgroups or according to the main SVaMA diagnosis records K74 to K76 (Ischemic Heart Disease [IHD]) within 3 months from the SVaMA evaluation. The Institutional Review Board of the Social and Health-Care Local Unit (ULSS) 16, Padua, Italy, approved this study. Informed consent was given by participants who underwent SVaMA evaluation and/or by their proxies for clinical records to be used in clinical studies. The mean follow-up was 2.1 ± 2.2 years. The Registry Offices of cities where patients were residents at the time of the first evaluation were used to assess vital status during the follow-up, recording the dates of death from death certificates.

SVaMA is the instrument officially recommended since 2000 by the National Health Care System in the Veneto Regional Health System for multidimensional assessment by health professionals to establish accessibility of community-dwelling older persons to home care services or nursing home admission. The following SVaMA domains and variables were used for MPI calculation: (1) age, (2) gender, (3) main diagnosis, (4) nursing care needs (VIP) assessed by a validated numeric 11-item scale; (5) cognitive status (VCOG), assessed by the Short Portable Mental Status Questionnaire;

(6) pressure sores risk (VPIA), assessed by the Exton-Smith Scale; (7) activities of daily living (VADL); (8) mobility (VMOB) assessed by the Barthel Index; and (9) social support (VSOC), assessed by a numeric 16-item scale that explores the presence of a support network during day and night. The following cut-off points were estimated for the normalized MPI-SVaMA 1-year mortality rate prediction: 0 to 0.33 (MPI-SVaMA-1 mild risk), 0.34 to 0.47 (MPI-SVaMA-2 moderate risk), 0.48-1.0 (MPI-SVaMA-3 severe risk). To calculate the MPI-SVaMA, software for Windows may be downloaded for free at the following address: *http://www.mpiage.eu* (English version). Further information on reliability, accuracy, calibration, and validation of the MPI based on the SVaMA can be found elsewhere.[9] To extract the individual medication use, the whole study population was linked to the Pharmaceutical Prescription database of the Azienda ULSS 16, Padua. Statins and other drug prescriptions were determined according to the Anatomical Therapeutic Chemical codes. Statin prescription was determined by C10 Anatomical Therapeutic Chemical code. Subjects were considered statin users if they received statin prescriptions after the first registered evidence of the CAD diagnosis. In the present study, we included all statin users who achieved a treatment adherence coverage, that is, the ratio between treatment duration (in days) and individual follow-up duration (in days) of at least 90% for the first year and 80% and 70% when considering the outcome at 2 and 3 years of follow-up, respectively. We defined statin nonusers as the older subjects who never received statin prescriptions. We included prescriptions within 3 months after initial diagnosis of CAD. As a proxy of patients' polypharmacy, we used the mean monthly past treatment rate defined as the total number of drug boxes taken before the enrollment divided by the total number of months between the first prescription and enrollment.

Frequencies (percentages) and mean restandard deviation (SD) were used to describe categorical and continuous baseline variables, respectively. Comparisons between men and women were performed using the Pearson chi-square test and Mann−Whitney *U* test, whereas linear trends across MPI-SVaMA risk subgroups were analyzed using analysis of variance models or the Mantel−Haenszel chi-square tests for continuous or categorical variables, respectively. Mortality rates were computed as the number of deaths per 100 person-years and compared using Poisson regression models. To control possible confounding effects on the association between statins treatment and mortality risk, the propensity score (PS) method was applied.[12] PS logistic regression models were built to predict the probability of receiving statins according to all variables used for the calculation of MPI-SVaMA at treatment assignment: age, gender, VIP, VCOG, VPIA, VADL, VMOB, VSOC, the main diagnoses of fractures, cancer, dementia, stroke, hypokinetic syndrome and cardiovascular, respiratory, neurologic, or other diseases, and the past treatment rate of any drug (in tertiles). PS logistic models were selected stepwise, and model building was stopped when an adequate balance of covariates was achieved.[12] Residual imbalances of covariates in PS quintiles were assessed at each step with a 2-way analysis of variance where each confounder was considered as an outcome and PS quintiles and treatment as factors. To verify that the data can

Table 1
Baseline characteristics of community-dwelling frail older patients with coronary artery disease (CAD) divided according to their Multidimensional Prognostic Index (MPI) risk group based on the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (SVaMA)

Variable	All	MPI-SVaMA-1 Mild risk	MPI-SVaMA-2 Moderate risk	MPI-SVaMA-3 Severe risk	p-value (test for trend)
Patients (%)	2597 (100%)	785 (30.2%)	1096 (42.2%)	716 (27.6%)	——
Age at SVaMA evalutation (years)	83.93±7.35	81.94±7.34	84.74±7.21	84.87±7.15	<0.001
Sex n males (%)	1155 (44.47%)	249 (31.72%)	452 (41.24%)	454 (63.41%)	<0.001
Activities of daily living	42.50±18.64	21.64±14.72	47.85±13.00	57.17±5.26	<0.001
Cognitive status	5.20±3.60	3.41±3.13	5.24±3.43	7.10±3.32	<0.001
Nursing care needs	7.88±8.42	2.82±4.69	6.20±6.35	15.99±8.58	<0.001
Mobility	30.55±11.85	17.01±11.03	34.67±6.84	39.10±2.15	<0.001
Pressure sore risk	5.05±6.26	0.14±1.28	4.33±5.27	11.55±5.30	<0.001
Social support	159.59±70.01	142.08±70.69	163.59±67.77	172.66±68.93	<0.001
Number of medications*	41.42±59.86	46.07±62.18	40.74±59.35	37.36±57.75	0.003
Main associated diagnoses					
Fractures	44 (1.69%)	13 (1.66%)	21 (1.92%)	10 (1.40%)	<0.001
Cancer	419 (16.13%)	122 (15.54%)	170 (15.51%)	127 (17.74%)	
Dementia	583 (22.45%)	182 (23.18%)	271 (24.73%)	130 (18.16%)	
Stroke	173 (6.66%)	34 (4.33%)	67 (6.11%)	72 (10.06%)	
Cardiovascular disease	615 (23.68%)	226 (28.79%)	254 (23.18%)	135 (18.85%)	
Respiratory disease	81 (3.12%)	20 (2.55%)	31 (2.83%)	30 (4.19%)	
Neurologic disease	110 (4.24%)	43 (5.48%)	38 (3.47%)	29 (4.05%)	
Hypokinetic syndrome	326 (12.55%)	57 (7.26%)	154 (14.05%)	115 (16.06%)	
Other diseases	246 (9.47%)	88 (11.21%)	90 (8.21%)	68 (9.50%)	
Follow-up time (years)	2.05±2.24	2.81±2.53	2.04±2.14	1.24±1.68	<0.001
Mortality at 1 year ev/py (ir %)[†]	1081/1765 (61.2%)	217/619 (35.1%)	431/771 (55.9%)	433/375 (115.4%)	<0.001
Mortality at 2 years ev/py (ir %)[†]	1336/2941 (45.4%)	283/1079 (26.2%)	543/1282 (42.4%)	510/579 (88.0%)	<0.001
Mortality at 3 years ev/py (ir %)[†]	1519/3789 (40.1%)	338/1442 (23.4%)	641/1638 (39.1%)	540/709 (76.2%)	<0.001

* Number of all medications per month, taken before the patient's enrollment.

[†] ev/py: events/person-years, ir %: incidence rate (number of events per 100 person-years).

support a comparison of treatment and control groups that are balanced on all covariates, the distribution of the estimated PSs for the treated and control groups should be checked for adequate overlap. This can be accomplished by creating overlapping histograms or by comparing quintiles of the estimated PSs for the treatment and control groups. If there is no overlap in the PS distribution across exposure groups, then no estimates of the treatment effect can be made. For this reason, subjects in treated and control groups with nonoverlapping PS distribution were excluded from the analysis. Separate PS logistic models were run for the overall sample and MPI-SVaMA subgroups. Multivariate and PS quintiles−adjusted Cox regression models were used to assess the effect of statins use on 3-year mortality rate, and results were reported as hazard ratios (HRs) and 95% confidence intervals (CIs). In addition, to check the robustness of our findings, a 5 to 1 greedy 1:1 PS-matching algorithm was performed. PS 1:1 matching identified a unique matched control for each patient treated with statins. Adequacy of covariate balance in the matched sample was eventually assessed with the McNemar or Wilcoxon signed rank test. For the overall sample and for specific MPI-SVaMA risk subgroups, adjusted HRs of statins use for 3-year mortality were reported along with numbers of events and subjects per group and mortality rates. Multivariate models included statin treatment, age, gender, main diagnoses, all domains of MPI-SVaMA, and the past treatment rates of any drug as

covariates. As the PS-matched sample did not consist of independent observations, a marginal survival model with robust standard errors was used. p Values assessing the presence of a heterogeneous effect of statin treatment between MPI-SVaMA risk subgroups were also calculated and reported.[13] Two-sided p values <0.05 were considered statistically significant. All analyses were performed using the SAS 9.1.3 statistical package (SAS Institute, Cary, North Carolina).

Results

Of a total population of 22,744 subjects aged ≥65 years who underwent a SVaMA evaluation over the study period, 3,172 (13.95%) were diagnosed with CAD. Of these, 334 and 241 subjects were excluded from analysis because of a time lag >3 months between CAD diagnosis and SVaMA evaluation or statin prescription, respectively. Thus, the final study population included 2,597 patients, 1,155 men (44.5%) and 1,442 women, with a mean age of 83.9 mo7.4 years. Men were younger than women (81.7 ea7.3 vs 85.7 856.8 years, p <0.001) and had higher MPI (0.37 ea0.1 vs 0.31 0.0.1, p <0.001), VIP (8.96 0.8.7 vs 7.01 .78.1, p <0.001), prevalence of cancer (25.8% vs 8.4%, p <0.001), and mortality rate over the 3-year follow-up (48.1% vs 34.5%, p <0.001). Women had a greater cognitive impairment than men (VCOG 5.52 ± 3.5 vs 4.80 ± 3.5, p <0.001) and a higher

Table 2
Pre-matching baseline characteristics of frail community-dwelling older patients with coronary artery disease (CAD) according to statin treatment

	Not treated	Treated	p-value	Standardized mean difference
Patients (%)	1532 (58.99%)	1065 (41.01%)	——	——
Age at SVaMA evaluation (years)	85.81±7.10	81.22±6.84	<0.001	-65.796
Sex (n males, %)	618 (40.34%)	537 (50.42%)	<0.001	20.358
Activities of daily living	44.55±17.92	39.55±19.26	<0.001	-26.856
Cognitive status	5.67±3.56	4.52±3.54	<0.001	-32.344
Nursing care needs	7.49±8.05	8.43±8.91	0.023	11.164
Mobility	31.60±11.48	29.04±12.23	<0.001	-21.628
Pressure sore risk	5.48±6.34	4.44±6.08	<0.001	-16.648
Social support	162.90±69.29	154.82±70.80	0.002	-11.536
Fractures	31 (2.02)	13 (1.22)	0.119	-6.359
Cancer	192 (12.53)	227 (21.31)	<0.001	23.583
Dementia	385 (25.13)	198 (18.59)	<0.001	-15.870
Stroke	98 (6.40)	75 (7.04)	0.517	2.578
Cardiovascular disease	364 (23.76)	251 (23.57)	0.910	-0.451
Respiratory disease	46 (3.00)	35 (3.29)	0.682	1.626
Neurologic disease	74 (4.83)	36 (3.38)	0.071	-7.313
Ipokinetic syndrome	216 (14.10)	110 (10.33)	0.004	-11.534
Other diseases	126 (8.22)	120 (11.27)	0.009	10.274
MPI-SVaMA (continuous)	0.40±0.11	0.38±0.11	<0.001	-19.057
MPI-SVaMA -1 mild risk	406 (26.50%)	379 (35.59%)	<0.001	19.732
MPI- SVaMA-2 moderate risk	669 (43.67%)	427 (40.09%)		-7.250
MPI- SVaMA-3 severe risk	457 (29.83%)	259 (24.32%)		-12.427
Number of medications* 1°tertile-Low	717 (46.80%)	187 (17.56%)	<0.001	-65.907
Number of medications* 2°tertile-Med	477 (31.14%)	344 (32.30%)		2.503
Number of medications* 3°tertile-High	338 (22.06%)	534 (50.14%)		61.130

MPI = Multidimensional Prognostic Index; SVaMA = Standardized Multidimensional Assessment Schedule for Adults and Aged Persons.

* Number of all medications prescribed within one year before patient's enrollment.

Table 3
Overall and subgroup analyses for frail community-dwelling older patients with coronary artery disease (CAD) statin users vs non-users: multivariate and propensity score (PS) quintiles adjusted models

	Deaths	Patients	Person-years	Three-year mortality rate (n° events per 100 person-years)				Multivariable models*			PS quintiles adjusted models		
				All	Statin use		Change†	HR	95% CI	p-value	HR	95% CI	p-value
					No	Yes							
MPI-SVaMA risk group													
MPI-SVaMA-1 mild risk	338	785	1442	23.4	33.1	15.7	-17.4	0.36	0.29-0.43	<0.001	0.45	0.37-0.55	<0.001
MPI-SVaMA-2 moderate risk	641	1096	1638	39.1	53.8	24.6	-29.2	0.39	0.32-0.47	<0.001	0.44	0.36-0.53	<0.001
MPI-SVaMA-3 severe risk	540	716	709	76.2	129.3	38.1	-91.2	0.19	0.14-0.28	<0.001	0.28	0.21-0.39	<0.001
Age													
65-74.9 years	182	326	534	34.1	64.5	24.1	-40.4	0.24	0.16-0.34	<0.001	0.38	0.27-0.53	<0.001
75-84.9 years	574	1051	1637	35.1	53.3	23.4	-29.9	0.34	0.28-0.41	<0.001	0.45	0.38-0.54	<0.001
≥85 years	763	1220	1618	47.2	62.0	24.4	-37.6	0.37	0.30-0.45	<0.001	0.44	0.37-0.54	<0.001
All	1519	2597	3789	40.1	59.0	23.8	-35.2	0.35	0.30-0.39	<0.001	0.44	0.39-0.49	<0.001

MPI-SVaMA = Multidimensional Prognostic Index-Standardized Multidimensional Assessment Schedule for Adults and Aged Persons.

* Models were adjusted for: age at SVaMA evaluation, sex, nursing care needs (VIP), cognitive status (VCOG), pressure sores risk (VPIA), activities of daily living (VADL), mobility (VMOB), social support (VSOC) (all MPI-SVaMA domains), the needing of care assistants, the main diagnoses of fractures, cancer, dementia, stroke, hypokinetic syndrome and cardiovascular, respiratory neurological or other diseases and number of all medications prescribed within one year before patient's enrollment (tertiles).

† Difference of mortality rates between statins users versus non-user.

prevalence of dementia (26.4% vs 17.5%, p <0.001). Past drug treatment of any drug was similar in men and women, but the proportion of subjects starting statin treatment was greater in men than in women (46.5% vs 36.6%, p <0.001).

Table 1 lists the characteristics of older patients with CAD divided according to their MPI-SVaMA risk group: 785 (30.2%), 1,096 (42.2%), and 716 (27.6%) were at mild, moderate, and severe risk of mortality, respectively. Patients

with greater MPI-SVaMA values were more likely to be men (p for trend <0.001) and older (p for trend <0.001) and had significantly greater VADL, VCOG, VIP, VMOB, VPIA, and VSOC scores (p for trend <0.001 for all domains). Three-year mortality rates were 23.4%, 39.1%, and 76.2% in the mild, moderate, and severe MPI-SVaMA risk subgroups, respectively (p for trend <0.001). Overall, 1,065 older patients with CAD (41.01% of the total study population) were treated with statins. Statin users were younger (p = 0.001) and included more men than statin nonusers (p <0.001; Table 2). Statin users had less impairment in VCOG (p <0.001), VPIA (p <0.001), VADL (p <0.001), and VMOB (p <0.001) scores, lower MPI-SVaMA values (p <0.001), and greater VIP values (p = 0.023) than statin nonusers. Moreover, statin users were more frequently in the MPI-SVaMA-1 group (35.6% vs 26.5%, p <0.001) and in the highest tertile of medication number than nonusers (3-tertile, 50.1% vs 22.1%, p <0.001).

Multivariate analysis adjusted for age, gender, main diagnoses, MPI-SVaMA domains, and the past treatment rate showed that statin treatment was associated with lower 3-year mortality risk, irrespective of the MPI-SVaMA risk subgroup (p for trend <0.001; Table 3). A statistically significant association between statin treatment and lower mortality prevailed after adjustment for PS quintiles. Similarly, statin treatment was associated with lower mortality risk within each risk group of MPI-SVaMA. HRs (95% CIs) were 0.45 (0.37 to 0.55), 0.44 (0.36 to 0.53), and 0.28 (0.21 to 0.39) for MPI-SVaMA-1, MPI-SVaMA-2, and MPI-SVaMA-3, respectively (interaction test p = 0.202). The association of statin treatment with lower mortality was also age independent, with PS quintiles—adjusted HRs (95% CIs) of 0.38 (0.27 to 0.53), 0.45 (0.38 to 0.54), and 0.44 (0.37 to 0.54) in patients aged 65 to 74, 75 to 84, and ≥85 years, respectively (interaction test p = 0.597). The PS-based greedy matching algorithm successfully matched 733 of 1,065 statin-treated patients. The results fully supported overall analyses and conclusions. The adequacy of covariate balance in the matched sample is provided in Supplementary Table 1. Results of statin treatment effects from marginal univariate Cox regression models, with robust standard errors, were fully overlapping with those reported in Table 3 (Supplementary Table 2).

Discussion

Our real-world retrospective observational study demonstrated that high adherence to statin treatment was associated with lower 3-year mortality rate in community-dwelling frail older patients with CAD and that this association was independent of overall health and functional status or advanced age. Therefore, the present findings suggested that even a substantially compromised health or functional status, or an extremely advanced age, should not contraindicate statin use as secondary prevention in older patients with CAD, provided that patients may have high adherence to treatment.

Only few studies and meta-analyses of randomized clinical trials (RCTs) have suggested a reduced mortality in older patients treated with statins.[1,14] Moreover, the finding of age—statin interaction in observational studies, with

reduced protection over the age of 80 years,[15] has raised controversies about the prescription of statins in older patients. The prevalence of statin use in this older population with CAD (41%) is comparable to recent population-based studies conducted on older sample without stratification for the presence of cardiovascular disease[1,16] but much lower than that reported in a study of older people with IHD.[17] This low prevalence of statin use might reflect the reluctance of physicians to treat our older patients who were frail because of a burden of concomitant diseases, functional limitations, and social problems. In particular, with advancing age, quality of life is increasingly affected by frailty, cognitive decline, and the consequences of a variety of chronic diseases, including cardiovascular disease.[3,18] At present, the impact of statin treatment in older subjects on outcomes such as frailty, physical and cognitive function, and institutionalization is controversial.[1,16,19,20]

In a Canadian population-based cohort of older patients who survived myocardial infarction, the association between the use of chronic (statins) and acute therapy (reperfusion) and life expectancies was seen not only in patients with limited prognosis but also in those who were expected to live for 10 to 15 years,[21] suggesting that the persistent treatment care gaps may reflect clinicians' synthesis about frailty and life-expectancy gains.[19] A recent Australian population-based study suggested that optimal medical therapy was associated with better survival in men with IHD, whereas exposure to ≥2 of the 4 guideline-recommended medications was associated with lowest risk of institutionalization, independently of the presence of geriatric syndromes (frailty, falls, urinary incontinence, and cognitive impairment).[17] Of the 4 guideline-recommended medications, antiplatelet medications followed by statins appeared to confer the greatest benefit to participant survival.[17] Furthermore, a prospective study on 342 patients >65 years surviving after an acute coronary syndrome suggested that frailty, cognitive impairment, and co-morbidity were associated with worse long-term prognosis, particularly all-cause mortality.[22] On the contrary, a retrospective analysis failed to show a survival benefit attributable to statins in subjects aged ≥80 years hospitalized with acute or chronic manifestations of CAD,[23] although lack of inclusion of several common co-morbidities such as chronic lung disease and cancer may have influenced the decision to prescribe statins and might be expected to favor the statin group.

In the present study, we adopted the MPI based on the SVaMA to evaluate the mortality risk,[9,24,25] whose variables include multidimensional assessment of patients' clinical, functional, cognitive, and social status. In previous studies, the MPI score was extremely accurate in predicting mortality in different settings,[25] with a significantly higher predictive power for all-cause mortality compared to 3 other widely used frailty instruments.[26] In the present study, notwithstanding indications, statin-treated patients were younger; had less clinical, cognitive, and functional impairments; and had a significant lower mortality risk than statin nonusers. To address this selection bias, PS-matching methods were used to define cohorts which differed only for statin treatment. Both the PS-adjusted models and the analyses within the PS-matched cohorts confirmed that the benefit from statin treatment was evident in patients with

CAD independently of MPI risk group. The subgroup analyses for heterogeneity, moreover, showed that the reduction in mortality associated with statin treatment was not significantly different in patients with different mortality risk. In fact, the largest relative reduction in mortality associated with statin use was observed in patients with the greatest MPI-estimated overall risk.

Some limitations of the present study have to be acknowledged. PS matching can address selection bias; however, residual confounding due to baseline unobserved covariates should play still a role and those events which can happen during the follow-up such as some adverse events which usually drive nonadherence to the treatment. Unfortunately, we did not have these time-varying covariates, and therefore, we cannot use more appropriated and sophisticated statistical methods as marginal structural models. The efficacy of statins was assessed only in terms of reduced all-cause mortality, without analyzing the different causes of deaths or taking into account nonfatal events. Furthermore, we included only statin-adherent patients, who obviously had no or only minor adverse events. Therefore, the patients who were not treated with statins in this cohort were more likely to have adverse events, which may limit the upside of a more liberal use of statins in older age. Also, we did not have laboratory variables (serum cholesterol and other lipids) available for our analysis, to investigate whether they might have an impact on treatment decisions. Finally, because the follow-up was limited to 3 years, we cannot exclude that significant difference in effectiveness in patients with different mortality risk could emerge with a longer observation time.

Real-world prospective trials specifically designed for inclusion of frail older patients with or without CAD and examining the impact of statin treatment on important clinical outcomes in older age are now called for.[22] The STAtins for Reducing Events in the Elderly trial will be the first RCT determining the effects of statin therapy versus placebo on overall survival or disability-free survival over an average 5-year treatment period in an apparently healthy elderly cohort of approximately 12,000 older Australians (>70 years) living independently in the community.[18] Until the results of this trial are known, treatment decisions regarding administration of cholesterol-lowering agents for very old and frail patients must be based on observational studies and extrapolations from the RCTs in younger people. The lower mortality rate associated with high adherence to statin use in the present retrospective observational study may suggest a significant impact of statin treatment also in community-dwelling multimorbid and frail older patients with CAD to home care services or nursing home admission.

Disclosure

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.08.042.

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