Statins and Selective Serotonin Reuptake Inhibitors are Associated with Longer Survival in Nursing Home Residents

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ABSTRACT:
Background: Statins and selective serotonin reuptake inhibitors (SSRIs) have beneficial effects on health outcomes in the general population. Their effect on survival in debilitated nursing home residents is unknown.
Objectives: To assess the relationships between statins, SSRIs, and survival of nursing home residents.
Methods: Baseline patient characteristics, including chronic medications, were recorded. The association of 5-year survival with different variables was analyzed. A sub-group analysis of survival was performed according to baseline treatment with statins and/or SSRIs.
Results: The study comprised 993 residents from 6 nursing homes. Of them, 285 were males (29%), 750 (75%) were fully dependent, and 243 (25%) were mobile demented. Mean age was 85 ± 7.6 years (range 65–108). After 5 years follow-up, the mortality rate was 81%. Analysis by sub-groups showed longer survival among older adults treated with only statins (hazard ratio [HR] for death 0.68, 95% confidence intervals [95%CI] 0.49–0.94) or only SSRIs (HR 0.6, 95%CI 0.45–0.81), with the longest survival among those taking both statins and SSRIs (HR 0.41, 95%CI 0.25–0.67), and shortest among residents not taking statins or SSRIs ($P < 0.001$). The survival benefit remained significant after adjusting for age and after conducting a multivariate analysis adjusted for sex, functional status, body mass index, mini-mental state examination, feeding status, arrhythmia, diabetes mellitus, chronic kidney disease, and hemato-oncological diagnosis.
Conclusion: Treatment with statins and/or SSRIs at baseline was associated with longer survival in debilitated nursing home residents and should not be deprived from these patients, if medically indicated.

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KEY WORDS: geriatric, nursing home, selective serotonin reuptake inhibitors (SSRIs), statins, survival

Although the population of older adults is growing worldwide, patients above 65 years of age have been under-represented in clinical trials [1,2]. Moreover, people age at a heterogeneous pace and on reaching their 8th and 9th decades their physiology and well-being differ from one another. Only a few studies have addressed drug treatment in a nursing home population. Previous research has focused on polypharmacy, on safe ways to reduce the medication burden, or on effective symptom control in nursing home residents [2,3]. Little is known regarding mortality as a result of medications in this population.

The belief that most of those patients are at the end of their lives and mainly need palliative care is wrong. Although some patients fit this description, most residents, even those diagnosed with dementia, can still enjoy life and have a life expectancy of years rather than months. These residents receive advanced treatments besides palliative care, and therefore should not be prevented from receiving evidence-based treatments for their chronic conditions. We found that polypharmacy in nursing home patients was not associated with mortality and that residents treated with lipid-lowering medications and selective serotonin reuptake inhibitors (SSRIs) may survive longer [4]. Since the beneficial effect of statins in debilitated old patients is doubtful [5], our objective was to examine whether treatment with these drugs was associated with longer survival in very old, dependent, demented nursing home residents. These data should be taken into consideration for treatment choices by physicians caring for these patients.

PATIENTS AND METHODS

STUDY POPULATION

Residents older than 65 years of age and living in one of six nursing homes located in central Israel were included in the study. Nursing homes in Israel provide chronic care, including nursing services and supervision. All participants were insured by the Clalit Health Services health fund and had lived in the

nursing home for at least one month prior to data collection. Residents of the three smaller Israeli health funds were not included due to the complexity of obtaining ethics committee approvals. The Rabin Medical Center institutional review board approved the study prior to collection of data and participant consent was not required.

STUDY DESIGN

We conducted a prospective observational study. Baseline data were collected between November 2011 and February 2012, and included age, sex, length of stay, co-morbidities, functional status (mobile vs. fully dependent), feeding method (oral vs. tube feeding), body mass index (BMI), and types of chronic medications administered at least one month prior to enrollment. Medications included oral, injectable, percutane-

ous, and inhalable products. As needed medicines were not recorded and herbal and other over-the-counter medications are not available in nursing homes. The Charlson Comorbidity Index (CCI) was calculated for each resident. Polypharmacy rates, medication classes, and the lack of association between the number of drugs and 2-year mortality were previously described in this cohort [2,4]. We identified 29 classes of medications, 26 of which were included in the analysis ("other" and "inhalations" were excluded as they did not contribute to the model). NSAIDs were used by only one patient.

OUTCOME MEASURES

The outcome was 5-year survival and its association with statins and SSRIs medications at baseline, controlled for multiple confounders.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). Continuous variables were represented as mean and standard distribution (SD) and categorical variables as frequency and percentage. A P value of < 0.05 was considered significant. Baseline characteristics and medication use were compared among patients who were not being treated with either lipid lowering drugs or SSRIs, patients treated only with lipid lowering drugs, patients treated only with SSRIs, and patients treated with both types of medications. Characteristics of the study patients were compared by chi-square test for categorical variables and analysis of variance for continuous variables. Time to event was calculated as the time from the initial check up until death or the last follow up. Death rates were analyzed according to medication use. Universal cox regression analysis was separately performed for each of the baseline characteristics and major risk factors to demonstrate the age-adjusted hazard ratio (HR) for the incidence of death and 95% confidence intervals (95%CI). Multivariate HRs and 95%CI for death were estimated by the cox proportional hazard model adjusted for potential cofounders. Conventional risk factors were selected for the model and an association with death in the univariate analysis. The survival curves demonstrated the differences in survival between the four groups.

Table 1. Baseline resident characteristics according to status of treatment with statins and selective serotonin reuptake inhibitors

	Total N=993	None N=545	Only statins N=141	Only SSRI N=227	Both N=80	P value
Males (%)	285 (29)	162 (29.7)	46 (32.6)	60 (26.4)	17 (21.3)	0.253
Age in years ± SD (range)	85 ± 7.6 (65–108)	85.8 ± 7.3	82.0 ± 7.6	86.1 ± 7.6	82.2 ± 6.6	‹ 0.001
BMI ± SD	25.5 ± 5.2	24.9 ± 5.1	26.9 ± 5.1	25.6 ± 5.2	27.1 ± 5.5	‹ 0.001
CCI score ± SD	2.5 ± 2.0	2.4 ± 2.3	2.9 ± 1.9	2.3 ± 1.5	3.0 ± 1.5	0.003
LOS in months ± SD	36 ± 35	41 ± 38.3	29.7 ± 32.7	33.9 ± 30.6	24.5 ± 24	‹ 0.001
Mini-mental test score ± SD (range)	13 ± 7.4 (1–30)	12.2 ± 7.3	14.5 ± 7.1	13.6 ± 7.2	12.3 ± 7.6	0.028
Fully dependent (%)	750 (75.5)	418 (76.7)	92 (65.2)	185 (81.5)	55 (68.8)	0.002
Tube feeding* (%)	97 (9.8)	79 (14.5)	3 (2.1)	15 (6.6)	0 (0.0)	‹ 0.001
HTA (%)	688 (69)	353 (64.8)	110 (78.0)	163 (71.8)	62 (77.5)	0.004
CHF (%)	216 (22)	101 (18.5)	30 (21.3)	58 (25.6)	27 (33.8)	0.007
IHD (%)	250 (25)	117 (21.5)	47 (33.3)	57 (25.1)	29 (36.3)	0.003
Arrhythmia (%)	149 (15)	84 (15.4)	21 (14.9)	29 (12.8)	15 (18.8)	0.607
COPD	145 (15)	82 (15.0)	25 (17.7)	28 (12.3)	10 (12.5)	0.032
DM (%)	285 (29)	138 (25.3)	56 (39.7)	57 (25.1)	34 42.5)	‹ 0.001
Dyslipidemia (%)	344 (35)	93 (17.1)	130 (92.2)	47 (20.7)	74 (92.5)	‹ 0.001
Hypothyroidism (%)	205 (21)	115 (21.1)	18 (12.8)	51(22.5)	21 (26.3)	0.060
CVA/TIA (%)	300 (30)	142 (26.1)	47 (33.3)	67 (29.5)	43 (53.8)	‹ 0.001
Extrapyramidal syndromes (%)	186 (19)	101 (18.5)	26 (18.4)	44 (19.4)	15 (18.8)	0.994
CKD (%)	137 (14)	63 (11.6)	27 (19.1)	36 (15.9)	11 (13.8)	0.090
Hemato-oncology (%)	58 (6)	33 (6.1)	8 (5.7)	13 (5.7)	4 (5.0)	0.983
Hematology non-malignant (%)	336 (34)	197 (36.1)	49 (34.8)	71 (31.3)	19 (23.8)	0.130
Depression (%)	426 (43)	101 (18.5)	29 (20.6)	217 (95.6)	79 (98.8)	‹ 0.001
Dementia (%)	927 (93)	514 (94.3)	130 (92.2)	209 (92.1)	74 (92.5)	0.814

*naso-gastric or percutaneous gastrostomy

BMI = body mass index, CCI = Charlson co-morbidity Index, CHF = congestive heart failure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CVA/TIA = stroke or transient cerebral inschemia, DM = diabetes mellitus, HTA = arterial hypertension, IHD = ischemic heart disease, LOS = length of stay, SD = standard deviation, SSRI = selective serotonin reuptake inhibitors

RESULTS

Baseline demographic and clinical characteristics from commencement of the study for the entire cohort (993 residents) and the medication sub-groups are presented in Table 1. There were significantly more residents in the no-statin-no-SSRI sub-group than the statin + SSRI sub-group (545 vs. 80). The statin + SSRI sub-group had a significantly higher BMI and CCI scores compared with the no-statin-no-SSRI sub-group (27.1 ± 5.5 vs. 24.9 ± 5.1 and 3.0 ± 1.5 vs. 2.4 ± 2.3, respectively).

The statin + SSRI sub-group also significantly differed from the no-statin-no-SSRI sub-group with higher rates of depression (98% vs. 18%), stroke (54% vs. 26%), dyslipidemia (92.5% vs. 17%), ischemic heart disease (36% vs. 21.5%), congestive heart failure (34% vs. 18.5%), and diabetes mellitus (42% vs. 25%). The no-statin-no-SSRI sub-group had a higher mean age (85 ± 7.6 vs. 82.2 ± 6.6 years), longer length of stay in the nursing home (41 ± 38.3 vs. 24.5 ± 24 months), and a higher prevalence of tube-fed residents (14.5% vs. none).

Pharmacological treatment at baseline by medication groups is presented in Table 2. The differences in treatment rates in the four sub-groups corresponded to differences in the prevalence of the respective diagnoses. Rates of treatment with beta-blockers (46% vs. 24%), diuretics (41% vs. 23%), anti-aggregants (71% vs. 35%), angiotensin-converting-enzyme inhibitor inhibitors, and angiotensin receptor blockers (37.5% vs. 26%) were all higher in the statin + SSRI group, where prevalence of stroke, ischemic heart disease, and congestive heart failure was also higher compared to the no-statin-no-SSRI sub-group.

Sub-group analysis revealed that the mortality rate was highest in the no-statin-no-SSRI sub-group (84%), with declining rate in the only-statin or only-SSRI sub-group (77% and 78%, respectively) and the statin + SSRI sub-group (71%) ($P = 0.008$) [Table 3]. This difference remained significant after adjusting for age. HR for death was 0.68 (CI95%, 0.49–0.94) in only the statin sub-group, 0.6 (CI95%, 0.45–0.81) in only the SSRI sub-group, and 0.41 (CI95%, 0.25–0.67) in the statin + SSRI sub-group with each sub-group compared to the no-statin-no-SSRI sub-group ($P < 0.001$). In addition, after adjusting for multiple confounders (such as age, sex, functional status, BMI, mini-mental state examination, feeding status, arrhythmia, DM, chronic kidney disease, and hemato-oncological diagnosis), the differences were significant with HR for death 0.82 (CI95%, 0.67–1.02) in only the statin sub-group, 0.78 (CI95%, 0.65–0.93), in only the SSRI sub-group and 0.73 (CI95%, 0.55–0.98) in the statin + SSRI sub-group ($P < 0.001$).

DISCUSSION

In this prospective observational cohort study of nursing home residents, a positive association was found between treatment with statins and SSRIs at baseline and 5-year survival after controlling for multiple confounders. Survival was longest in the sub-group treated with both statins and SSRIs and shortest in the sub-group not treated with any of these medications. To the best of our knowledge, our study is the first to demonstrate long-term survival benefits in nursing home residents treated with these medications.

Published recommendations for primary and secondary prevention of cardiovascular events consider older adults. For primary prevention, the 2014 National Institute for Health and Care Excellence (NICE) guidelines suggest the use of atorv-

Table 2. Pharmacological treatment of residents at baseline by medication groups according to their treatment status with statins and/or selective serotonin re-uptake inhibitors

	Total N=993	None N=545	Only statins N=141	Only SSRI N=227	Both N=80	P value
Beta blockers (%)	286 (29)	128 (24)	62 (44)	59 (26)	37 (46)	‹ 0.001
Calcium channel blockers (%)	210 (21)	108 (20)	47 (33)	36 (16)	19 (24)	0.001
Alpha1 blocker (%)	89 (9)	43 (8)	15 (11)	20 (9)	11 (14)	0.320
Nitrates (%)	39 (4)	11 (2)	12 (8.5)	9 (4)	7 (9)	‹ 0.001
Anti-arrhythmic (%)	59 (6)	33 (6)	7 (5)	14 (6)	5 (6)	0.962
Diuretics (%)	267 (27)	127 (23)	44 (31)	63 (28)	33 (41)	0.004
ACEI or ARB (%)	308 (31)	141 (26)	68 (48)	69 (30)	30 (37.5)	‹ 0.001
Anti-aggregants (%)	403 (41)	191 (35)	76 (54)	79 (35)	57 (71)	‹ 0.001
Anti-coagulants (%)	81 (8)	41 (7.5)	13 (9)	20 (9)	7 (9)	0.880
PPI/H2 blocker (%)	477 (48)	257 (47)	66 (47)	113 (50)	41 (51)	0.845
Benzodiazepines (%)	465 (47)	227 (42)	75 (53)	116 (51)	47 (59)	0.006
Neuroleptics (%)	383 (39)	213 (39)	57 (40)	78 (34)	35 (44)	0.412
Hypnotics non-benzodiazepines (%)	107 (11)	56 (10)	16 (11)	24 (11)	11 (14)	0.818
Anti-epileptics (%)	90 (9)	49 (9)	16 (11)	16 (7)	9 (11)	0.479
AChEI/memantine (%)	32 (3)	16 (3)	6 (4)	5 (2)	5 (6)	0.292
Anti-Parkinson's (%)	141 (14)	74 (14)	18 (13)	37 (16)	12 (15)	0.735
Bisphosphonates (%)	31 (3)	15 (3)	5 (3.5)	6 (3)	5 (6)	0.378
Eye drops (%)	118 (12)	65 (12)	16 (11)	29 (13)	8 (10)	0.923
Anti-diabetes (%)	212 (21)	95 (17)	44 (31)	44 (19)	29 (36)	‹ 0.001
Thyroid hormone (%)	179 (18)	101 (19)	16 (11)	44 (19)	18 (22.5)	0.126
Steroids (%)	45(4.5)	28 (5.1)	9 (6.4)	8 (3.5)	0 (0.0)	0.116
Analgesics non-NSAIDS (%)	48 (5)	24 (4.4)	6 (4.3)	13 (5.7)	5 (6.3)	0.786
Narcotics (%)	12 (1.2)	4 (0.7)	2 (1.4)	5 (2.2)	1 (1.3)	0.398
Antibiotics chronic (%)	13 (1.3)	8 (1.5)	1 (0.7)	3 (1.3)	1 (1.3)	0.919

ACEI = angiotensin converting enzyme inhibitor, AChEI = acetylcholinesterase inhibitor, ARB = angiotensin II receptor blockers, NSAIDS = nonsteroidal anti-inflammatory drugs, PPI/H2 = proton pump inhibitors/ H2 receptor blockers, SSRI = selective serotonin reuptake inhibitors

Table 3. Death rates and adjusted hazard ratio by statin and selective serotonin re-uptake inhibitors sub-groups

	Total N=993	None N=545	Only statins N=141	Only SSRI N=227	Both N=80	P value
Death rate (%)	802 (81)	460 (84)	109 (77)	176 (78)	57 (71)	0.008
Multivariate adjusted hazard ratio* (range)		1.0	0.82 (0.66–1.02)	0.78 (0.65–0.93)	0.73 (0.55–0.98)	‹ 0.001

*adjusted for age, gender,dependence, body mass index, tube feeding, arrhytmia, diabetes mellitus, chronic kidney disease, hemato-oncological diagnosis
SSRI = selective serotonin reuptake inhibitors

astatin in high-risk patients above 85 years old, whereas the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend the use of statins in high-risk patients older than 75 years of age [6,7]. Savarese and colleagues [8], in a meta-analysis of randomized controlled trials (RCTs), found a lower incidence of myocardial infarction and stroke in subjects above 65 years old treated with statins versus placebos for primary prevention. The use of statins for secondary prevention of cardiovascular events in older adults is strongly recommended similar to treatment decisions as in younger patients. NICE guidelines recommend high dose statins, the ACC/AHA support statin continuation and the initiation of de novo treatment if indicated. Strandberg et al. [9] state that statins should be given to older adults for secondary prevention. Although no RCTs included patients above 85 years old at baseline, multiple studies (such as the Scandinavian Simvastatin Survival Study (4S) [9], Heart Protection Study [10], PROSPER trial [11], and SAGE trial [12]) included patients above 65 years old (up to the age of 85 in the SAGE trial). These trials showed a statistically significant benefit of statin treatment for secondary prevention in fatal and non-fatal coronary events and strokes, hospitalizations for cardiovascular events, and all-cause mortality [10-12]. In some RCTs there are no nonagenarian participants; however, that does not mean that there is a lack of treatment efficacy in this sub-group. No studies have as yet addressed the benefits of statin treatment in a nursing home setting. Parikh et al. [13] reported under-utilization of statins despite a clear indication. Pilotto and colleagues [14] analyzed a cohort of community-dwelling older adults with DM and found statin treatment benefits for 3-year survival in all age sub-groups (including patients above 85 years of age) and frailty levels (as measured by a multidimensional prognostic index–multidimensional assessment schedule tool). Similar findings were reported by the same authors in a cohort of older adults with congestive heart failure [15]. Recently, a large meta-analysis concluded that statin therapy for secondary prevention significantly reduces major vascular events and lowers cardiovascular mortality, irrespective of age [16].

Statins do not only reduce cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase but also improve endothelial function, reduce inflammation and thrombus formation, and stabilize atheromas. Therefore, their protective effect starts days to weeks from the beginning of treatment rather than years, as would probably occur if cholesterol lowering was their only action [17]. This finding might explain the possible benefits of statins in very old adults with a relatively limited survival. It must be stressed that as age is the main risk factor for vascular events, the older the person, the greater the net benefit (or absolute risk reduction) derived from statins. Multiple trials have demonstrated that the number needed to treat was lower in the elderly than in younger patients in the prevention of recurrent cardiovascular events [18].

Statins have beneficial effects in non-cardiovascular conditions such as reducing the risk of infections; facilitating recovery from pneumonia, sepsis, and septic shock; countering cognitive decline; and preventing deterioration of heart failure [19,20]. These pleiotropic effects are being intensively studied in pre-clinical and clinical settings; however, further investigations are needed before statins can be prescribed for non-vascular indications. Statins do not increase the risk of cancer and memory loss as shown in intensive epidemiological studies. Most likely, the only established and clinically relevant undesired events of statins are myalgias and a slightly higher risk of DM, both much over-publicized [21].

An association between a low cholesterol level and mortality risk was described in the literature [22], although the causality of this association has been reliably ruled out and low cholesterol has been shown to be a marker of frailty rather than a cause of shorter survival [23].

The second class of medicines associated with longer survival in our cohort was selective serotonin re-uptake inhibitors. SSRIs have been linked to other benefits aside from mood modification, such as longer survival after heart failure and ischemic heart disease [24], reduction in inflammatory markers and platelet activation, increase of endothelial function after acute coronary syndrome, improvement of outcomes in stroke, and enhancement of cognition in vascular dementia [25].

LIMITATIONS

Our study was an observational cohort study, which may have unknown biases, even after thoroughly controlling the results for known confounders. Moreover, the cohort included only residents insured by one healthcare fund and geographically covered only one region in the country; however, most of the older adult population in Israel belongs to this health fund and the location should not have influenced our findings. In addition, in the original data records, medication groups were described as "statins and other lipid lowering medications" and SSRI/SNRI, instead of "statin" and "SSRI". Regretfully, we had no access to the original patient files after 5 years and could not categorize medications more precisely. Nevertheless, as the authors were very familiar with the types of medications prescribed in the nursing homes, it is almost certain that cases where possibly fibrates or ezetimibe were prescribed and falsely categorized as statins were rare. The same conclusion pertains to SSRI/SNRI. Moreover, this inaccuracy would cause an under-estimation and not over-estimation of statin or SSRI benefit.

An additional limitation was that data collection was conducted at baseline without recording any follow-up information (such as hospitalizations, infections, cardiovascular events, changes in drug regimens, or cause of death) other than survival. There also could be a prescription bias resulting in higher prescription rates of SSRIs and statins in healthier residents (both statins and SSRI patient groups were signifi-

cantly younger, had higher BMI, and were more mobile, which indicate better general conditions). Such a bias is common in observational studies. Some of the heterogeneities in the baseline characteristics of the four sub-groups, such as tube feeding rate or length of stay, were higher in the no-statin-no-SSRI sub-group and could be suggestive of more advanced dementia. However, some other characteristics were apparently detrimental in the other sub-groups when clinically comparing to the no-statin-no-SSRI sub-group, such as higher CCI, stroke or ischemic heart disease rate in the statin + SSRI group.

STRENGTHS

The final model was controlled for all confounders, therefore the results should not be contaminated by the aforementioned differences. The strengths of the study were its prospective design, large size, comprehensive collection of multiple data elements, survival follow up after 5 years, and the novelty of the study in addressing survival benefits of medications in this under-studied patient population.

CONCLUSIONS

Statins and SSRI treatment at baseline are associated with longer survival in geriatric nursing home residents. Statins and/or SSRIs should not be deprived from old and debilitated nursing home patients, if medically indicated. Further studies, with a prospective design and thorough follow up, including health events and cause of death, are warranted to clarify the causative link.

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"The future belongs to those who believe in the beauty of their dreams"

Eleanor Roosevelt (1884–1962), American political figure, diplomat, and activist, served as first lady of the United States during her husband's four terms as president