Association Between Statin Use at Admission to Inpatient Rehabilitation and Functional Status at Discharge among Older Patients

Alessandro Morandi,^{1,2} Timothy D Girard,^{3–6} Ayumi Shintani,⁷ Renato Turco,^{1,2} Fabio Guerini,^{1,2} Tiziana Torpilliesi,^{1,2} Simona Gentile,^{1,2} Marco Trabucchi,^{2,8} and Giuseppe Bellelli^{2,9}

Abstract

The effect of statins on functional status in older patients is unclear. Statins might carry a deleterious effect on muscle function leading to myopathy and therefore affecting functional recovery. We evaluated the relationship between statin exposure at in-hospital rehabilitation admission and functional outcome at discharge. This was a retrospective cohort study of older patients 70 years and older consecutively admitted to an in-hospital rehabilitation after an acute hospitalization. Statin exposure was measured at the time of rehabilitation admission. Functional status was defined with the Barthel Index (BI) score at the time of discharge. A multi-variable linear regression model was used to evaluate the association between statin exposure and functional status at discharge adjusting for potential confounders through a propensity score for statin exposure. A total of 2435 patients were included. The cohort had a mean age of 81.1 years. Of these 9% ($n=220$) were on statins at the time of admission. In the multi-variable analysis, the use of statins at the time of admission was independently associated with an improved functional status at discharge (point estimate 5.2; 95% confidence interval 1.5–8.9; $p<0.01$) after adjusting for relevant confounders. Patients who were receiving statins at the time of admission had a BI score 5 points higher compared to those who were not receiving statins. The use of statins was overall safe in a group of co-morbid older patients undergoing rehabilitation training after an acute hospitalization. Additionally, a possible benefit was found given the positive association between statin use and higher functional status at discharge.

Introduction

EVERY YEAR AN INCREASING NUMBER of older patients are admitted to rehabilitation facilities after an acute hospitalization.¹ This number is expected to grow given the global aging of the population worldwide and the shorter length of stay in acute hospital of patients with unresolved medical conditions who cannot be directly discharged to home.^{1–4} Most of these patients have stable or unstable cardiovascular diseases as a primary reason of admission or as a co-morbid disease.⁵

The reductase inhibitors of hydroxymethyl glutaryl coenzyme A (statins) are commonly prescribed in these patients.⁶

The current evidence for statins treatment in the older population is, however, scant, and little information is available on the possible side effects of this pharmacological treatment.⁷ Several reports have raised questions on the safety of statin use on musculoskeletal functions in the general populations and specifically in the older adults.^{8–10} However, the concern about possible side effects may lead clinicians to discontinue statins therapy in patients undergoing rehabilitation to prevent potential detrimental effects on muscle and thus on functional outcomes. Few observational studies^{11–15} have specifically addressed the association between statins use and functional status in older patients in outpatient clinics and inpatients rehabilitation settings. Preliminary evidence

¹Department of Rehabilitation and Aged Care, Ancelle Hospital, Cremona, Italy. ²Geriatric Research Group, Brescia, Italy.

³Center for Quality Aging, ⁴Center for Health Services Research, and ⁵Division of Allergy, Pulmonary, and Critical Care Medicine in the Department of Medicine at the Vanderbilt University School of Medicine, Nashville, Tennessee.

⁶Geriatric Research, Education and Clinical Center Service at the Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, Tennessee.

⁷Department of Clinical Epidemiology and Biostatistics, Graduate School of Medicine, Osaka University, Osaka, Japan.

⁸University of Tor Vergata, Rome, Italy, Rome.

⁹Department of Health Sciences, University of Milano-Bicocca and Geriatric Medicine, San Gerardo Hospital, Monza, Italy.

suggests that statins might be safe overall in this population.^{11,12} Indeed, community-dwelling patients receiving statins perform modestly better than non-users in functional status, as measured with the timed chair stands^{11,12} and as the change in Barthel Index (BI) score between admission and discharge in inpatients' rehabilitation setting.^{11,12}

Although statins have been reported to be safe overall, few data have reported an association between statins with possible muscle performance decline and increased fall risk.¹⁴ The current evidence on statins safety is, however, limited by the lack of evaluation of possible important confounders such as co-morbidity, pre-admission functional status, type of admission, systemic inflammatory status, and the consideration of an indication bias (*i.e.*, the "healthy user" effect) where patients with better prognosis have a higher likelihood of being prescribed with statins at the time of hospital admission, which could cause a bias in the estimated effect of statin use.

Given the limitations of prior investigations and the current uncertainties on the use of statins in the older population, the aim of this investigation was to evaluate the safety of statins' relationship between statin use at in-hospital rehabilitation admission and functional status at discharge in a cohort of adults aged 70 years and older.

Methods

We conducted a retrospective cohort study of patients 70 years of age and older consecutively admitted to the Department of Rehabilitation and Aged Care of the Ancelle Hospital in Cremona, Italy, after an acute-care hospitalization between January, 2004, and June, 2011. This setting and population have been described previously.^{5,16} We excluded patients who were younger than 70 years of age and those who died during the rehabilitation stay, were transferred from another rehabilitation setting, or were admitted from home or skilled nursing facilities. We selected the age cutoff given the recent call to focus on "very old" patients.¹⁷ The Ethics Committee of Gerontological Sciences of the Geriatric Research Group approved the study, the study protocol, and the waiver of informed consent given the retrospective nature of the study.

Data sources

All data were collected through existing administrative databases.

Data collection

All patients at the time of rehabilitation hospital admission were evaluated with a comprehensive multi-dimensional geriatric assessment as part of the clinical practice. Demographics included age and sex. Co-morbidity was defined with the Cumulative Illness Rating Score (CIRS),¹⁸ a co-morbidity index that assesses chronic medical illness burden while taking into account the severity of chronic diseases. The score for each of the 14 conditions can range from 1 (absence of pathology) to 5 (maximum level of severity of the disease). The CIRS severity index is the average score of the first 13 items. Admission diagnoses were recorded. Overall functional status was assessed by expert geriatricians in consensus with physiotherapists with the BI^{19,20}

through patient and surrogate interview referring to two time points—1 month before the rehabilitation admission and admission to the rehabilitation facility. The BI score ranges from 0 (total functional dependency) to 100 (total functional independency). Instrumental Activities of Daily Living (IADLs)²⁰ were also recorded through patient and surrogate interview referring to 1 month before the rehabilitation admission. The total number of drugs was also recorded.

Co-variables

Co-variables included delirium on admission, use of angiotensin-converting enzyme (ACE) inhibitors, aspirin, β -blockers, age, gender, admission diagnosis, length of stay in the acute hospital, C-reactive protein (CRP) levels at admission, and the delta-BI (difference between total BI on admission and before rehabilitation admission). Presence of delirium at the time of admission was screened for with the Confusion Assessment Method (CAM) algorithm, and it was confirmed by a gold standard clinical assessment using the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition, text revision) (DSM-IV-TR) by geriatricians trained in delirium and dementia assessment.

Exposure definition

Exposure to statins was defined as the use of statins at the time of rehabilitation admission. All patients who were admitted on a statin continued to receive the statin throughout the rehabilitation stay.

Outcome definition

Functional status at discharge was assessed by expert geriatricians in consensus with physiotherapists with the total BI score.^{19,20}

Statistical analysis

Demographics and clinical variables were summarized using mean $\pm$ standard deviation (SD) for continuous variables or proportions for categorical variables.

A multi-variable linear regression model was used to analyze the association between exposure to statins and functional status at discharge after adjusting for *a priori*-selected co-variables chosen because previous research and biological rationale suggested these variables may confound the association between statin use and functional status at discharge. To deal with an indication bias (*i.e.*, healthy cohort effect), we constructed the propensity score to adjust for the patients' likelihood of being on a statin at the time of admission, which was computed as the predicted probability of a logistic regression model predicting use or non-use of a statin at the time of admission as a function of the following variables: Chronic medical illness of the CIRS (hypertension, heart, vascular, liver, kidney, muscular, neurological, behavioural), CIRS severity index, age, gender, variables collected at admission (including delirium, ACE-inhibitors, β -blockers, aspirin), and the difference between total BI scores on admission and before admission. All statistical analyses were performed using STATA v. 13 (www.stata.com/stata13), and statistical significance was set at a *p* value < 0.05.

Results

A total of 6383 patients were admitted to the rehabilitation hospital during the study period. Of these 3948 were excluded: 896 were transferred from other rehabilitation settings, 2144 were admitted from home or skilled nurse facilities, 812 were younger than 70 years of age, and 96 died during the rehabilitation stay. The remaining cohort of 2435 is described in Table 1. Of these 9% ($n=220$) were on statins at the time of admission. Patients receiving statins at the time of admission were younger, with a higher level of co-morbidity, and, as expected, with a higher prevalence of cardiovascular diseases as indicated by the single items of the CIRS. Overall, the global function status, as indicated by the total BI, was higher in the patients receiving statins pre-admission, on admission, and at discharge. Interestingly, patients on statins had a lower prevalence of delirium (14% vs. 20%) compared to the other counterpart.

In the multi-variable linear regression model, the presence of statins at the time of admission was independently associated with better functional status at discharge (point estimate, 5.2; 95% confidence interval 1.5–8.9; $p<0.01$) after adjusting for relevant confounders (Table 2). Other factors associated with better functional status were the use of aspirin, β -blockers, and ACE inhibitors at the time of

admission. Three factors were inversely associated with functional status at discharge—delirium on admission, age, and CRP levels (*i.e.*, level of systemic inflammation).

Discussion

This study examines the possible harms and benefits of statin use in a population of adults aged 70 years and older admitted to in-hospital rehabilitation. Evidence was not found to suggest that statin use might adversely affect functional status; in fact, patients on statins had an average 7 points higher BI score than non-users at discharge. Indeed, it is worth noticing that a 5-point change in the total BI might be clinically significant if we consider that a patient might move from being dependent in walking (walking BI sub-item <15) to being independent (BI sub-item >12).

These findings are important because they confirm and extend previous observational studies.^{11–15} Previous studies have reported possible positive effects on functional status related to statin use but were limited by the absence of relevant confounders possibly leading to biased associations. Potential confounders include co-morbidities, pre-admission functional status, admission diagnoses, systemic inflammatory status, and a “healthy user” effect. Majumdar and colleagues²¹ have reported the importance of including

TABLE 1. CHARACTERISTICS OF 2435 PATIENTS ELDERLY PATIENTS 70 YEARS AND OLDER ADMITTED TO A REHABILITATION SETTING ACCORDING TO STATIN USE^a

Variable	Entire cohort	Statins (n=220)	No statins (n=2215)	p value
Age	81.1 $\pm$ 6.4	77.9 $\pm$ 0.3	81.2 $\pm$ 0.1	0.01
Gender (female)	1749 (72%)	148 (67%)	1601 (72%)	0.12
CIRS severity index	1.7 (1.5–1.8)	1.8 $\pm$ 0.2	1.7 $\pm$ 0.1	<0.01
CIRS heart	2.1 $\pm$ 1.1	2.5 $\pm$ 0.8	2.1 $\pm$ 0.2	<0.01
CIRS hypertension	2.4 $\pm$ 0.9	2.7 $\pm$ 0.1	2.4 $\pm$ 0.2	<0.01
CIRS vascular	1.8 $\pm$ 0.9	1.9 $\pm$ 0.1	1.8 $\pm$ 0.2	<0.01
CIRS respiratory	1.7 $\pm$ 1.1	1.6 $\pm$ 0.1	1.8 $\pm$ 0.1	0.02
CIRS liver	1.2 $\pm$ 0.5	1.1 $\pm$ 0.1	1.2 $\pm$ 0.1	0.10
CIRS kidney	1.3 $\pm$ 0.6	1.3 $\pm$ 0.1	1.3 $\pm$ 0.1	0.64
CIRS muscular	2.6 $\pm$ 1.1	2.5 $\pm$ 0.1	2.6 $\pm$ 0.1	0.05
CIRS nervous system	1.7 $\pm$ 1.1	1.7 $\pm$ 0.1	1.7 $\pm$ 0.1	0.95
CIRS psychiatry	1.9 $\pm$ 1.1	1.7 $\pm$ 0.1	1.9 $\pm$ 0.1	<0.01
Admission diagnosis				
Orthopedic	1009 (41%)	81 (36%)	928 (42%)	0.11
Neurologic	392 (16%)	41 (19%)	351 (16%)	0.15
Cardiovascular	255 (10%)	49 (22%)	206 (9%)	<0.01
Respiratory	428 (18%)	27 (12%)	401 (18%)	0.02
Gait disturbances	243 (10%)	8 (4%)	237 (5%)	<0.01
Others	105 (4%)	13 (6%)	95 (4%)	0.22
Delirium on admission	483 (20%)	31 (14%)	457 (20%)	0.02
Barthel Index pre-admission	93 (77–100)	90.1 $\pm$ 1.15	83.8 $\pm$ 0.43	<0.01
Barthel Index admission	43 $\pm$ 24.1	53.4 $\pm$ 1.60	42.3 $\pm$ 0.50	<0.01
Barthel Index discharge	70 $\pm$ 28.4	79.1 $\pm$ 1.76	69.3 $\pm$ 0.61	<0.01
Delta-Barthel Index ^b (pre-admission-admission)	41 $\pm$ 22	37 $\pm$ 22	42 $\pm$ 22	0.02
IADL total	4 (1–7)	4.01 $\pm$ 0.21	3.97 $\pm$ 0.62	0.95
Number of drugs on admission	6 (4–7)	7.25 $\pm$ 0.19	5.71 $\pm$ 0.06	<0.01
ACE inhibitors on admission	888 (36%)	119 (54%)	780 (35%)	<0.01
Aspirin on admission	658 (27%)	106 (48%)	584 (26%)	<0.01
β -blockers on admission	683 (28%)	101 (45%)	567 (26%)	<0.01

^aVariables are reported using mean $\pm$ standard deviation (SD) for continuous variables or proportions for categorical variables.

^bThe delta-Barthel index is the difference between the total Barthel Index Score on admission and the total Barthel Index Score before admission.

CIRS, Cumulative Illness Rating Score; IADL, Instrumental Activities of Daily Living; ACE inhibitors, angiotension-converting enzyme inhibitors.

TABLE 2. MULTIVARIATE LINEAR REGRESSION ANALYSIS OF THE ASSOCIATION BETWEEN STATIN USE ON REHABILITATION ADMISSION AND FUNCTIONAL STATUS AT DISCHARGE, DEFINED WITH THE TOTAL BARTHEL INDEX SCORE

Predictor	Point estimate	95% Confidence interval	p value
Statins on admission	5.2	1.5–8.9	<0.01
Delirium on admission	–18.3	–21; –15	<0.01
ACE inhibitors on admission	3.6	1.4–5.8	0.00
Aspirin on admission	5.1	2.5–7.6	<0.01
β -blockers on admission	6.3	3.9–8.8	<0.01
C-reactive protein (CRP) levels on admission (mg/L)	–0.6	–0.8; –0.4	<0.01
Age (years)	–1.1	–1.3; –0.9	<0.01
Gender	–0.9	–3.2; 1.3	0.31
Admission orthopedic	–1.7	–28.9; 25.7	0.94
Admission neurologic	–19.5	–47; 8.1	0.17
Admission cardiologic	–9.1	–36.7; 18.6	0.52
Admission respiratory	–7.1	–34.6; 20.5	0.61
Admission gait disturbances	–9.8	–37.5; 17.8	0.48
Admission others	–14.5	–42.4; 13.4	0.31
Delta-Barthel Index	–0.19	–0.2; –0.1	<0.01
Length of stay acute hospital	–0.1	–0.8; 0.1	0.08
Propensity score for statin use ^a	–22.9	–37.2; –8.6	0.02

^aThe delta-Barthel index is the difference between total Barthel Index on admission and before rehabilitation admission.

^bThe propensity score was created to adjust for the patients' likelihood of being on statin at the time of rehabilitation admission. A logistic regression model with statin use at the time of rehabilitation admission as dichotomous variable was constructed, and independent variables included selected chronic medical illness of the CIRS (hypertension, heart, vascular, liver, kidney, muscular, neurological, behavioral), CIRS severity index, age, gender, variables collected at rehabilitation admission (*i.e.*, delirium, ACE inhibitors, β -blockers, aspirin), and the delta-Barthel Index (difference between total Barthel Index on admission and before rehabilitation admission).

ACE inhibitors, angiotensin-converting enzyme inhibitors; CIRS, Cumulative Illness Rating Score.

a propensity score when evaluating the effect of statins on other outcomes (*e.g.*, reduced mortality in patients with community-acquired pneumonia). The association between statins and mortality reduction disappeared when a propensity score was included in multi-variable regression, suggesting that in observational studies this approach is essential to provide the best possible evidence. Additionally, we specifically selected a population of patients aged 70 years and older to reflect the “real-world” patients currently admitted to in-hospital rehabilitation.

Our findings regarding the better functional status in statin users might be potentially explained by the possible pleiotropic effects of these medications and in particular by their anti-inflammatory role.²² In fact, inflammation has been implicated in the pathogenesis of sarcopenia and drugs such as statins might indirectly affect the systemic inflammation and counteract the circle, which leads to sarcopenia.²³ Statin use has been also reported to contribute to an

improvement of skeletal muscle response and reduction of sarcopenia in older patients undergoing high-intensity physical training.²⁴ Another possible implication of the action of statins on inflammation might be explained by the lower prevalence of delirium in statin users. This could partially support the recent findings of the reduction induced by statins in the odds of delirium in critically ill patients.^{22,25,26} As in previous studies,^{25,26} we did not limit the analysis either to new statin users or chronic users because we believed statins have the potential to play a role on outcomes, specifically in our study on functional outcomes, when considering the timing of the effect of statins related to an acute hospitalization rather than the timing of statin initiation. In fact, in our study, we considered a patient as a statin user if a patient was admitted on a statin and continued to receive the statin throughout the rehabilitation stay. Finally, statin users might indeed have a lower incidence of infections or cardiovascular events during the rehabilitation stay, leading to a reduction of the interruption of the rehabilitation course. Nonetheless, we did not record this information, and future studies should further evaluate the mechanisms of possible beneficial effects of statins in this population.

However, despite statins maintaining the independent predictive power after adjusting for several variables including the propensity score, we cannot definitely exclude that their protective effect should be, at least partially, related to a better global health status before admission than non-users. The association between delirium, ACE inhibitors, and functional status in our study also deserves a few comments. Delirium has been previously described to be negatively associated with functional status in older patients admitted to rehabilitation settings and, in particular, when delirium occurs in the context of dementia.^{27–29}

Conversely, the literature on the association between ACE inhibitors and functional status is controversial. Observational studies have shown that the use of ACE inhibitors is associated with a slower decline in muscle mass, muscle strength, and walking speed in older community-dwelling subjects, suggesting a direct role of these medications on skeletal muscle.^{30,31} However, in a recent randomized clinical trial, the use of ACE inhibitors did not increase the effect of exercise training, in particular endurance, in older patients with functional impairment.³² Our findings of a positive association between ACE inhibitors and functional status might be due to the retrospective nature of the study with possible residual confounding but also to the different measure of functional outcome we have used. Indeed, we have evaluated the global functional status with the BI and not the patients' endurance with the 6-min walking test.

Our study has important strengths along with limitations. Strengths include a large population of adults aged 70 years and older and the inclusion of a propensity score for “healthy user.” However, this was a single-center retrospective cohort study, and, therefore, the findings should be interpreted with caution. We did not collect information on different types of statins (*e.g.*, lipophilic vs. hydrophilic) and we have not collected information specifically on muscle strength. Finally, we cannot exclude residual confounding related to other variables indicative of a healthy user, such as socio-economic status and caregiver support.

Conclusions

This study did not find evidence of possible harm related to statin use in a population of adults aged 70 years and older admitted to in-hospital rehabilitation. A possible positive effect was found on the association between statin use and higher functional status at discharge, supporting an overall safety of the use of statin medications, even in a group of co-morbid older patients.

Acknowledgments

Dr. Girard received support from the National Institutes of Health (AG034257) and the Veterans Affairs Tennessee Valley GRECC and received honoraria from Hospira.

Author Disclosure Statement

No competing financial interests exist.

References

- Buntin MB. Access to postacute rehabilitation. *Arch Phys Med Rehabil* 2007;88:1488–1493.
- Qian X, Russell LB, Valiyeva E, Miller JE. 'Quicker and sicker' under medicare's prospective payment system for hospitals: New evidence on an old issue from a national longitudinal survey. *Bull Econ Res* 2011;63:3307–3378.
- Corsonello A, Lattanzio F, Pedone C, Garasto S, Laino I, Bustacchini S, Pranno L, Mazzei B, Passarino G, Incalzi On Behalf Of The Pharmacosurveillance In The Elderly Care Pvc Study Investigators RA. Prognostic significance of the short physical performance battery in older patients discharged from acute care hospitals. *Rejuvenation Res* 2012; 15:41–48.
- Bellelli G, Bernardini B, Pievani M, Frisoni GB, Guaita A, Trabucchi M. A score to predict the development of adverse clinical events after transition from acute hospital wards to post-acute care settings. *Rejuvenation Res* 2012; 15:553–563.
- Morandi A, Bellelli G, Vasilevskis EE, Turco R, Guerini F, Torpilliesi T, Speciale S, Emiliani V, Gentile S, Schnelle J, Trabucchi M. Predictors of rehospitalization among elderly patients admitted to a rehabilitation hospital: The role of polypharmacy, functional status, and length of stay. *J Am Med Dir Assoc* 2013;14:761–767.
- Robinson JG, Booth B. Statin use and lipid levels in older adults: National health and nutrition examination survey, 2001 to 2006. *J Clin Lipidol* 2010;4:483–490.
- Schiattarella GG, Perrino C, Magliulo F, Ilardi F, Serino F, Trimarco V, Izzo R, Amato B, Terranova C, Cardin F, Militello C, Leosco D, Trimarco B, Esposito G. Statins and the elderly: Recent evidence and current indications. *Aging Clin Exp Res* 2012;24:47–55.
- Mansi I, Frei CR, Pugh MJ, Makris U, Mortensen EM. Statins and musculoskeletal conditions, arthropathies, and injuries. *JAMA Intern Med* 2013;173:1–10.
- Stone NJ, Intwala S, Katz D. Statins in very elderly adults (debate). *J Am Geriatr Soc* 2014;62:943–945.
- Rich MW. Aggressive lipid management in very elderly adults: Less is more. *J Am Geriatr Soc* 2014;62:945–947.
- Agostini JV, Tinetti ME, Han L, McAvay G, Foody JM, Concato J. Effects of statin use on muscle strength, cognition, and depressive symptoms in older adults. *J Am Geriatr Soc* 2007;55:420–425.
- Lynch JE, Henderson NR, Ramage L, McMurdo ME, Witham MD. Association between statin medication use and improved outcomes during inpatient rehabilitation in older people. *Age Ageing*. 2012;41:260–262.
- Ni Chroinin D, Callaly EL, Duggan J, Merwick A, Hannon N, Sheehan O, Marnane M, Horgan G, Williams EB, Harris D, Kyne L, McCormack PM, Moroney J, Grant T, Williams D, Daly L, Kelly PJ. Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: The North Dublin Population Stroke Study. *Stroke* 2011;42:1021–1029.
- Scott D, Blizzard L, Fell J, Jones G. Statin therapy, muscle function and falls risk in community-dwelling older adults. *QJM* 2009;102:625–633.
- LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Newman AB, Kooperberg CL, Black H, Curb JD, Greenland P, Woods NF. Statin use and incident frailty in women aged 65 years or older: Prospective findings from the women's health initiative observational study. *J Gerontol A Biol Sci Med Sci* 2008;63:369–375.
- Bellelli G, Magnifico F, Trabucchi M. Outcomes at 12 months in a population of elderly patients discharged from a rehabilitation unit. *J Am Med Dir Assoc* 2008;9:55–64.
- Yoshikawa TT. Future direction of geriatrics: "Gerogeriatrics." *J Am Geriatr Soc* 2012;60:632–634.
- Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the cumulative illness rating scale in a geriatric residential population. *J Am Geriatr Soc* 1995;43:130–137.
- Mahoney FI. Functional evaluation: The Barthel Index. *Md State Med J* 1965;14:61–65.
- Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–186.
- Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: Population based prospective cohort study. *BMJ* 2006;333:999.
- Morandi A, Hughes CG, Girard TD, McAuley DF, Ely EW, Pandharipande PP. Statins and brain dysfunction: A hypothesis to reduce the burden of cognitive impairment in patients who are critically ill. *Chest* 2011;140:580–585.
- Witham MD, Sumukadas D, McMurdo ME. ACE inhibitors for sarcopenia—as good as exercise training? *Age Ageing*. 2008;37:363–365.
- Riechman SE, Andrews RD, Maclean DA, Sheather S. Statins and dietary and serum cholesterol are associated with increased lean mass following resistance training. *J Gerontol A Biol Sci Med Sci* 2007;62:1164–1171.
- Page VJ, Davis D, Zhao XB, Norton S, Casarin A, Brown T, Ely EW, McAuley DF. Statin use and risk of delirium in the critically ill. *Am J Respir Crit Care Med* 2014;189:666–673.
- Morandi A, Hughes CG, Thompson JL, Pandharipande PP, Shintani AK, Vasilevskis EE, Han JH, Jackson JC, Laskowitz DT, Bernard GR, Ely EW, Girard TD. Statins and delirium during critical illness: A multicenter, prospective cohort study. *Crit Care Med* 2014;42:1899–1909.
- Kiely DK, Jones RN, Bergmann MA, Murphy KM, Orav EJ, Marcantonio ER. Association between delirium resolution and functional recovery among newly admitted postacute facility patients. *J Gerontol A Biol Sci Med Sci* 2006;61:204–208.
- Marcantonio ER, Simon SE, Bergmann MA, Jones RN, Murphy KM, Morris JN. Delirium symptoms in post-acute

- care: Prevalent, persistent, and associated with poor functional recovery. *J Am Geriatr Soc* 2003;51:4–9.
29. Morandi A, Davis D, Fick DM, Turco R, Boustani M, Lucchi E, Guerini F, Morghen S, Torpilliesi T, Gentile S, MacLulich AM, Trabucchi M, Bellelli G. Delirium superimposed on dementia strongly predicts worse outcomes in older rehabilitation inpatients. *J Am Med Dir Assoc* 2014;15:349–154.
30. Onder G, Penninx BW, Balkrishnan R, Fried LP, Chaves PH, Williamson J, Carter C, Di Bari M, Guralnik JM, Pahor M. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: An observational study. *Lancet* 2002;359: 926–930.
31. Di Bari M, van de Poll-Franse LV, Onder G, Kritchevsky SB, Newman A, Harris TB, Williamson JD, Marchionni N, Pahor M. Antihypertensive medications and differences in muscle mass in older persons: The health, aging and body composition study. *J Am Geriatr Soc* 2004;52:961–966.
32. Sumukadas D, Band M, Miller S, Cvorov V, Witham M, Struthers A, McConnachie A, Lloyd SM, McMurdo M. Do ACE inhibitors improve the response to exercise training in functionally impaired older adults? A randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2014; 69:736–743.

Address correspondence to:

*Alessandro Morandi
Department of Rehabilitation and Aged Care
Ancelle Hospital
Via Aselli 16
Cremona, 26100
Italy*

E-mail: morandi.alessandro@gmail.com

Received: August 6, 2014

Accepted: September 30, 2014