# Statins in cardiovascular prevention in the oldest-old. A black hole

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Elderly population is increasing rapidly together with the incidence of cardiovascular diseases (CVDs) and cardiovascular (CV) mortality. The evaluation of total CV risk is necessary for prevention of CV events, but the most used assessment tools do not include the elderly population. Among CV risk factors, hypercholesterolemia increases with the age, but the results about the association between total cholesterol (TC) levels and mortality in the elderly population are controversial. Statins are the first-choice drug for lipid-lowering therapy in the elderly due to their efficacy and safety. In primary prevention there are no recommendations to the use of statins in older adults because they do not reduce the risk of CV and all-cause mortality. On the contrary, statin treatment is recommend both in older than in younger people in secondary prevention because of the reduction of CV and all-causes mortality. High-intensity statins are more effective in the elderly population, but these dosages are associated to an increased incidence of adverse reactions, especially liver dysfunction. Finally, the degree of clinical frailty is inversely related to total cholesterol in the elderly and, accordingly, lower cholesterol levels are associated to higher mortality in this population. There are no studies that specifically evaluated the benefit of lipid-lowering therapy in severely frail older adults and a narrative-based approach, instead of an evidence-based one, has been used to choose the better treatment plan.

**Key words**: Cholesterol, Statins, Cardiovascular risk, Elderly

## INTRODUCTION

The elderly population is rising rapidly: more than 580 million people are 60 years of age or older, and the number is estimated to increase to 1 billion by 2020. This increase in life expectancy has shifted the leading causes of death from infectious diseases to cardiovascular diseases (CVDs) and from younger to older individuals [1]. In fact, CVDs account for over 80% of deaths in the elderly [2]. All current guidelines on the prevention of CVDs recommend the assessment of total cardiovascular (CV) risk [3]. Among the available risk assessment tools, the most useful and used is the Systemic Coronary Risk Estimation (SCORE) that includes a population aged between 40 and 65 years old, excluding in this way elderly people [4]. CV risk factors rise progressively with the increase of population age [5]. Moreover, several epidemiological studies have shown a high prevalence of hypercholesterolemia in later life among the CV risk factors, with Western countries having the highest prevalence [6]. However, in contrast to the expectations, only a few number of observational studies, about the relationship between total cholesterol (TC) levels and mortality in the elderly, found a U-shaped association, where high TC levels were associated with
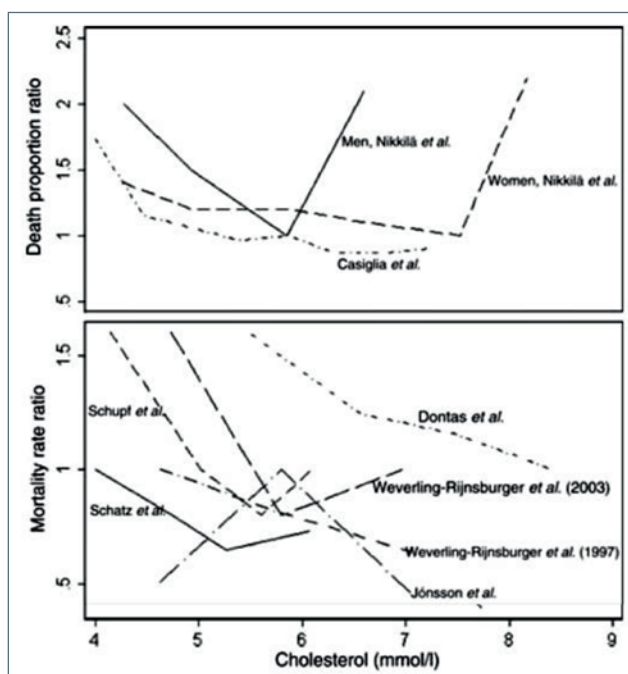
**Figure 1.** All-cause mortality and cholesterol in the elderly. At the x-axis, the cholesterol was plotted as an exact measure of Total Cholesterol (mmol/l). In the top panel, one study has two U-shaped plots corresponding to women and men, respectively, and one study a reverse J-shaped configuration. The middle panel showed six studies: three describing 'a reverse J-shaped configuration', two describing an almost declining curve and one study an inverted U-shaped configuration (from Petersen LK, Christensen K, Kragstrup J, 2010, mod.) [7].

increased mortality. Most of the studies showed a J-shaped association, with highest TC levels associated to lowest all-cause mortality. Finally, low TC (< 100 mg/dl) is associated with increased mortality among > 80 years old (Fig. 1) [7]. This confused scenario shows how many complex issues are involved in the decision to whether and how introduce an effective lipid-lowering therapy in the elderly. Thus, this review summarizes the management of lipid disorders in primary and secondary prevention in the elderly.

## STATINS

Statins are the drugs most extensively used for lipid-lowering therapy in the elderly, because of their efficacy, safety, and benefits through Hydroxy-Methyl-Glutaryl-CoA (HMG-CoA) reductase reversible inhibition [8]. Statins induce a reduction in cholesterol biosynthesis and, consequently, in intracellular cholesterol concentration, resulting in an increased expression of low-density lipoprotein (LDL) receptors on the surface of the

hepatocytes which leads than increased uptake of LDL-Cholesterol (LDL-C) from the blood and its decreased plasma concentration [9]. The degree of LDL-C reduction is dose dependent and varies between the different statins [10]. Although statins are generally well tolerated, there are adverse effects to be considered when statins are prescribed [3]. Muscle symptoms, such as rhabdomyolysis, myalgia and myopathy, are the most frequent, but a recent systematic review and meta-analysis about these adverse events in the elderly showed little or no evidence of a difference in risk between treatment and placebo groups [11]. Another side effect is the hepatotoxicity, assessed by the elevations in serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). To date, there is not enough evidence to indicate that the incidence of hepatotoxicity or elevations of aminotransferases is higher in elderly patients receiving statins compared with younger patients [12]. Statins also increase the risk of dysglycaemia and development of type 2 diabetes mellitus and this risk is higher in the elderly, especially with high-intensity statins, and in the presence of other risk factors for diabetes such as overweight or insulin resistance [13 14].

## PRIMARY PREVENTION

Because of the lack of clinical studies or meta-analysis, European Society of Cardiology (ESC) guidelines on the management of dyslipidemia indicate IIb class with a B level of evidence for statin therapy in oldest people without previous CV events [3]. One of the first primary prevention studies in patients aged > 70 years was the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study. This study randomized 5804 patients with a mean age 75.4 ± 3.3 at high risk for CVDs to pravastatin 40 mg per day or placebo group. The primary endpoint was a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke. After 3.2 years of follow-up, pravastatin lowered LDL cholesterol concentrations by 34% and the primary endpoint by 15%. In particular pravastatin 40 mg daily reduced coronary events by 19% and coronary deaths by 24%. Although there was no effect on stroke and cognition over that period, transient ischemic attacks were reduced by 25%. The data supported the use of pravastatin in the elderly, especially given its safety and tolerability [15]. At the same time another primary prevention trial, the Heart Protection Study (HPS), investigated a high-risk population of 20.536 individuals, including 5806 (28%) patients aged ≥ 70 years randomized into a placebo group and a group treated with simvastatin 40 mg. The HPS divided the statins group into age groups of < 65, 65 to 69, and ≥ 70 years.

Primary outcomes were mortality (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity. Statins achieved a 24% reduction in major vascular events in the statins compared to placebo groups supporting that statins are beneficial in the elderly [16]. A recent meta-analysis on the primary prevention with statins in elderly individuals at high CV risk included 8 randomized clinical trials (RCTs), enrolling 24.674 subjects and showed a reduced risk of myocardial infarction (MI) by 39.4% compared with placebo (Relative Risk: 0.60 [95% Confidence Interval: 0.43 to 0.84]) and stroke by 23.8% compared with placebo (Relative Risk: 0.76 [95% Confidence Interval: 0.62 to 0.92]). However, statins did not significantly reduce the risk of all-cause death compared with placebo (Relative Risk: 0.94 [95% Confidence Interval: 0.85 to 1.03]) and the risk of CV death (Relative Risk: 0.90 [95% Confidence Interval: 0.68 to 1.19]) [17].

Also the US Preventive Services Task Force (USPSTF) Recommendation Statement establishes indication to statin therapy in adults aged 40-75 years with no history of CVD, ≥ 1 CVD risk factors, and calculated 10-years CVD event risk ≥ 10% or 7.5-10% with a Grade of Certainty B and C respectively. However, it also establishes that there is no recommendation to the use of statins in adults 76 years and older with no history of CVD with a Grade I of Certainty, that corresponds to insufficient current evidences to assess the balance of benefits and harms of the treatment [18].

Finally, statin therapy is not directly recommended for primary prevention in the elderly because they only reduce the risk of CV and cerebrovascular events, but not CV and all-cause mortality. Because of the lack of evidence in this population, a possible approach could be based on "start low and go slow": starting from a lower dosage and increasing it progressively, also in function of the onset of any side effects.

In Table I are indicated most of the "primary" prevention studies described above.

## SECONDARY PREVENTION

ESC guidelines on the management of dyslipidemia assigns to statin treatment in older adults with established CVDs a Class I and Level of Evidence A, as for younger patients [3]. A meta-analysis on the use of statins in elderly individuals for secondary prevention collected data from 18 double-blind RCTs of statins vs. placebo

**Table I.** Summary of major statin studies involving elderly patients.

| Author | Year | Type of study | Prevention | Age | Results |
|---|---|---|---|---|---|
| Shepherd et al. [15] | 2002 | RCT | Primary | 75.4 ± 3.3 | Pravastatin 40 mg daily given for 3 years reduces the risk of coronary disease in elderly patients. |
| Heart Protection Study Collaborative Group [16] | 2002 | RCT | Primary | 40–80 years<br><br>28% patients aged ≥ 70 years | Long-term simvastatin 40 mg daily reduces the rates of myocardial infarction, stroke and revascularization in high-risk populations independently of age. |
| Cannon et al. [24] | 2004 | RCT | Secondary<br><br>High-intensity vs. moderate intensity | 58.3±11.3<br><br>30% patients aged ≥ 65 years | High-intensity statin regimen provides greater protection against death or major CV events than standard regimen (pravastatin 40 mg) in younger but also in elderly patients. |
| Deedwania et al. [25] | 2007 | RCT | Primary and secondary prevention<br><br>High-intensity vs. moderate intensity | 72.6 ± 5.2 | High intensity statin therapy (atorvastatin 80 mg) is associated with major reductions in cholesterol, major acute CV events and death than moderate-intensity statin (pravastatin 40 mg) in elderly patients. |
| Ridker et al. [23] | 2008 | RCT | Primary | 66 (median)<br><br>32% patients aged ≥ 70 years | Rosuvastatin 20 mg significantly reduces the incidence of major CV events both in younger than in older patients without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels. |
| Chaturvedi et al. [22] | 2009 | RCT | Secondary | 72.5 ± 0.2 | Aotrvastatin 80 mg reduces the incidence of CV events both in younger than in older patients, but it reduces the incidence of cerebrovascular events (stroke and TIA) only in younger patients. |

RCT: Randomized Controlled Trials; CV: Cardiovascular

accounting 51.351 persons of which 31.633 (62%) were aged 60 years or older. This meta-analysis showed that statins reduced all-cause mortality by 15% (Relative Risk: 0.85, 95% Confidence Interval: 0.78-0.93), coronary heart disease (CHD) death by 23% (Relative Risk: 0.77, 95% Confidence Interval: 0.71-0.85), fatal or nonfatal myocardial infarction by 26% (Relative Risk: 0.74, 95% Confidence Interval: 0.70-0.78) and fatal or nonfatal stroke by 24% (Relative Risk: 0.76, 95% Confidence Interval: 0.65-0.90) [19]. Another meta-analysis showed that the proportional reduction in the incidence of coronary revascularization per 1.0 mmol/L reduction in LDL cholesterol was significantly larger in the trials of more vs. less intensive therapy than in those of statins vs. control not only in subjects aged 65 or less, but also in those aged 65-75 or more (Fig. 2) [20].

Nevertheless, a very recent "Quasi-experimental study" (i.e. no randomization trial) evaluated the safety and effectiveness of statin treatment for secondary prevention in 12.156 older patients divided in two groups of 6.078, one of control and one in treatment with statins, regardless of strength and treatment duration. Statins were associated with protective effect in the 60-79 age group (Hazard Risk: 0.73, Confidence interval: 0.57-0.94) but showed a non-significant result in the ≥ 80 group (Hazard Risk: 1.06, Confidence interval: 0.78-1.44). Data also suggest an increased risk of falls (Hazard Risk: 1.36, Confidence interval: 1.17-1.60) and fractures (Hazard Risk: 1.33, Confidence interval: 1.04-1.69) in the first 2 years of treatment, particularly in the ≥ 80 group. Treatment was also associated with lower all-cause mortality (Hazard Risk: 0.62, Confidence interval: 0.57-0.68) [21]. The results of this study were similar to other trial and meta-analysis results as regards to statins effectiveness for the secondary prevention in patients aged 60-79

years. Unfortunately, the reduction of CV events, in particular myocardial infarction, in the group of patients aged 80 years and older, is not statistically significant and it also shows a significant increase in the risk of falls and fractures in this group. Although this study is performed with a "Quasi-experimental" method, it raises questions that require further investigation.

Actually, statin therapy is strongly recommended for secondary prevention in elderly population as well as in younger people because of the reduction of CV and all-cause mortality. However, evidences in patients older than 80 are poor.

In Table I are indicated most of the "secondary" prevention studies described above.

## HIGH-INTENSITY STATINS AND ADVERSE EVENTS

Atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg are defined high-intensity statins. Among the major studies involving elderly patients, only JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) studies used high-intensity statins. In particular, SPARCL evaluated the risk of recurrent fatal and nonfatal stroke in a cohort of 4731 patients aged ≥65 years with a history of prior stroke or transient ischemic attack (TIA) randomized to atorvastatin 80 mg or placebo, in order to evaluate whether this class of patients had the same benefit from statin treatment as younger patients. The SPARCL study showed a statistically significant reduction of any cardiovascular event and stroke or TIA in younger patients (p = 0.00360; p ≤ 0.0001 respectively), but a statistically
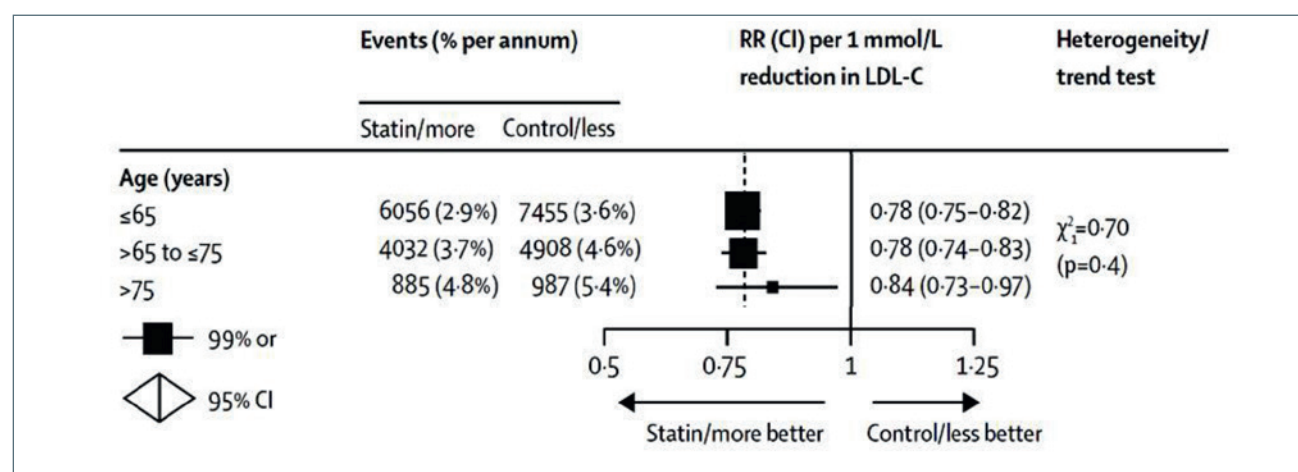


**Figure 2.** Risk ratio for all-cause mortality from 14 studies of secondary prevention with statins in the elderly. Note that the statins' protective effect decreases from 65-7 to ≥ 75 years old (from Cholesterol Treatment Trialists' (CTT) Collaboration, mod.) [20].

significant reduction of only any CV event in the older cohort but not of stroke and TIA (p = 0.0005; p = 0.2643 respectively) [22]. The JUPITER trial assessed the efficacy of rosuvastatin 20 mg *vs* placebo in primary prevention. In this trial 32% of participants were aged ≥ 70 years. The primary outcome was the occurrence of a first major CV event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. Secondary endpoints included the components of the primary endpoint considered individually and death from any cause. Patients who received rosuvastatin had significantly lower rates of both primary and secondary endpoints when compared with patients on placebo [23]. In both these studies the occurrence of serious adverse events between the two groups was not statistically significant, regardless of the age.

There are only two studies comparing high-intensity with intermediate-intensity statins: PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) and SAGE (Study Assessing Goals in the Elderly), which is the only conducted entirely in the elderly. PROVE IT-TIMI 22 trial was designed to compare the efficacy of pravastatin 40 mg *vs* atorvastatin 80 mg with a LDL-C goal of 70 mg/dL and a primary endpoint of secondary prevention of death or major cardiovascular events. In this study 30% of patients were aged ≥ 65 years. The study showed a statistically significant reduction of LDL-C in the atorvastatin group than in the pravastatin group (62 mg/dl *vs* 95 mg/dl; p < 0.001). Kaplan–Meier curves showed a reduction of the rates of the primary endpoint at two years of 26.3% in the pravastatin group and 22.4% in the atorvastatin group, reflecting the superiority of the more intensive regimen *vs* the standard one (p = 0.005) with same results for older and younger patients [24]. The SAGE study examined differences in the occurrence of episodes of myocardial ischemia in elderly patients aged between 66 to 85 years receiving intensive *vs* moderate statin therapy (atorvastatin 80 mg *vs* pravastatin 40 mg, respectively). Atorvastatin-treated patients experienced greater LDL reductions, fewer major acute cardiovascular events (Hazard Ratio = 0.71; 95% Confidence Interval, 0.46, 1.09; p = 0.114), and a significantly greater reduction in all-cause death (Hazard Ratio = 0.33; 95% Confidence Interval, 0.13, 0.83; p = 0.014) than pravastatin-treated patients 25. In both these studies the rate of adverse events was similar between the 2 treatment groups with the exception of liver dysfunction, defined as ALT or AST > 3 times the upper limit of normal, that was more frequent in the atorvastatin than in the pravastatin group in SAGE (4.3% *vs* 0.2% respectively, p < 0.001) and in PROVE IT-TIMI 22 (3.3% *vs* 1.1% respectively, p < 0.001).

As regards the risk of cancer related to the use of statins, meta-analyses above mentioned [17][19] showed the absolute absence of statistically significant correlation. In a meta-analysis about cancer risk in older people receiving statin therapy, 12 RCTs involving 62.927 patients (31.517 in statin therapy group and 31.410 in control group) were analyzed showing that neither the variety nor the chemical properties of the statin therapy did not affect the overall incidence of cancer (Odds Ratio: 1.03, 95% Confidence Interval: 0.94-1.14, p = 0.52) in this population [26].
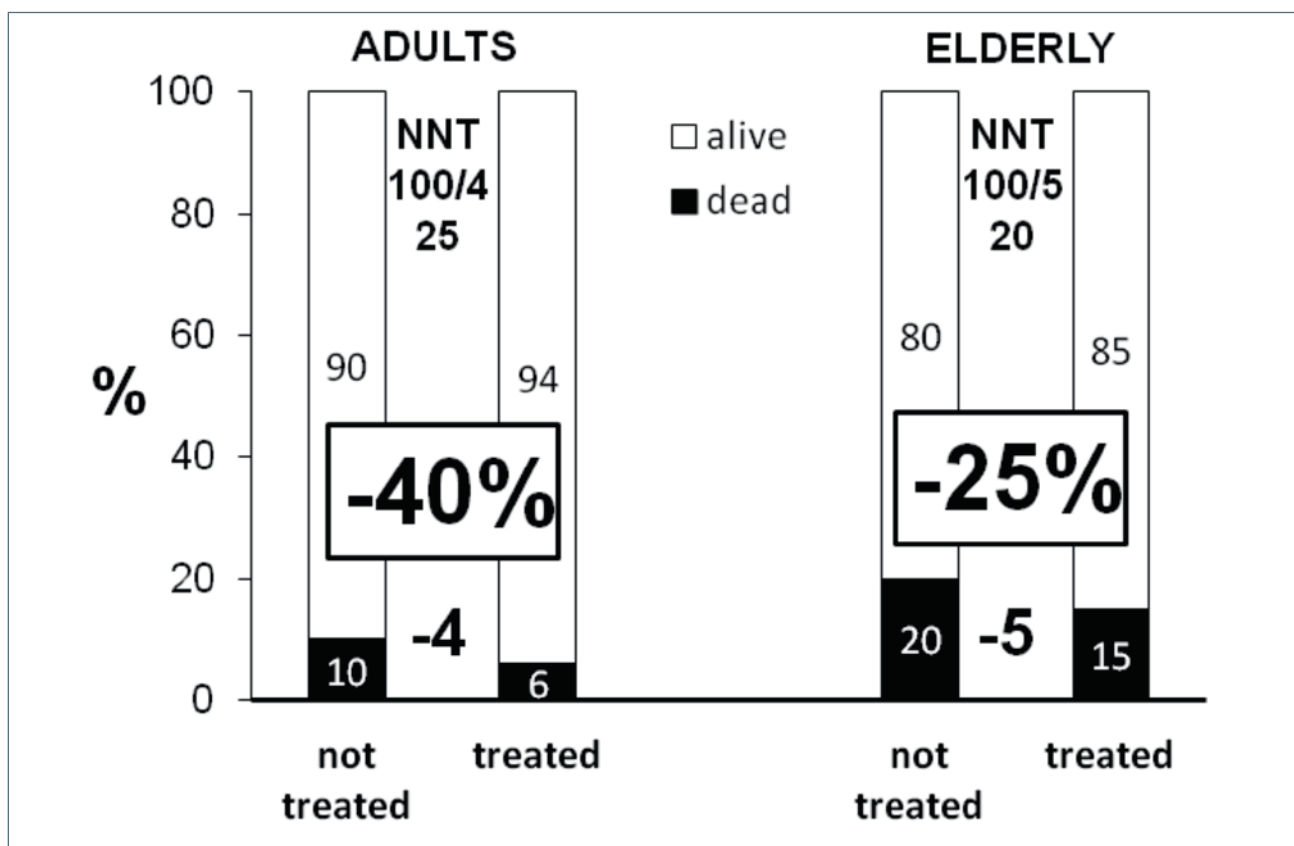
## ELDERLY PARADOX

An analysis of the results of the above mentioned JUPITER study shows a relative risk reduction as a percentage from treatment with rosuvastatin compared with placebo higher in younger patients than in older patients both for the primary and the secondary endpoint. However, a reduction in the absolute risk was higher in older than in younger patients [27].

Although these results may seem contradictory and may suggest an ineffectiveness of the statin treatment in the elderly, this phenomenon is defined "elderly paradox" and it is very frequent in intervention trial in older populations. This phenomenon is cleary explained in Fig. 3. If you consider the absolute reduction of mortality in "adult" patients (from n. 10 to n. 6 = n. 4), the relative reduction is 40%. In contrast, as mortality in elderly patients is higher, the absolute reduction of mortality in "elderly" patients is higher (from n. 20 to n. 15 = n. 5), but the relative reduction is lower (25%). Therefore, the number of patients needed to be treated (NNT) to prevent an event is less in the elderly (100/20 = 5) when compared to adult ones (100/25 = 4).

## COMORBID/FRAIL ELDERLY

Frailty is currently defined "primary" or "pre-clinical" when the state is associated with a vulnerability state [28], and "secondary" or "clinical" when it is associated with known comorbility and/or disability [29]. The characteristics of clinical frailty include not only comorbility and disability but also polipharmacy and relative adverse drug reactions, hospitalization, health service utilization, age-associated sensory deficits, and lack of social support [30][31]. The concept of frailty helps to identify elderly patients most susceptible to adverse outcomes, such as loss of independence, hospitalization and death, alone and in association with chronic disorder such as chronic heart failure [32]. Very interstingly, it has been recently showed that the degree of clinical frailty

**Figure 3.** Elderly paradox (see text for the explanation).

is inversely related to TC in the elderly and the value less of 100 mg/dl is related to the highest frailty index (Fig. 4) [33]. Accordingly, as indicated before, several studies showed a "U" curve mortality-related total cholesterol indicating that very low and very high cholesterol levels are associated to higher mortality 7 [34-36]. In particular the concomitant presence of low blood pressure, low body mass index and low serum TC is associated with higher mortality in the elderly, leading to a new phenotype, i.e., "reverse metabolic syndrome" [37]. In contrast, in 2597 community-dwelling patients aged ≥ 65 years with a previous hospitalization for coronary artery disease assessed with the Multidimensional Prognostic Index (MPI), based on the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (SVaMA), higher 3-years mortality rate was associated with lower rates of statin treatment [38].

These findings, together with the lack of studies specifically evaluating the benefit of lipid-lowering therapy in severely frail older adults, may encourage the definition of controlled studies on the use of statins in this group of patients [39] [40].
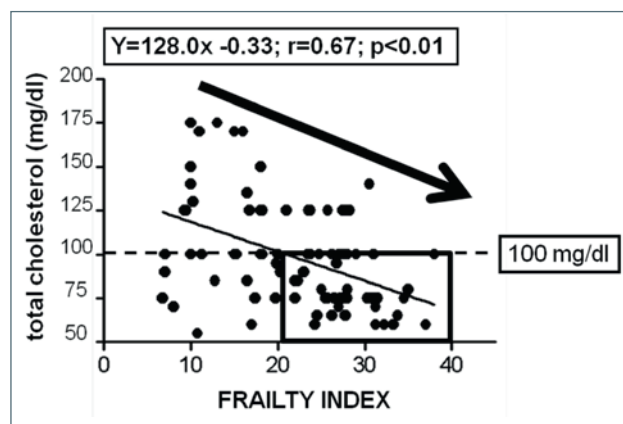


**Figure 4.** Total cholesterol is inversely realted to clinical frailty evaluated by "Frailty index" (from Abete et al., 2017, mod.) [33].

## CONCLUSIONS

- Statin therapy should be considered in older adults in primary prevention, particularly in the presence of cardiovascular high risk pattern (i.e., hypertension, smoking, diabetes and dyslipidemia);

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- treatment with statins is recommended for older adults in secondary prevention in the same way as for younger patients;
- at high dosage statins should be used with great caution since older people often have comorbidities that may determine the stop of the therapy (10%);
- particularly attention for older than 75 years and comorbid/frail elderly patients in whom evidence-based medicine is limited.

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