**MANAGEMENT OF DYSLIPIDEMIA IN THE ELDERLY**

**Elani Streja, Ph.D.,** Assistant Professor of Medicine, Division of Nephrology, Department of Medicine, Director of Outcomes Research, Harold Simmons Center for Kidney Disease, Research and Epidemiology, UC Irvine School of Medicine, Orange, Ca, Health Science Specialist, Tibor Rubin VA Medical Center, Long Beach, Ca, 101 The City Drive, City Tower, Suite 424, Orange Ca 92868, Email: estreja@uci.edu

**Dan A Streja, MD, FRCPC, FACP, FACE,** Clinical Professor, David Geffen School of Medicine at UCLA, Greater Los Angeles VA Healthcare System, West Los Angeles VA Medical Center, Division of Endocrinology, Diabetes and Metabolism, Building 500 Los Angeles, CA 90073, E-mail: dstreja@ucla.edu

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**ABSTRACT**

This chapter provides an overview of the important factors to be considered during the decision-making process of recommending a lipid lowering medication to an older patient. In the elderly age group, as in the younger age group, lowering of the concentration of cholesterol containing atherogenic particles via lipid lowering therapies, is effective in reducing cardiovascular risk. This chapter summarizes the current knowledge about the factors affecting the decision-making process in patients age 75 years and older, in whom there is no direct evidence of benefit for cholesterol lowering. In these patients, the clinician makes a recommendation to the patient and his/her family based on the evaluation of the risk of atherosclerotic versus non-atherosclerotic cardiovascular disease, comorbidity burden, quality of life, survival prognosis, lifestyle/socioeconomic status and presence of frailty. In this group, the ultimate decision for lipid altering therapy is based on the patient’s and the patient’s family preference. In this chapter, we present the clinical trial evidence and knowledge necessary for the evaluation of risk versus benefit for cholesterol lowering in the older elderly age group.

**INTRODUCTION**

The relationship between serum cholesterol and the risk of cardiovascular disease, particularly that lowering of serum cholesterol results in a reduction in cardiovascular morbidity ([1](#_ENREF_1)), has been known for over 35 years. During this time, multiple clinical trials have documented the cardiovascular benefit of treatment of hyperlipidemia with “lipid lowering drugs”. Nonetheless, elderly populations, which are at a greater risk of cardiovascular morbidity and mortality, are often excluded in lipid lowering therapy trials and consequently from the related guidelines. Therefore, when deciding on appropriate lipid management and cardiovascular risk prevention strategies for these elderly patients, clinicians are often left with individualizing the decision-making process while taking into consideration factors, such as patient preferences, comorbidity burden, and quality of life. In this chapter, we will review factors related to aging and elderly patients and how these factors can impact various lipoprotein levels, their associations with and predictability of mortality and cardiovascular outcomes in the elderly, guidelines related to marker levels and lipid altering therapies in the elderly, and safety considerations for these drugs in older patients. The definition of elderly population in the most recent Guideline on the Management of Blood Cholesterol ([2](#_ENREF_2)) is the group of subjects older than 75 years. This review will thereby outline the evidence of the benefit and also the risk of lipid lowering in the elderly patients of age 75 years or older. We believe the latter is essential information that clinicians should have and can be presented to the elderly patients and their respective families to allow them and to better assist them in making informed decisions regarding the best strategy for treatment.

**CHARACTERISTICS OF THE AGING PROCESS RELEVANT TO LIPID INTERVENTION**

The US population is aging. According to census projections, the population in Medicare age range (65 and older) is expected to more than double between 2012 and 2060, from 43.1 million to 92.0 million. The older population would represent just over one in five US residents by the end of the period, up from one in seven today ([3](#_ENREF_3)). In this segment of the population, cardiovascular disease is by far the main cause of mortality in both men and women.

Aging can increase the burden of atherosclerosis and other cardiovascular conditions. There is more than a doubling of the prevalence of peripheral arterial disease (PAD), cerebrovascular disease, and abdominal aortic aneurism with each decade of life ([4](#_ENREF_4)). In atherosclerosis, the vascular wall is continuously remodeled until culmination in the final stage of calcification. A study using intravascular ultrasound has documented that in young survivors of myocardial infarction (MI), the culprit vessel undergoes constrictive remodeling (shrinkage), usually associated with plaque erosion, while in older subjects expansive remodeling (enlargement) predominates ([5](#_ENREF_5)). Expansive vascular remodeling can result in increased irreversible arterial stiffness, particularly in calcified vessels and in fibrotic plaques ([6](#_ENREF_6)). In this condition, the likelihood for a cardiovascular event attributed to a ruptured plaque decreases, but the likelihood of the event being related to increased arterial stiffness increases. Although lipid lowering is statistically successful, its success may depend on the pathology of the arterial wall. The current belief is that the main mechanism of action of lipid lowering drugs is through the stabilization of atherosclerotic plaques. It is therefore conceivable that in older patients with advanced atherosclerosis, lipid intervention might be less successful.

Aging is also associated with changes in social-economic status which increase the risk of heart disease and may constitute barriers to effective cardiovascular prevention. Among seniors age 80 and older, 11.4 percent lived in poverty, compared with 8.2 percent of seniors age 65 to 69. More women than men (2.8 million vs. 1.6 million men , respectively) age 65 and older were living at or below the poverty threshold ([7](#_ENREF_7)). Asians and Hispanics are twice as likely to live in poverty as Non-Hispanic Whites, and African-Americans are three times more likely. In addition, social isolation is a risk factor characteristic for the older age group, since one third of the women age between 65 and 74, and half of the women 75 years or older live alone. In couples, disability of one spouse places the other spouse into the position of caregiver, which can result in an increase in cardiovascular risk for the latter ([8](#_ENREF_8)). Health problems are frequently compounded by the occurrence of cognitive impairment affecting the understanding of the concept of preventive health care. All these socio-economic factors can contribute to increased burden and limitations in access to healthcare and therapeutic modalities in older age groups.

**CHANGES OF LIPOPROTEINS WITH AGING**

Across all age groups, total cholesterol, low density lipoprotein cholesterol (LDLc) and triglycerides (TG) increase with age, and reach a peak in men age 50-59 and in women age 60-69 years. ([9](#_ENREF_9),[10](#_ENREF_10)). With increasing age, the total cholesterol, apolipoprotein B (ApoB), and the prevalence of small dense LDL and TG concentration increases. In addition, lipoprotein kinetics studies have shown a decrease in fractional clearance rate of very low-density lipoprotein cholesterol (VLDLc), intermediate density lipoprotein cholesterol (IDLc) and LDLc-Apo B, as well as an increase in VLDLc-Apo B production in older patients and patients with metabolic syndrome of all ages([11-15](#_ENREF_11)).

High density lipoprotein cholesterol (HDLc) does not seem to vary with age in men and postmenopausal women ([10](#_ENREF_10)). Menopause but not age has an impact on the concentration of HDLc and HDLc subfractions ([16](#_ENREF_16)). Aging has, however, an effect on HDL function since the HDL collected from older subjects has diminished cholesterol efflux capacity ([17](#_ENREF_17)). While the concentration and or the function of these lipoproteins changes with age, the average lipoprotein (a) [Lp(a)] level seems to be unchanged but it is higher in older women than in men ([18](#_ENREF_18)).

In addition to these changes detectable in fasting state, aging induces significant changes in postprandial lipemia. After ingestion of a fatty meal, the peak and area under the curve for serum TG is higher in older patients and higher in men than in women ([19](#_ENREF_19)). These data were confirmed using a meal containing retynyl palmitate and squalene as markers of postprandial lipoprotein metabolism ([20](#_ENREF_20)). The peak concentration of retynyl palmitate and of squalene were markedly delayed in older subjects. The authors attributed their findings as indicating an impairment of the removal mechanism occurring with aging. In keeping with this concept, when an emulsion containing labeled cholesterol was injected intravenously, the fractional catabolic rate was found to be age dependent with a marked prolongation of the removal in elderly subjects ([21](#_ENREF_21)). The effect of age on postprandial lipoprotein metabolism is attenuated in elderly who are physically active ([22](#_ENREF_22)). Walking solely during the postprandial phase had an attenuating effect only in some studies ([23](#_ENREF_23)) but not in others ([24](#_ENREF_24)). The increase in postprandial atherogenic particles with aging is believed by some authors to be mediated by the increase in prevalence of metabolic syndrome ([25](#_ENREF_25)). The pathophysiological mechanisms have been extensively reviewed ([26-28](#_ENREF_26)). In summary the primary defect seems to be a decreased uptake of chylomicrons resulting in an accumulation of postprandial lipoproteins as well as endogenously produced VLDL particles competing for the same removal sites. Hormonal changes contribute to the dysregulation of this mechanism.

# Table 1 shows the average total cholesterol and TG in the older age groups in the most recent National Health and Nutrition Examination Survey (NHANES) ([29](#_ENREF_29)), which demonstrates a decrease in the average concentration of cholesterol and TG in individuals over 75 when compared with individuals age 60 to 65 years..

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| **Table 1. Average Lipoprotein Levels in the US in NHANES 2018-2019** |
|  | **Age 60-65** | **Age 65-70** | **Age 70-75** | **Age over 75** |
| Total Cholesterol | 202+/- 44 | 197+/- 44 | 194+/- 44 | 192+/- 45 |
| Triglycerides | 166+/- 133 | 158+/- 101 | 154+/- 89 | 153+/- 122 |

Data as Mean +/- Standard Deviation

**Factors Effecting Lipid Levels in Older Individuals**

In 2007, a seminal publication by Kalantar-Zadeh et al ([30](#_ENREF_30)) reviewed the risk factor paradox in wasting diseases and classified old age as a wasting disease. Poor socioeconomic status/malnutrition, frailty, and comorbidity explain in part this classification. In addition, drug therapy and attrition contribute to the lower average cholesterol and TG in a large segment in the very old. The changes in cholesterol occurring in the very old are statistically associated with nutritional changes ([31](#_ENREF_31)) or weight changes ([32](#_ENREF_32)) but changes in behavior, weight, medication or comorbidity cannot explain them completely ([33](#_ENREF_33),[34](#_ENREF_34)). Lipid lowering drugs are also more likely to be used in older patients but only 27% of the decrease of atherogenic lipoproteins in the elderly can be accounted for by an increased frequency of statin therapy in these patients ([35](#_ENREF_35)).

SOCIOECONOMIC FACTORS/MALNUTRITION

Socioeconomic factors/malnutrition contribute to changes in lipoproteins in the elderly. Once medical care and other costs of living are factored in, the number of people 65 and older living in poverty jumps to 16.1 percent, according to a new Census Bureau analysis ([36](#_ENREF_36)). Of these, 41.6% reported not having natural teeth. As measured by the Healthy Eating Index, only 9% of poverty level elderly adults over age 65 years have a “good” rating for healthy eating.

METABOLIC SYNDROME

Most studies have shown that the prevalence of metabolic syndrome increases with aging ([37-41](#_ENREF_37)). In the 60-69 years age group, the prevalence of metabolic syndrome approaches 50% of the age-specific population, with the highest prevalence in Hispanic and Non-Hispanic Black women. The increased prevalence of metabolic syndrome in the elderly is not associated with changes in energy intake, but rather with decreases in energy expenditure, which in turn is associated with changes in body composition and decreased functionality ([42-45](#_ENREF_42)). In addition, the trends towards the reduction of body weight seen in longitudinal studies of elderly subjects are associated with a disproportionate reduction in lean body mass, further decreasing the ability for the body to function ([46](#_ENREF_46)). The results of this process is the occurrence of frailty which is the biological equivalent of the wasting syndrome observed in other conditions.

As related to the increased prevalence of metabolic syndrome, there is an increased prevalence of diabetes in the elderly, consequent to an increase in intra-abdominal fat, since the prevalence of disorders of carbohydrate metabolism does not increase with age after adjustment for visceral obesity ([43](#_ENREF_43)). The presence of diabetes with suboptimal glycemic control results in abnormalities of lipoproteins of the same type as those of metabolic syndrome, but much more severe, in proportion to the degree of hyperglycemia.

FRAILTY

Frailty is a syndrome associated with aging and increases with age. It is usually also associated with a lowering of total, LDL and non-HDL cholesterol (non-HDLc) ([47](#_ENREF_47),[48](#_ENREF_48)). The current definition is referred to as the “Fried phenotype” and comprises three or more of: unintentional weight loss, self-reported exhaustion, weakness (reduced grip strength), slow walking speed, and low physical activity([49](#_ENREF_49)). Low cholesterol and high inflammatory markers are associated with frailty in older subjects, and low cholesterol precedes the development of disability features characteristic to the frailty phenotype ([50-52](#_ENREF_50)). Inflammatory marker levels are positively correlated with the number of features of the Fried phenotype ([53](#_ENREF_53)). Elevation of labels of inflammatory markers precedes the occurrence of the Fried phenotype in a large number of cohorts of elderly patients ([54-60](#_ENREF_54)).

ATTRITION

Attrition contributes the national decreases in atherogenic particles observed in older age groups by selecting survivors in the older population groups with lower levels of major risk factors. Consequently, the prevalence of severe familial dyslipidemias diminishes in the older age groups. However, the decreases in the concentration of atherogenic particles cannot be entirely attributed to attrition, since these decreases are also reported in prospective long-term observation of patients ([32](#_ENREF_32)).

ILLNESS

Some of the changes in cholesterol concentration occurring in presence of a fatal illness remain unexplained since they seem to precede the diagnosis. In lymphoma patients the cholesterol level shows a steep decline three to four years prior to the diagnosis of the malignancy ([61](#_ENREF_61)). In a population of patients age 80 to 105 years the authors observed a steep decline in serum cholesterol in the two years preceding death, irrespective of the cause of death ([62](#_ENREF_62)). Similarly, in the Korean National Health Insurance Service Cohort, patients who had a decrease in serum cholesterol over an average follow up of eight years were more likely to die ([63](#_ENREF_63)). This observation remained significant after adjustment for all available confounders and after elimination of patients who died within the first two years from the index date. Inflammation seems to be an important factor associated with the cholesterol lowering process. In Finnish nonagenarians, the levels of interleukin 6 (IL-6) and C-reactive protein (CRP) were negatively correlated with LDLc and non-HDLc levels ([64](#_ENREF_64)). In hospitalized patients age 80 years or older, serum total cholesterol and LDLc are negatively associated with CRP and positively associated with prealbumin, indicating that both malnutrition and inflammation are determinants of the low serum cholesterol levels observed in this age group ([65](#_ENREF_65)). This relationship could not be detected in younger healthy controls. In the Aging and Longevity in Sirente Study, LDLc strongly correlated with CRP in patients over 85 years ([66](#_ENREF_66)). In the Cardiovascular Health Study declining cholesterol levels were associated with male gender, weight loss, and white blood cell count, another marker of inflammation, but not with CRP levels ([67](#_ENREF_67)).

SUMMARY

These data seem to confirm the hypothesis of decrease in cholesterol level as being a part of aging is analogous with the decrease in cholesterol observed in wasting disease.

The pathophysiological mechanism by which the cholesterol concentration is diminished seems to be a decrease in cholesterol absorption associated by a lack of a compensatory increase in cholesterol synthesis and these changes are a predictor of mortality in the very old ([68](#_ENREF_68),[69](#_ENREF_69)).

**LIPOPROTEINS AND CARDIOVASCULAR MORTALITY OR ALL-CAUSE MORTALITY IN THE VERY OLD**

**Cholesterol**

Cholesterol concentration decrease has been found to precede death or fatal illnesses therefore it is logical to assume that a high level of cholesterol, which is a marker of increased risk of cardiovascular events and death in middle aged patients is no longer a reliable risk predictor in the very old.

The association of low cholesterol and mortality in absence of fatal illness was first reported in an attempt to find markers of decreased survival in nursing home patients ([70](#_ENREF_70),[71](#_ENREF_71)). This association seems to be confined to the elderly with a low activity level, indicating that a functional deterioration may be associated ([72](#_ENREF_72)). The investigators of the Framingham Study reported that the relationship between total cholesterol level and all-cause mortality was positive at age 40 years, negative at age 80 years, and negligible at ages 50 to 70 years ([73](#_ENREF_73)). In the Whitehall Study, subjects in lower employment grades, with disease at baseline, with a history of recent unexplained weight loss, or who had been widowed, largely accounted for the relationships between lower cholesterol level and non-cardiovascular mortality ([74](#_ENREF_74)).

In another study, in patients age 85 years or older, there was a 15% decrease in mortality for each 1mM/L cholesterol increase, largely explained by non-cardiovascular mortality causes ([75](#_ENREF_75)). In a Kaiser Permanente study, the risk of hospitalization for respiratory diseases in men age 55 to 89 free of chronic lung disease decreased 20% for each increase of serum cholesterol by one standard deviation ([76](#_ENREF_76)). In the European Working Party on High Blood Pressure in the Elderly Study, serum cholesterol at baseline was inversely associated with total, non-cardiovascular and cancer mortality over follow-up in elderly hypertensive subjects ([77](#_ENREF_77)). The association between low cholesterol with non-cardiovascular mortality in elderly populations was confirmed by numerous cohorts ([78-83](#_ENREF_78)).

Longitudinally documented decreases in cholesterol concentration have been associated with increased cardiovascular mortality in the elderly ([84](#_ENREF_84)). It is particularly obvious in patients with low activity level ([72](#_ENREF_72)). The association of low cholesterol and mortality is weakened after a longer duration of follow-up ([72](#_ENREF_72),[85](#_ENREF_85)). It is not present in patients treated with lipid lowering drugs ([86](#_ENREF_86)) In some studies the authors reported that the association is weaker in women ([87](#_ENREF_87)) or stated that low cholesterol in women is not associated with mortality but rather that high cholesterol is protective ([88](#_ENREF_88)). Rate of cholesterol decline was associated with increased risk of cardiovascular mortality in a large Finnish cohort ([89](#_ENREF_89)).

There are inherent difficulties in assessing coronary disease risk in healthy patients over age 75 years. Studies have shown that the predictive power of cardiovascular risk calculators diminishes in elderly patients. Most calculators include age, gender, cholesterol, HDLc, systolic blood pressure, treatment of hypertension and smoking. These equations were tested in different populations and their predictive validity was found to decline with age. In the Rotterdam study, the use of the Framingham score to predict occurrence of a first coronary event in elderly subjects resulted in gross underestimation, worsening with increasing age and more in men than in women ([90](#_ENREF_90)). In the Leiden 85-Plus study, in healthy patients over age 85 years, the Framingham score did not predict cardiovascular death ([91](#_ENREF_91)). A meta-analysis of the relationship between total cholesterol and coronary events shows a significant association for men age 65 to 80 years, but none for women over 65 years or for men over 80 years ([92](#_ENREF_92)). Sussman et al ([93](#_ENREF_93)) have attempted to calibrate different equations to predict cardiovascular events in US veterans. The authors concluded that all available equations overestimate risk and generated a “VA-Risk Score-CVD” which was well calibrated. Cholesterol was included in the calculations along with an interaction factor: cholesterol X age.

Conversely, multiple studies have shown that elevated cholesterol in mid-life predicts coronary death in old age ([94-96](#_ENREF_94)). The concept of “life-time risk of a coronary event” ([97](#_ENREF_97)) was reported in 2003 and was introduced in the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol ([98](#_ENREF_98)), in order to assist difficult decisions concerning the need for statin therapy. The estimate of lifetime risk by elevated cholesterol is consistent across gender and race ([99](#_ENREF_99)). However, in clinical practice this approach is very seldom useful for decision making in the elderly because of the absence of long-term historical data on cholesterol in individual patients over his or her lifetime.

**Triglycerides**

Triglycerides are associated with cardiovascular risk in all age cohorts ([100](#_ENREF_100)). A meta-analysis including cohorts from 29 Western countries and 262,525 participants showed that the top quintile of serum TG had a 72% higher cardiovascular risk compared to the lowest quintile, with a very robust level of statistical significance ([101](#_ENREF_101)). A similar study including 96,224 participants from the Asia-Pacific region reported for the highest TG quintile, a 80% increase in the risk of coronary events, a 70% increased risk of coronary death and a 50% increased risk of stroke ([102](#_ENREF_102)). In large real-world cohorts high TG were associated with an increased risk of myocardial infarction, stroke and revascularizations in statin treated patients ([103](#_ENREF_103),[104](#_ENREF_104)). In very old patients, however, a paradoxical association similar to the one observed for cholesterol is observed for TG. In 930 Chinese oldest old (mean age 94.0 years) the authors reported that for each 1mmol/L increase in TG there was 21% lower 5-year all-cause mortality in fully adjusted models ([105](#_ENREF_105)). In another study TG were associated with recurrent stroke with hazard ratios of opposite directionalities in younger and older patients ([106](#_ENREF_106)).

**HDL Cholesterol**

HDL cholesterol is a powerful lipid predictor of cardiovascular risk in middle-age men and women. Subjects with high HDLc are more likely to achieve greater longevity ([107](#_ENREF_107),[108](#_ENREF_108)). Moreover, healthy subjects over age 80 years have higher HDLc levels compared with middle-age subjects. In centenarians and near-centenarians in Hong-Kong the only biological marker of “successful aging” was a high HDLc ([109](#_ENREF_109)). Successful aging was measured on four scales: 1) physical and functional health, 2) psychological well-being and cognition, 3) social engagement and family support, and 4) economic resources and financial security. Cholesterol efflux capacity, the main method used to explore the function of high density lipoprotein (HDL) was not associated with the burden of atherosclerosis determined as coronary calcium score in very old, cardiovascular event-free subjects ([110](#_ENREF_110)).

Cohort studies have documented the fact that HDLc loses much less of its predictive power with advancing age, as compared to LDLc. In the Cardiovascular Health Study, low HDLc was the only lipoprotein associated with the risk of MI ([111](#_ENREF_111)). In the Honolulu Heart Study, low HDLc was a powerful predictor of non-hemorrhagic stroke ([112](#_ENREF_112)). In the Leiden 85-Plus Study, subjects in the lower tertile of low HDLc had 2 times the risk of coronary death and 2.6 times the risk of fatal stroke when compared with those in the upper tertile ([75](#_ENREF_75)). In this older age group, HDLc is also a predictor of total mortality. In nursing home residents, low HDLc and low albumin were proposed as a means to diagnose frailty and predicted a 2.5 to 4 fold increase in short term mortality ([113](#_ENREF_113)). Since frailty is associated with both low HDLc and low total cholesterol, the ratio of these parameters was proposed to predict cardiovascular events in elderly subjects. In an analysis of the data of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) Study, the investigators reported that low HDLc in elderly patients predicts the risk of fatal and non-fatal coronary events and stroke as well as predicts the benefit of statin therapy ([114](#_ENREF_114)).

Although a high HDLc is considered to be a marker of decreased risk of cardiovascular events, paradoxical associations of very high HDLc with increased total mortality have been reported in the general population ([115](#_ENREF_115),[116](#_ENREF_116)) and in some patient groups with specific comorbid conditions ([117](#_ENREF_117),[118](#_ENREF_118)).

**Apolipoproteins**

ApoB and Apolipoprotein A1 (ApoA1) are important predictors of cardiovascular risk and some studies have reported that they might even be superior to the measurement of standard lipid parameters even in patients age over 70 years ([119](#_ENREF_119)). In 77-year-old men in the Uppsala Longitudinal Study, low ApoA1 concentration was the best predictor of coronary death ([120](#_ENREF_120)). The measurement of ApoB is included as an alternative target for lowering with statins in the guidelines (if ApoB ≥130 mg/dL) and is particularly useful in patients with hypertriglyceridemia since it helps determining whether the patient’s hypertriglyceridemia is an atherogenic condition ([2](#_ENREF_2)).

Apolipoprotein E (ApoE) isomorphs were shown in 38,537 participants from six European population-based cohorts to be predictors of mortality risk in the elderly ([121](#_ENREF_121)). During a mean follow-up of 11.7 years, compared with homozygous ApoE-ε3 carriers, ApoE-ε2 carriers were at lower risk of death, whereas ApoE-ε4 carriers were at increased risk of death. These differences were statistically highly significant. ApoE was associated with mortality risk in a dose-dependent manner, with risk estimates lowest for homozygous ApoE-ε2 and highest for homozygous ApoE-ε4. In the Leiden 85-Plus Study, ApoE concentration was documented to be a powerful predictor of cardiovascular death, independent of ApoE genotype and lipid levels ([122](#_ENREF_122)).

**Lipoprotein (a)**

Lipoprotein (a) [Lp(a)] has a molecular structure consisting of a molecule of ApoB covalently bond to a specific apolipoprotein referred to as Apo(a) which has varying sizes. Lp (a) has recently emerged as a powerful predictor of coronary artery disease ([123](#_ENREF_123)) and cardiovascular mortality ([124](#_ENREF_124),[125](#_ENREF_125)). This association is particularly striking in Latin Americans and South Asians ([126](#_ENREF_126)) and in statin treated patients ([127](#_ENREF_127)). Lp(a) was shown to be a risk factor for coronary heart disease and stroke by epidemiologic studies ([128](#_ENREF_128)) and by Mendelian Randomization ([129](#_ENREF_129)) and genome-wide association studies ([130](#_ENREF_130)). The findings provide support for a causal role of Lp(a) in coronary disease. In the elderly, elevated Lp(a) continues to be associated with increased cardiovascular risk. In the PROSPER Study, after adjustment for baseline risk factors there was a statistically significant association between baseline Lp(a) and the risk of the primary endpoint (coronary heart disease death, non-fatal MI and fatal or non-fatal stroke) ([18](#_ENREF_18)). In the Italian Longitudinal Study on Aging, compared with those in the lowest tertile, subjects in the highest tertile of Lp(a) had a significantly higher fully adjusted risk of non-fatal CAD ([131](#_ENREF_131)). In the area of Cremona (Lombardy, Italy), in patients age greater than 65 years, a Lp(a) ≥ 30 mg/dl predicted coronary heart disease and stroke mortality over a median of 6.3 years of follow-up([132](#_ENREF_132)). In the Cardiovascular Health Study, the risk of stroke increased 3 times, the risk of coronary death increased 2.5 times and that of death from all causes twice, if the participant was in the higher quintiles of Lp(a) ([133](#_ENREF_133)). In 3251 high-risk Medicare patients from this study, over a 22.5-year follow-up, the Lp(a) upper tertile (>65 mg/ml) predicted cardiovascular disease and total mortality. There was also a graded increase in healthcare cost with increasing Lp(a) levels ([134](#_ENREF_134)). In the Northern Manhattan Stroke Study, elevated Lp(a) levels were independently associated with increased stroke risk with a significant linear dose-response relationship, suggesting that Lp(a) is a risk factor for ischemic stroke, across white, Black and Hispanic race/ethnic groups ([135](#_ENREF_135)). In Greek patients over age 70 years, multivariate logistic regression analysis showed a significant association of acute ischemic stroke with Lp(a) levels and small Apo(a) isoform size ([136](#_ENREF_136)). In this study, compared to subjects with Lp(a) levels in the lowest quintile, those within the highest quintile had a 3.2-times higher adjusted risk of having an acute ischemic stroke. Finally, in a cross-sectional study of patients enrolled in INCHIANTI, after adjustment for potential confounders, participants in the highest quartile of the Lp(a) distribution (≥ 32.9 mg/dl) were 3.8 times more likely to have PAD defined as an ankle-brachial index (ABI) <0.70 compared to those in the lowest quartile ([137](#_ENREF_137)).

In exploring the pathophysiology of this association in elderly patients, Lp(a) is an independent determinant of aortic stiffness ([138](#_ENREF_138)) and is associated with hypoechoic carotid lesions, which correspond histologically to lipid-rich, unstable plaques ([139](#_ENREF_139),[140](#_ENREF_140)). Calcific aortic stenosis is a condition of the elderly that increases in prevalence with age and elevated Lp(a) is associated with increased calcification of the valve ([141](#_ENREF_141)) and severity of the calcific stenosis ([142](#_ENREF_142)).

Paradoxically, however, centenarians have higher levels of Lp(a) when compared with younger elderly groups ([143](#_ENREF_143),[144](#_ENREF_144)). This indicates a lack of effect of attrition in patients with elevated Lp(a).

**GUIDELINE RECOMMENDED RISK ENHANCERS TO BE CONSIDERED AND THEIR USE IN THE ELDERLY**

The 2018 Guideline on the Management of Blood Cholesterol ([2](#_ENREF_2)) states: “In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy.Risk-enhancing factors include family history of premature atherosclerotic cardiovascular disease (ASCVD); persistently elevated LDLc levels ≥160 mg/dL (≥4.1 mmol/L); metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (e.g., South Asian); persistent elevations of TG ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, ApoB ≥130 mg/dL, high-sensitivity CRP ≥2.0 mg/L, ABI <0.9 and Lp(a) ≥50 mg/dL or 125 nmol/L, especially at higher values of Lp(a)” The authors of the guideline also add “if a decision about statin therapy is uncertain, consider measuring coronary artery calcium (CAC)” placing the CAC score (CACS) determination as a very important factor in the decision making process. We will review the validity of these enhancers in the elderly.

**Family History**

Traditionally, cardiovascular family history is focused on premature onset of atherosclerosis, at age <55 years in men and <65 years in women. In elderly patients, due to attrition, the likelihood of encountering patients with familial disorders associated with premature cardiovascular events diminishes, and because of this, obtaining an adequate family history is usually neglected. There are, however, two distinct situations in which family history could assist decision making concerning primary prevention of cardiovascular events through treatment of dyslipidemias: family history of disorders expressing themselves at an older age such as PAD and stroke as risk-enhancers and a family history of longevity as a risk-lessener.

In the San Diego Population Study, in fully adjusted models, family history of PAD was associated with significantly higher odds of PAD, and even stronger odds for severe PAD ([145](#_ENREF_145)). Studies in monozygotic and dizygotic twins indicated that 48% of the observed variability in ABI values could be attributed to additive genetic effects ([146](#_ENREF_146)). Since PAD onset is more likely to occur in an older person, a positive family history can assist the decision to treat hyperlipidemias.

Similarly, stroke occurs at an older age, particularly in non-Hispanic whites, and is characterized by a strong inheritance. The role of family history in estimating stroke risk has been extensively studied, but there is no study addressing it in patients age 70 years and older ([147](#_ENREF_147)). The evidence of inheritance of cerebrovascular disease risk pertains to thrombotic or hemorrhagic stroke, but not thromboembolic stroke ([147](#_ENREF_147),[148](#_ENREF_148)). Inheritance of stroke risk increases with the number of relatives affected ([147](#_ENREF_147)) and might be attributable to the genetic predisposition to hypertension ([148](#_ENREF_148)).

Parents of centenarians have a seven fold higher likelihood of having lived in their nineties, and the offspring of long living parents often seem to have a favorable risk factor profile for cardiovascular disease ([149](#_ENREF_149),[150](#_ENREF_150)). The offspring also seem to have better cognitive performance in middle age ([151](#_ENREF_151)). In a study comparing cardiovascular risk between offspring of nonagenarian siblings and their spousal partners (non-nonagenarian sibling offspring), the presence of a nonagenarian sibling parent seems to confer a protective effect for mortality, cardiovascular events and cardiovascular risk factors ([152](#_ENREF_152)). The Asklepios Study additionally introduced the “extended family history definition”, which takes into account later onset of disease, second-degree relatives and number of affected relatives when collecting a family history of disease ([153](#_ENREF_153)). The authors pointed that absence of cardiovascular disease (including late onset) in any first-degree relative is a significant negative predictor of atherosclerosis. This nontraditional way of assessing the family history is far from being incorporated into the guidelines.

Genetic testing for precision medicine is in its infancy and longevity genes have been described but the effect is relatively small ([154](#_ENREF_154)). Most likely, longevity is polygenic, attributable to synergistic effects of multiple genes. In a recent meta-analysis, genetic variations associated with exceptional longevity were noted in populations with very different genetic backgrounds ([155](#_ENREF_155)). The authors concluded that a systems-based approach will be necessary to discover the synergistic and antagonistic effects of these many gene variants and their roles in extending lifespan and health-span.

**Chronic Kidney Disease (CKD)**

Chronic kidney disease (CKD) is a progressive and irreversible condition associated with a high risk of cardiovascular (CV) morbidity and mortality, and a marked increase in healthcare expenditures ([156](#_ENREF_156)). Kidney Disease: Improving Global Outcomes (KDIGO) defines clinical CKD by an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m2 or lower, or an albumin creatinine ratio (ACR) of 30 mg/g or higher ([157](#_ENREF_157)). The 2016 ACC guideline introduced CKD as a criteria for classification in a higher risk group, requiring a more aggressive cholesterol lowering intervention with a lower target of LDLc ([158](#_ENREF_158)) and this was maintained in the 2018 guideline ([2](#_ENREF_2)). Presence or absence of CKD was the only option given for estimating the level of risk. For the elderly, there is, however, doubt that the KDIGO definition of CKD selects a patient at higher risk. Renal function slowly decreases with age as a normal biological phenomenon ([159](#_ENREF_159)). Although this process is associated with loss of nephron mass and a process of sclerosis of glomeruli and arterial walls, it is not necessarily a manifestation of disease but rather part of the process of senescence. A modest, persisting reduction of eGFR (around 45-59 ml/min/1.73 m2) without abnormal protein­uria does not seem to confer much of an adverse effect on mortality and remain­ing life expectancy in older adults ([160](#_ENREF_160)). Delanaye et al ([161](#_ENREF_161)) have proposed an age adjusted equation for defining CKD and defined CKD in patients over age 65 years without increased ACR by an eGFR of 45 ml/min/1.73 m2 or lower. In a large community study of patients age over 75 years in the United Kingdom ([162](#_ENREF_162)), there was a graded and independent increase in all-cause and cardiovascular mortality risk with declining eGFR below 45 ml/min/1.73 m2 but not in the group witheGFR 45-60 ml/min/1.73 m2

The risk of cardiovascular death is increased by the presence of CKD irrespective of the eGFR threshold below which the patient is considered to have it, or of age and of type of population included in the cohort ([163](#_ENREF_163)). Presence of CKD in elderly patients is also associated with a significantly increased risk of stroke ([164](#_ENREF_164)), PAD ([165](#_ENREF_165)) and hospitalizations ([166](#_ENREF_166)) irrespective of the presence or severity of traditional cardiovascular risk factors. In most cohorts studied, the associations of most traditional risk factors with cardiovascular disease were minimal in the oldest old, whereas diabetes, eGFR, CRP, and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) were associated with cardiovascular disease across older age strata ([167](#_ENREF_167)). However, the relative mortality risk with moderate CKD decreases with age ([168](#_ENREF_168)). The rate of decline of eGFR is also a predictor of heart failure, MI and PAD after adjustment for baseline renal function ([169](#_ENREF_169),[170](#_ENREF_170)).These associations are gender dependent with women having a slower decline in GFR and a better patient and renal survival ([171](#_ENREF_171)).

Elevated ACR is associated with an increased risk of cardiovascular and all-cause mortality in all age groups from 68 to 102 years independently from eGFR ([172](#_ENREF_172)). Bansai et al ([173](#_ENREF_173)) attempted to calculate a prediction equation for risk of mortality in very old patients. The final model for 5-year mortality risk included eGFR, urine albumin-to-creatinine ratio in addition to traditional risk factors (age, sex, race, smoking, diabetes mellitus) and comorbidity (history of heart failure and stroke).

**Chronic Inflammatory Disorders**

Although many studies have shown an increased risk of cardiovascular events in patients with chronic inflammatory disorders, to date there is no study that specifically addresses this association in elderly patients. In a large study, using the data released by the National Board of Health and Welfare and Statistics Sweden, the authors reported that 20 and 15 of the 32 inflammatory disorders studied, respectively, were associated with an increased risk of ischemic and hemorrhagic stroke during the follow-up ([174](#_ENREF_174)). Sixty three percent of patients were age over 70 years. Although the strength of the association declined as the patients aged, the data showed a statistically significant increase in ischemic stroke after ten years follow-up for patients with psoriasis, rheumatoid arthritis, autoimmune thyroiditis, polymyalgia rheumatica, and pernicious anemia. In a similar study, the same group using the same database reported on the incidence of coronary events ([175](#_ENREF_175)). At ten years follow up, the increased risk was significant for ankylosing spondylitis, Bechet’s disease, autoimmune thyroiditis, discoid lupus, pernicious anemia, polymyalgia rheumatica, polymyositis, psoriasis, rheumatoid arthritis, Sjogren’s syndrome, systemic sclerosis, and Wegener’s granulomatosis. These data are convincing enough to bring in discussion the coexistence of these morbidity when discussing risk in primary prevention in patients age over 75 years.

**C Reactive Protein (CRP)**

As mentioned above, CRP is a very commonly used indicator of inflamamtion. Multiple meta-analyses have documented the powerful ability of high sensitivity CRP (hsCRP) in predicting risk, and studies have documented the benefit of targeting hsCRP when titrating statin therapy in high-risk patients. A set of engines for predicting cardiovascular risk in women and men included this measurement ([176](#_ENREF_176),[177](#_ENREF_177)). The engines were recommended for use up to age 79 years. The Cardiovascular Health Study has documented that hsCRP remains a powerful predictor of 10-year coronary disease risk in participants over age 65 years, independent of any other known risk factor ([178](#_ENREF_178)). The risk of total mortality is even stronger when participants have other elevated inflammatory markers ([179](#_ENREF_179)). The risk appears to be higher for the immediate outcomes rather than for the remote future. hsCRP has been associated with the burden of atherosclerosis documented as decreased ABI, increased carotid intima-media thickness and vascular calcifications ([180](#_ENREF_180)).

There are two reasons why there is resistance to the use of hsCRP as a predictive marker in the elderly. Studies have shown that hsCRP testing provides only a modest contribution to reclassification of risk when added to traditional risk factors ([181-185](#_ENREF_181)). The second reason is the progressive loss of specificity of hsCRP as a cardiovascular risk marker, which occurs with aging, frailty and comorbidity.

**Coronary Artery Calcium Score**

The 2010 ACC Foundation (ACCF)/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults recommended the use of Computed Tomography (CT) for CACS in cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10-year risk) and intermediate risk (10% to 20% 10-year risk) and the current guideline strongly supports this recommendation ([2](#_ENREF_2)).

In older patients, CACS is a powerful predictor of mortality. In a cohort of patients age over 80 years, compared to a CACS of 0 to 10, patients had a 6.3 times higher risk of death for a CACS of 11 to 100, 5.3 times higher for a CACS of 100 to 400 and 11.7 times higher for a CACS over 400 ([186](#_ENREF_186)). Vascular calcification noted in routine Xrays is not a specific marker for coronary events in this age group. In the Study of Osteoporotic Fractures, of 9,704 Caucasian women age 65 years or more, 2,056 had aortic calcifications ([187](#_ENREF_187)). Over 13 years follow up, calcifications were associated with a higher risk of not only cardiovascular death, but also cancer death (after multivariate adjustment) and non-cardiovascular, non-cancer death. In elderly women enrolled in the Cardiovascular Health Study, CACS was also associated with gait speed ([188](#_ENREF_188)), while low gait speed is also a marker of frailty ([49](#_ENREF_49)). In the Multiethnic Study of Atherosclerosis (MESA), the authors selected a group of elderly according to the criteria of enrollment in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial (JUPITER) ([189](#_ENREF_189)). Approximately 47% of this MESA JUPITER population had CACS=0, and coronary heart disease event rates in this group were <1 per 1000 person-years. Over 2/3 of all coronary heart disease events occurred in the 25% of participants with CACS >100 (20.2 per 1000 person-years). In patients age over 80 years, CAC is a determinant of mortality, dementia and coronary artery disease ([190](#_ENREF_190)). In the Pittsburgh Field Center of the Cardiovascular Health Study, of patients over 70 years, CACS was a predictor of stroke, coronary artery disease and cardiovascular disease ([191](#_ENREF_191)). In the prospective Rotterdam Coronary Calcification Study, a markedly graded association was found between coronary calcification and stroke (average age 71 years) ([192](#_ENREF_192)).

The correlation between CACS and CRP is modest. In the Prospective Army Coronary Calcium Study, there was no correlation between CRP and CACS ([193](#_ENREF_193)). In MESA, inflammatory markers were weakly associated with CAC presence and burden. The authors believed that their data support the hypothesis that inflammatory biomarkers and CAC reflect distinct pathophysiology ([194](#_ENREF_194)). Using intravascular ultrasound, Kubo et al showed that CRP was associated with the size of the necrotic core of the plaque, but not with the the percentage of dense calcium, fibrofatty tissue, and fibrous tissue ([195](#_ENREF_195)). In appropriately selected asymptomatic patients, the absence of CAC predicts excellent survival with a 10-year event rate of approximately 1% ([196](#_ENREF_196)). In view of this, the unanswered question is whether atherogenic particle lowering in elderly with high CACS will be successful in preventing events.

The CACS test has no widespread use, probably because of the fear of radiation exposure and its cost. However CT calcium scoring produces the same amount of radiation as 1 to 2 mammograms performed on each breast ([197](#_ENREF_197)) and the cost in the elderly appears to be acceptable. In a study including two cohorts of asymptomatic individuals totaling over 35,000 subjects, and after adjustment for age, gender, ethnicity, hypertension, hyperlipidemia, diabetes, smoking and family history, CACS remained a strong predictor of mortality at 5 years and 12 years follow-up ([198](#_ENREF_198)). Progression of CAC is a powerful predictor of events in untreated patients ([199](#_ENREF_199)) but not in patients treated with statins ([200](#_ENREF_200)).

The detection of CAC seems to have a powerful impact on aggressivity of the intervention by the physician and in patient’s acceptancy and compliance ([201](#_ENREF_201)). The resistance of the insurance companies to assure coverage for the expenses of CACS testing is based on the reduced cost of statins in discordance to the price reduction of the procedure ([202](#_ENREF_202)). This makes statin prescribing cost-effective if the guidelines are followed. This position, however, does not take in consideration either the preference of patients for whom “statins for all” does not appeal to their health preferences in primary prevention or the cases in which the guidelines are not clear about the need for lipid intervention. The latter include all patients age over 75 years free of clinical ASCVD.

**Ankle-Brachial Index**

ABIs are also diagnostic of atherosclerosis with high specificity and are strong predictors of cardiovascular events ([203](#_ENREF_203),[204](#_ENREF_204)). In patients over 80 years of age, low ABI is associated with an increased risk of stroke ([205](#_ENREF_205)) and cardiovascular death ([206](#_ENREF_206)). In older studies, addition of ABI to equations of prediction of cardiovascular risk resulted in improvement of the predictability of the model ([207](#_ENREF_207)). More recent studies, using the net reclassification index (NRI) ([208](#_ENREF_208)) have evaluated the ability of ABI to improve the classification of level of risk. Some studies showed a clinically significant improvement ([209](#_ENREF_209)) but in other studies the improvement was modest or non-existent ([185](#_ENREF_185),[210](#_ENREF_210),[211](#_ENREF_211)).

In the opinion of the authors of this chapter, irrespective of the contribution of a low ABI to evaluation of the cardiovascular risk, a low ABI could be also considered diagnostic of PAD and would automatically place an elderly patient in the high-risk statin intervention group.

**Premature Menopause**

Young women with natural or surgically induced menopause have an increased risk of cardiovascular events which have justified placing this type of condition on the list of risk-enhancers ([212-215](#_ENREF_212)). There is however a paucity of data reporting on this association in patients older than 75 years. In a large international study, compared with women who had menopause at age 50–51 years, women with premature and early menopause had a substantially increased risk of a non-fatal cardiovascular disease event before the age of 60 years, but not after age 70 years ([216](#_ENREF_216)). Premature menopause was associated with decreased walking speed and grip strength implying an increased risk of frailty and its cardiovascular consequences but the studies included mostly younger women ([217](#_ENREF_217),[218](#_ENREF_218)). In Chinese women older than 65 years, an increased risk of hemorrhagic stroke was noted when menopause occurred late ([219](#_ENREF_219)). Similarly, in elderly American women who had late menopause, another study reported an increased risk of cardiovascular death ([220](#_ENREF_220)).

In summary the premature occurrence of menopause is insufficiently documented to be used as a risk enhancer in discussions with patients age over 75 years and their family addressing lipid intervention.

**LIPID INTERVENTION FOR CARDIOVASCULAR PREVENTION IN THE ELDERLY**

**Lifestyle Changes, Lipoproteins and Cardiovascular Risk Reduction**

Most guidelines for cardiovascular prevention recommend lifestyle changes as an important measure for therapeutic intervention. In observational studies, adherence to lifestyle guidelines by elderly patients seems to decrease mortality ([221-223](#_ENREF_221)). The Mediterranean diet has been recommended for cardiovascular intervention, and adherence to a Mediterranean diet has been associated with decreased mortality in the elderly ([224](#_ENREF_224)).

Smoking cessation is strongly advised in patients at increased cardiovascular risk irrespective of age. In the elderly, smoking is associated with increased mortality and this increase is attenuated progressively with the time elapsed since smoking cessation ([225](#_ENREF_225),[226](#_ENREF_226)).

The Cardiovascular Healthy Study demonstrated a strong association of level physical activity with cardiovascular outcomes in elderly patients, including those age 75 years or older ([227](#_ENREF_227)). However, other studies in elderly groups have indicated problems with adherence to exercise regimens over time ([228](#_ENREF_228)), Therefore, although lifestyle changes can be useful in preventing cardiovascular outcomes, implementing these changes may prove to be challenging for elderly patients,

The current guidelines ([2](#_ENREF_2)) recommend: “Patients should consume a dietary pattern that emphasizes intake of vegetables, fruits, whole grains, legumes, healthy protein sources (low-fat dairy products, low-fat poultry (without the skin), fish/seafood, and nuts), and nontropical vegetable oils; and limits intake of sweets, sugar-sweetened beverages, and red meats. This dietary pattern should be adjusted to appropriate calorie requirements, personal and cultural food preferences, and nutritional therapy for other medical conditions including diabetes. Caloric intake should be adjusted to avoid weight gain, or in overweight/obese patients, to promote weight loss. In general, adults should be advised to engage in aerobic physical activity 3-4 sessions per week, lasting on average 40 minutes per session and involving moderate-to vigorous-intensity physical activity.” This recommendation is based primarily on observational data.

There are very few data from randomized clinical trials with clinical endpoints addressing the benefit of different lifestyle recommendations in the older age group. Prevencion con Dieta Mediterranea (PREDIMED) enrolled 7447 persons, age range: 55 to 80 years with 2,671 enrollees 70 years or older ([229](#_ENREF_229)). The subjects were randomized to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). The primary end point was the rate of major cardiovascular events (MI, stroke, or death from cardiovascular causes). After 4.8 years the hazard ratio for the primary endpoint was significantly lower in the two Mediterranean diets when compared with the control diet. In patients aged 70 and over the hazard ratio for the primary endpoint for combined Mediterranean diets was 0.71 (95% CI: 0.51–0.98). The study reported a 39% reduction in stroke in patients of all ages randomized to Mediterranean diets.

The benefits of weight reduction programs in patients older than 75 years have not been properly explored and there is concern because of the “obesity paradox” (better survival of the patients with higher BMI) occurring in the very old ([230](#_ENREF_230))

**CHOLESTEROL LOWERING DRUGS AND CARDIOVASCULAR PREVENTION IN PATIENTS OVER 75 YEARS OF AGE**.

Cholesterol lowering is the main form of lipid intervention and statins are the main drug of choice because of their clinical efficacy, low cost and extensive experience with their use. The fact that in some of the elderly there is a decrease in cholesterol levels which does not paralell a decrease in the ASCVD risk should not imply that these patients will not benefit from statin therapy since statins have been shown to decrease cardiovascular risk irrespective of how low the cholesterol level is ([231-233](#_ENREF_231)). In the elderly there are limitations of our knowledge of clinical benefit of statins derived from clinical trials, therefore we will also present data derived from observational studies.

**Randomized Statin Clinical Trials**

The Cholesterol Treatment Trialists Collaboration published in 2019 a meta-analysis of individual participant data from 28 randomized controlled trials concerning the efficacy and safety of statin therapy in older people ([234](#_ENREF_234)). The studies enrolled 14,483 patients age over 75 years. In these patients there was a significant decrease in major atherosclerotic cardiovascular events (MACE) with a Risk Ratio per 1 mm LDL cholesterol reduction - RR: 0.87 (95%CI: 0.77-0.99). This analysis included four trials done exclusively among people with heart failure or receiving renal dialysis, for whom statin therapy shows little or no benefit. A second analysis was performed after elimination of these trials and the results were: RR: 0.82 (95%CI: 0.70-0.95). The major coronary events were significantly reduced with RR: 0.82 (95%CI: 0.70-0.96). Cardiovascular death and stroke risk were also reduced but statistical significance was not reached because of low numbers. When patients were classified according to previous vascular disease, those who had it showed significant benefit from statin use with RR: 0.85 (95%CI: 0.73-0.98). Cholesterol reduction in primary prevention in patients older than 75 years failed to show significant benefit. Overall, the authors reported slightly smaller proportional risk reductions in major vascular events and vascular deaths with increasing age.

In summary, only a small number of patients age over 75 years were enrolled in clinical trials and the results were not robust. They supported the use of statin in secondary prevention in this age group but not a primary prevention intervention. The question of up to which age is statin intervention effective remained unanswered. In order to support the data of clinical trials and while awaiting more randomized trials to be completed, cohort studies could be used for guidance. The limitation of this source of information is the presence of confounders that could completely distort the results.

**Observation Cohort Studies**

SECONDARY PREVENTION COHORTS

An early study included 7,220 individuals with angiographically defined significant coronary artery disease with 655 patients age over 80 years ([235](#_ENREF_235)). Patients were followed up for 3.3 + 1.8 years. Among patients age 80 years or older, statins remained statistically significant in preventing death. Statins reduced the risk of mortality by more than 50% in this age group (Hazard Ratio – HR: 0.50 (95%CI: 0.26, 0.96)). This risk estimate was essentially unchanged by controlling for other covariates and the effect of statins in this very elderly age group remained greater than the risk estimates in the younger groups. The main caveat of this study was a marked imbalance in distribution of risk factors between patients treated and not treated with statins.

The ICONS study identified older adults hospitalized with ischemic heart disease and followed them for at least one year or until death ([236](#_ENREF_236)). The study aimed at comparing health services utilization and mortality for statin users and non-statin users. Of 4232 older adults discharged alive from the hospital, 1629 received a statin after discharge. In multivariate models using a propensity score, statins were associated with a 26% reduction in all- cause mortality. However, statin use was not associated with subsequent reductions in health service utilization, including re-hospitalizations, physician visits, or coronary revascularization procedures. The propensity score reduces or eliminates the effect of known confounders but is limited to data available and unknown confounders might still be present.

In survivors of MI age over 80 years followed for up to five years, statin therapy decreased the risks of death and of cardiovascular death by 45% each and the risk of recurrent MI by 47% ([237](#_ENREF_237)). Similar results were obtained in the cohort of patients who survived after the first year indicating that statins were not omitted in patients because they had terminal illness. In nursing home residents with known cardiovascular disease, statin users had a 31% lower risk of death after one year follow up compared to non-users in a propensity score matched analysis ([238](#_ENREF_238)). The risk was significantly decreased by 28% in the subgroup of patients age over 85 years. However, statin therapy did not improve the risk of re-hospitalization or the decline in physical function. The effect of statin dose was explored in a cohort of elderly patients with PAD ([239](#_ENREF_239)). Treatment with a high statin dose as compared with moderate dose resulted in a 48% reduction in mortality and a 42% reduction in MACE.

Not all cohorts reported data concordant to the clinical trials. In 1,262 survivors of MI, age over 80 years, after propensity score adjustment the effect of statin on mortality was not significant ([240](#_ENREF_240)). In 65,000 Medicare patients surviving an acute MI, statin therapy was associated with decreased mortality only in patients younger than 80 years ([241](#_ENREF_241)). There was a linear relationship of age and mortality in older statin treated patients with the point of switch at 85 years, where the statin was associated with lower death risk in patients younger than 85 years and trended toward higher risk thereafter. In another study the authors used the data from the UK Clinical Practice Research Datalink to propensity score match 6,078 statin users with non-satin users ([242](#_ENREF_242)). Statin therapy was associated with a significant benefit in the 60–79 years but not in the 80+ age group. Disease burden did not affect these estimates. In addition, the authors reported a significant increase in the risk of falls and fractures in statin treated patients.

COHORTS OF PATIENTS WITH DIABETES

The association of statin intervention with mortality was explored in 639 patients with diabetes in the Age, Gene/Environment Susceptibility-Reykjavik Study, mean age 77 years. Statin use was associated with a 50% lower cardiovascular mortality and lower all-cause mortality ([243](#_ENREF_243)). The effect was independent of the level of glycemic control. The authors concluded that their data suggest that in the general population of older people with diabetes, statin use markedly reduces the excess cardiovascular and all-cause mortality risk, irrespective of the presence or absence of coronary heart disease or glucose-lowering medication. These data were confirmed in a large Chinese study ([244](#_ENREF_244)). When 10,104 pairs of diabetic patients were propensity score matched according to statin use, the statin users had a 50% lower incidence of cardiovascular events and a 60% lower all-cause mortality. Even lower incidence of cardiovascular events and mortality were achieved if LDLc was decreased to less than 100 mg/dl.

The association of statin therapy on occurrence of stroke in Asian patients with diabetes age over 75 years and free of ASCVD was reported in 1,016 patients from the Japan cholesterol and diabetes study ([245](#_ENREF_245)). Compared with non-statin users, prevalent statin users had 49% reduction in the risk of stroke and new statin users had a 79% lower risk. There was no difference in associations between the type of statins used.

The association of statins with all-cause mortality in community dwelling frail, elderly patients with diabetes was evaluated in an Italian study ([246](#_ENREF_246)). The patients were stratified according to age (65 to 75, 75 to 85 and over 85 years) and according to risk of death and studied with a propensity score adjustment. Patients treated with statins had a four-fold lower mortality irrespective of age and evaluated mortality risk group. A similar study enrolled multimorbidity patients with an average age of 81 years including 494 patients with diabetes ([247](#_ENREF_247)). In patients not treated with statins compared with statin treated patients, the mortality after an average 2.75 years follow-up was 50% higher.

The best constructed study of the association between statin use, age and outcomes in patients with diabetes was the study of the Catalan primary care system ([248](#_ENREF_248)). The authors studied 46,864 people age 75 years or more without clinically recognized atherosclerosis observed for 7.7 years, of which 7,780 had type 2 diabetes. In participants with diabetes, a benefit for statin use was identified in 75-84-year-old patients with HR: 0.76 (95%CI: 0.65, 0.89) for ASCVD and HR: 0.84 (95%CI: 0.75, 0.94) for all-cause mortality, while in participants with diabetes age 85 years or older, no benefit for statin use could be identified for either ASCVD or all-cause mortality. The estimate of HR for statin benefit by age for the entire population of patients with diabetes showed a progressive attenuation with loss of statistical significance at age 85 years, while at age 88 years and higher the association reversed to trend toward higher death risk with statin use.

In summary the cohort data of lipid intervention in patients with ASCVD and/or diabetes support the use of statins after age 75 years up to 85 years. The use of statins in patients older than 85 years remains controversial.

OTHER SELECTED COHORTS

Different cohorts (not only including patients with cardiovascular morbidity or high cardiovascular risk) were also studied for associations with statin use in the elderly. The use of statins in a primary care cohort was explored in the Physician Health Study ([249](#_ENREF_249)). The authors selected 1,130 propensity matched pairs of statin vs non-statin participants age 70 years or more. Statin treated patients had an 18% lower risk of all-cause mortality and a nonsignificant lower risk of cardiovascular events or stroke. The results did not appear to be different according to the age of the subject. Statin users with elevated high cholesterol had fewer coronary events than non-users. In another study, in home dwelling patients age 75 to 90 years, statin users had a 46% lower 6-year mortality rate ([250](#_ENREF_250)). A similar study reported on 1,278 pairs of propensity score matched patients free of ASCVD followed for 5.2 years ([251](#_ENREF_251)). Patients treated with statins had a 41% decrease in MACE and a 44% decrease in all-cause mortality. Another study selected only patients with multiple morbidities and high risk of all-cause death ([252](#_ENREF_252)). The one-year mortality was 34.5%. Statins or statins combined with ACE inhibitors and/or beta-blockers were associated with decreased mortality and improved risk of disability progression. A different approach was reported from a cohort of home-dwelling elderly in which statin users had a higher comorbidity burden than non-statin users but also a higher level of prealbumin ([253](#_ENREF_253)). The mortality rate was the same in both groups. The authors concluded that both statins and better nutrition compensated for to the effect of higher comorbidity on mortality.

Not all cohorts reported data documenting the benefit of statins. In the Concord Health and Ageing in Men Project, 1,665 patients age over 70 years were followed for 6.8 years ([254](#_ENREF_254)). In the adjusted models, baseline statin use was not statistically associated with increased risk of institutionalization or death. In a smaller cohort, statin treatment was associated with significant benefit but unrelated to cholesterol lowering, casting doubt about the mechanism of action ([255](#_ENREF_255)).

In summary the data from cohorts of primary prevention in very old patients remain controversial

**Ongoing Clinical Trials**

Three studies (table 2) are currently registered with the FDA addressing the use of statins in the elderly. They illustrate different concerns and consequently they have different endpoints. The fact that they all address primary prevention implies that, for the time being, statins should be used in patients with ASCVD of all ages.

|  |
| --- |
| **Table 2. Ongoing Studies of Statin Therapy in the Elderly** |
|  | **SCOPE-RCT** | **SITE** | **STAREE** |
| **Country** | South Korea | France | Australia |
| **Age** | >75 years | >75 years | >70 years |
| **Type of prevention** | Primary  | Primary  | Primary  |
| **Study Arms** | Moderate dosevs high dose statin | D/C statin vs not D/C statin | Atorvastatin 40 mg/day vs placebo |
| **Primary endpoint** | Statin-Associated Muscle Symptoms | Incremental cost per QALY gained, mortality | Death, dementia or disability |
| **Secondary endpoints** | Fatal and nonfatal CV events | New events: cardiovascular, cognitive, diabetes | Fatal and nonfatal CV events, diabetes, dementia, hospitalization, QALY, cost-effectiveness |
| **Duration** | 6 years | 3 years | 7 years |
| **Number of enrollees** | 2,234 | 2,430 | 18,000 |
| **Year of completion** | 2024 | 2021 | 2023 |

SCOPE-75 RCT STUDY (NCT03770312)

Thisis a multicenter, prospective, randomized, open label, clinical trial to compare efficacy and safety between low and high intensity statin for primary prevention of cardiovascular disease in elderly individuals. The study will enroll elderly individuals, age 76 to 85 years, free of ASCVD and either LDLc 160-189 mg/dl or LDLc 80 to 159 mg/dl and risk factors. They will be randomly assigned to moderate intensity statin group and low intensity statin group by a 1:1 manner. The total study duration will be 6 years. The primary outcome measures will be statin associated muscle symptoms (SAMS) defined as reports of new or increased myalgia, cramps, or muscle aching, unassociated with recent exercise persisting for at least 2 weeks resolving within 2 weeks of stopping the study drug and reoccurring within 4 weeks of restarting the medication. Secondary Outcome Measures will be cardiovascular death, nonfatal MI, nonfatal ischemic stroke or transient ischemic attack, coronary revascularization and hospitalization for unstable angina

Comment: This is primarily a safety trial. It remains to be seen how convincing it will be since the study is open label and therefore results could be biased.

# STATINS IN THE ELDERLY (SITE, NCT02547883)

# This is a single center, prospective, randomized, open label, clinical trial to evaluate the cost/effectiveness ratio, in real life, of statin cessation in people ≥ 75 years treated in primary prevention. The study will enroll elderly individuals, age over 75 years, free of ASCVD treated with statins for at least one year prior to the enrollment. Participants will be randomly assigned to continuation of statin and discontinuation of statin group and low intensity statin group by a 1:1 manner. The total study duration will be 6 years. The primary outcome measures will be incremental cost per quality-adjusted life year (QALY) gained and ratio between QALYs gained and cost for the French healthcare system as well as overall mortality. Secondary outcome measures will be quality of life and clinical events occurrence (cardiovascular events, diabetes, cognitive disorders)

Comment: The French National Health Insurance is spending around 200 million euros on statins for people ≥ 75 years so this is a study aimed at policy change. This study is also open label and enrolls by definition patients who are willing to discontinue the statin and thereby results may also be subject to biases.

A CLINICAL TRIAL OF STATIN THERAPY FOR REDUCING EVENTS IN THE ELDERLY (STAREE-NCT02099123)

This studywill include men and women age ≥70 years living independently in the community, free of ASCVD, dementia or diabetes. The study will be a multicenter randomized, quadruple blind (patient, investigator, primary care physician and adjudicator), placebo-controlled study of atorvastatin 40 mg/day and will enroll 18,000 patients. The total study duration will be 8 years. The primary outcome is death or development of dementia or development of disability or a major fatal or non-fatal cardiovascular event. There is a comprehensive list of secondary outcomes: cardiovascular death, fatal and non-fatal MI, hospitalizations reasons and length of stay, new onset diabetes, fatal and non-fatal cancer, cognitive decline excluding depression, quality of life measured by the Short Form Health Survey (SF-36), cost-effectiveness of statin, fatal and non-fatal stroke including hemorrhagic or thromboembolic stroke, approved need for permanent residential care, all cause dementia and frailty/disability.

Comment: This large ambitious study should give us all the answers concerning the use of statin in the elderly. Since the enrollment age starts at 70 years, hopefully the study will be large enough to evaluate outcomes stratified by the patients’ age group.

#### **Drugs Other Than Statins Used Primarily For Cholesterol Lowering**

EZETIMIBE

Ezetimibehas been used in addition to statin therapy in multiple trials with a cardiovascular endpoint, which will be mentioned further in the chapter. Only one trial randomized patients to ezetimibe versus placebo in presence of statin therapy. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated the effect of ezetimibe combined with simvastatin, as compared to that of simvastatin alone, in stable patients who had an acute coronary syndrome and whose LDLc values were within guideline recommendations ([256](#_ENREF_256)). The study enrolled 18,144 patient survivors of an acute coronary syndrome. At 7 years, there was a benefit of intervention with an absolute risk difference of 2.0 percentage points, HR: 0.94 (95%CI: 0.89, 0.99). A prespecified subgroup analysis showed a benefit with a HR: 0.80 (95%CI: 0.70, 0.90) in the 2,798 patients age over 75 years. The study demonstrated that in elderly patients at high cardiovascular risk, further cholesterol lowering is beneficial.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) INHIBITORS

PCSK9 inhibitors(evolocumab and alirocumab) have emerged as the most powerful class of cholesterol lowering drugs. They are administered as a subcutaneous injection every two or four weeks. They are monoclonal antibodies that bind and inactivate PCSK9, an important regulator of the number of hepatic LDL receptors. This results in a marked increase of LDL uptake and consequently a salient decrease in LDLc concentration.

FOURIER was a randomized trial of patients with documented ASCVD who received evolocumab in addition to maximal tolerated lipid lowering therapy ([257](#_ENREF_257)). The primary efficacy end point was the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, MI, or stroke. The median duration of follow-up was 2.2 years. The study enrolled 12,254 patients over age 65 years. In these patients there was a significant decrease in the primary outcome with treatment (HR: 0.85 (95%CI: 0.76, 0.95)) as well as a decrease in secondary outcome (HR: 0.81 (95%CI: 0.71, 0.92)). There were also no observed safety issues.

ODYSSEY-OUTCOMES was a randomized trial of survivors of an acute coronary syndrome ([258](#_ENREF_258)). Patients received alirocumab in addition to maximum tolerated lipid lowering therapy. The primary end point was a composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. The median duration of follow-up was 2.8 years. The study enrolled 5,084 patients over age 65 years. In these patients there was a significant decrease in the primary outcome with treatment (HR: 0.79 (95%CI: 0.68, 0.91)) which was nominally greater than that reported in younger patients. No safety issues were reported.

The main obstacle in prescribing this ideal medication is cost. Analyses of cost effectiveness of the drugs, which were originally marketed at a price of US $12,000-14,000 per year, suggests that the annual treatment price should be set below $4,600, at a societal willingness-to-pay of $100,000 per Quality Added Life Year ([259](#_ENREF_259),[260](#_ENREF_260)). In spite of the price reductions offered by the manufacturers these drugs are rarely prescribed to Medicare patients, who are the majority of the patients at risk because of the high out of pocket costs for beneficiaries ([261](#_ENREF_261)).

BILE ACID BINDING RESINS

Bile acid binding resins have not been used in cardiovascular clinical endpoint trials against placebo in the elderly.

**Statins in Patients with End Stage Renal Disease (ESRD) and Congestive Heart Failure (CHF)**

Patients with these two types of comorbidity have limited recommendations for statin use by the guidelines ([2](#_ENREF_2)). In patients with ESRD a few large trials have attempted to decrease cardiovascular events by cholesterol lowering and have included patients age over 75 years ([262-265](#_ENREF_262)). All trials have failed to show a benefit from use of statin initiation in these patients. Elderly patients have not been reported separately. Similarly in patients with CHF, trials have included elderly patients and have failed to show a benefit from statin intervention for heart failure endpoints ([266](#_ENREF_266),[267](#_ENREF_267)).

**TRIGLYCERIDE LOWERING DRUGS AS A TARGET FOR CARDIOVASCULAR PREVENTION**

The recent studies showing TG to be a risk factor for coronary events while HDLc to be only a marker ([268](#_ENREF_268)) have opened the door for a new approach in approaching the residual risk not eliminated by statin therapy.

**Fibrates**

Fibrates have shown some promise as lipid lowering agents as they are the most powerful medication class for decreasing triglycerides. A meta-analysis of six fibrate studies showed significant benefit when fibrates were compared with placebo in patients with hypertriglyceridemia and low HDLc ([269](#_ENREF_269)). However, five of the six studies did not include patients age over 75 years and in the only one that did ([270](#_ENREF_270)), patients older than 65 years had more events in the treated arm than in the placebo arm. Similar conclusions were presented in a Cochrane meta-analysis including only patients free of cardiovascular disease ([271](#_ENREF_271)) and again the conclusions were not applicable to elderly patients. A Cochrane meta-analysis including patients with ASCVD concluded, after exclusion of old clofibrate studies since this drug is no longer available, that fibrate treatment results in a significant reduction in the incidence of MI ([272](#_ENREF_272)). In this study patients age over 65 years benefited from treatment but patients age over 75 years were not reported. A meta-analysis of fibrate studies showed no benefit in the incidence of stroke but a reduction in fatal stroke in high risk patients ([273](#_ENREF_273)). This study included the clofibrate trials. Finally, a meta-analysis of two trials ([274](#_ENREF_274),[275](#_ENREF_275)) showed a reduction in major cardiovascular events and in cardiovascular death in patients with stage 3 chronic kidney disease treated with fibrates but both studies included patients younger than 75 years ([276](#_ENREF_276)).

In conclusion whether there is a benefit of fibrates in the elderly remains to be established.

**Niacin**

Niacin has been extensively used in the hope that, by increasing HDLc it will decrease residual risk in statin treated patients. This concept was abandoned after two large randomized studies have shown that niacin is not superior to placebo when added to statin therapy in high risk patients.([277](#_ENREF_277),[278](#_ENREF_278)). Neither one of these studies reported on patients age over 75 years.

A Cochrane analysis of all niacin studies reported that niacin does not reduce mortality, cardiovascular mortality, non-cardiovascular mortality, the number of fatal or non-fatal MI, nor the number of fatal or non-fatal strokes but is associated with side effects ([279](#_ENREF_279)). A more recent meta-analysis reported that patients treated with niacin added to statin therapy show no additional benefit ([280](#_ENREF_280)). The authors reported on the benefit of niacin monotherapy observed in trials performed in the seventies but this form of therapy is no longer in use. In addition, niacin therapy was associated with a 34% increased risk for new-onset diabetes and results were consistent regardless of whether participants received background statin therapy ([281](#_ENREF_281)). This equates to one additional case of diabetes per 43 initially non-diabetic individuals who are treated with niacin for 5 years.

With the information currently available niacin should not be used for cardiovascular prevention in the elderly.

**Omega-3-Acid Ethyl Esters Supplements From Fish Oils**

Multiple studies attempted to show a benefit of low dose long-chain omega 3 fatty acids supplements added to statin therapy but none of them resulted in significant benefit ([282-288](#_ENREF_282)). A thorough Cochrane analysis done in 2018 ([289](#_ENREF_289)) concluded that supplementing the diet with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the active components of fish oil, has little or no effect on mortality or cardiovascular health and that low-quality evidence suggests alpha linolenic acid (ALA) may slightly reduce CVD events and arrhythmia risk. Another meta-analysis published during the same year demonstrated that supplements containing omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events and that there is no support for recommendations for the use of such supplements in people with a history of coronary heart disease ([290](#_ENREF_290)). A third meta-analysis published immediately after the two precedent ones concluded that for adult patients with acute MI, omega 3 fatty-acids probably yield no benefit to “patient important outcomes” ([291](#_ENREF_291)). In all the trials analyzed the investigators used a mixture of EPA and DHA in low doses and did not select the patients to be hypertriglyceridemic.

A study of the effect of n-3 polyunsaturated fatty acids [n-3 PUFA] in patients with chronic heart failure reported a small benefit but not in terms of ASCVD events.There was a 9% statistically significant reduction in death or hospitalization for heart failure and 8% reduction in mortality in the n-3 PUFA treated group ([292](#_ENREF_292)). The median age of enrollees was 69 years and there was no difference in benefit according to age but patients older than 75 years were not separately reported.

The investigators of the Japan EPA Lipid Intervention Study (JELIS) randomized 18,645 patients to statin + a preparation containing 1800 mg EPA (but not DHA) or statin + placebo ([293](#_ENREF_293)). After 4.6 years, there was a significant reduction in the risk of major coronary events and non-fatal coronary events, each of 19%. Most of the events occurred in the secondary prevention subcohort. There was a significant 19% decrease in risk of major coronary events, a 28% decrease in the risk of unstable angina and a 20% reduction in stroke ([294](#_ENREF_294)), The study enrolled only patients age less than 75 years.

The results of the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) study was published in November 2018. It enrolled 8,179 patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting TG level of 135 to 499 mg per deciliter. The was no upper age limit for enrollment. The primary end point was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina. After 4.9 years, the intervention arm (2 grams twice a day of highly purified EPA) reported a 25% reduction in the primary endpoint, a 31% reduction in fatal and nonfatal MI, a 35% reduction in revascularizations, a 20% reduction in cardiovascular death and a 28% reduction in stroke. There was no heterogeneity of the results according to age. Although patients over age 75 years were not reported separately, in view of the excellent safety and tolerability data, this drug should be recommended as an add-on therapy to statins in hypertriglyceridemic elderly patients at high risk. It should be noted that the reduction in cardiovascular events was greater than would be expected from the triglyceride decrease suggesting that other factors, such as anti-inflammatory effects, membrane stabilization, anti-platelet effects, etc. played a role in reducing events.

**CURRENT GUIDELINES FOR LIPID LOWERING DRUGS IN THE ELDERLY**

The current guidelines for lipid intervention are the Guideline on the Management of Blood Cholesterol ([2](#_ENREF_2)) and the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidemias ([295](#_ENREF_295)). Both give specific recommendations for the elderly based on clinical trial evidence.

**US Guidelines**

* In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences
* In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences.
* In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy.
* In adults 75 years of age or older with an LDLc level of 70 to 189 mg/dL, initiating a moderate-intensity statin may be reasonable
* In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy
* In adults 76 to 80 years of age with an LDLc level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CACS of zero to avoid statin therapy

Compared with previous guidelines the new guidelines redefine elderly as patients age over 75 years, strongly recommend lipid intervention in elderly patients with documented ASCVD, include the presence of frailty in the evaluation of the patient and discuss the possibility of stopping statin therapy. They also give a high place to measurement of CAC in the decision-making process.

**EAS Guidelines**

The EAS guidelines are not as detailed on this subject. They define elderly as patients age over 65 years but add instructions for patients age over 75 years:

* Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.
* Initiation of statin treatment for primary prevention in older people age >75 years may be considered, if at high-risk or above.
* It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDLc treatment goals.

In essence there is agreement between the two guidelines in management of patients age over 75 years. Both guidelines admit that as the age of the patient increases the guidelines are less based on hard evidence but rather on extrapolation of clinical trial beneficial results outside the age range in which they were ascertained.

**EFFICACY AND SAFETY OF LIPID LOWERING DRUGS IN THE ELDERLY**

**Statins**

Statin efficacy is measured by the percent of LDLc and non-HDLc lowering. There is paucity of data on a heterogeneity of the efficacy according to age and the differences reported are small and favor older patients ([296-298](#_ENREF_296)). Statins are classified in three groups ([98](#_ENREF_98)) (table 3)

|  |
| --- |
| **Table 3. Statin Efficacy**  |
| **High Intensity Statins** | **Moderate Intensity Statins** | **Low Intensity Statins** |
| >50% Decrease in LDL-C | 30-50% Decrease in LDL-C | <30% Decrease in LDL-C |
| Atorvastatin 40-80 mg Rosuvastatin 20-40 mg | Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mgPravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg | Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg |

Most guidelines recommend the use of at least a moderate dose statin in order to achieve a significant reduction of ASCVD risk.

The safety of statins is of particular interest in the elderly since most authors believe that the risk of an adverse event increases with age and so are the doubts about a clinical benefit. The likelihood of a drug related adverse event to occur is associated with the individual susceptibility for a specific drug effect. In most cases this is either genetically determined ([299](#_ENREF_299)) or environmental and related to accumulation of toxic doses of the drug and/or its metabolites. This accumulation occurs through disease or through drug interaction.

An example of genetically determined susceptibility to drug related adverse events is the high concentrations of rosuvastatin present in the serum of Asian subjects upon administration of average doses ([300](#_ENREF_300)). Because of this, it is recommended that this drug be started at a lower dose and increased with utmost care when administered to an Asian patient.

Most reviewers agree that the risk of statin adverse effects is increased in elderly and most guidelines are taking this information into account. However, there is a paucity of data documenting this belief. Data from clinical trials do not even confirm the presence of statin induced myopathy, the most common adverse event report in observational studies ([301](#_ENREF_301)) but clinical trial patients might be different than clinical practice patients. This is also applicable for elderly patients in whom a meta-analysis showed that there was no evidence to suggest an increased risk of myopathy in older adults receiving statin therapy ([302](#_ENREF_302)). The authors reported, however, a slightly increased risk of rhabdomyolysis when compared with the general younger population. In general, reports from clinical trials are controversial. A review specifies that age over 65 years and female gender can increase the odds of myopathy by 9% and 95%, respectively ([302](#_ENREF_302)). The study also reported that, for rhabdomyolysis, the risk after age 65 years increases by 30% while being male rather than female is an additional risk factor.

Because of the difficulties in ascertaining the validity and frequency of mild and moderate complaints (of muscle pain or weakness) there is even more doubt about observational studies with the exceptions of the reports of rhabdomyolysis. A nested case-control study was conducted within a cohort of 252,460 new users of lipid-lowering medications across 11 geographically dispersed U.S. health plans ([303](#_ENREF_303)). Twenty-one cases of rhabdomyolysis confirmed by medical record review were compared to 200 individually matched controls without rhabdomyolysis. Statin users 65 years of age and older had four times the risk of hospitalization for rhabdomyolysis than those under age 65. The risk of rhabdomyolysis is increased if patients are concurrently receiving statins and fibrates. In hospitalized patients age 65 years or older, with diabetes mellitus, treated with both a statin and fibrate, the risk of rhabdomyolysis is increased 48-fold ([304](#_ENREF_304)). This publication however, did not separate fenofibrate from gemfibrozil cases.

In summary there are data suggesting that rhabdomyolysis occurs more often in older patients but there is no clinical trial evidence or large database evidence in support of this idea yet. However, common sense leads us to believe that this idea is probably true because disorders resulting in a higher likelihood of drug related adverse events are impairments of major organs such as CKD, liver disease, CHF, or endocrine disorders (diabetes, hypothyroidism), and are more likely to occur in older patients.

In situations in which the pathophysiology has been studied, drug related toxicity is attributed to drug accumulation to toxic concentrations. The risk of occurrence of this accumulation increases with age through a series of mechanisms:

* There is an age related decrease in glomerular filtration rate ([305](#_ENREF_305))
* There is an age related decrease in hepatic blood flow and decrease in drug clearance ([306](#_ENREF_306))
* Aging maybe associated with changes in induction and inhibition of different Cyp-450 enzymes ([307](#_ENREF_307)).
* Aging might be associated with an increased expression of P-glycoproteins resulting in alterations in the rate of drug transport across cellular membranes ([308](#_ENREF_308)) .
* Frailty (but not aging per se) has been associated with diminished drug esterase and conjugation activity ([309](#_ENREF_309)).

Unless large database studies disprove it, we will have to accept that there is a decreased safety of statin use with increasing age. Other data concerning safety of statins will be addressed further below.

Specific concern of increased risk of diabetes in statin treated patients arising from JUPITER data has been attributed to the 25% increased incidence of physician reported diabetes in the treated arm ([310](#_ENREF_310)). The validity of this finding was tested in a meta-analysis of all statin trials showing no significant effect, but a high level of heterogeneity ([311](#_ENREF_311)). In the West of Scotland Coronary Prevention Study (WOSCOPS), investigators reported a decrease in the risk of incident diabetes in statin treated patients ([312](#_ENREF_312)). Elimination of this trial from the meta-analysis reestablished the homogeneity of the data and showed a significant increase in the incidence of diabetes (RR:1.13 (95%CI: 1.03, 1.23) in the statin treated group. A more recent meta-analysis confirmed that statins increased the risk of incident diabetes, but the authors concluded that the risk was low both in absolute terms and when compared with the reduction in coronary events ([313](#_ENREF_313)). Statin related risk of incident diabetes is more frequent in older patients ([313](#_ENREF_313)) and with higher dose statin use ([314](#_ENREF_314)). In women age 77-82 followed for over 10 years the incidence of diabetes was 5% ([315](#_ENREF_315)). Filling a prescription for statins was associated with a risk of incident diabetes increase varying from17% to 51% according to the statin dose. The mechanism of action has not been identified and different authors have implied beta cell toxicity ([316](#_ENREF_316)), increased insulin resistance ([317](#_ENREF_317)) or a statin-induced proinflammatory response ([318](#_ENREF_318)).

The concern of elderly patients having a more rapid decrease in their cognitive function if treated with a statin has been inflated by the internet and the media. In 2012 the FDA issued a warning to all statin users: “There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These reported symptoms are generally not serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks)” ([319](#_ENREF_319)). PROSPER and HPS have enrolled large numbers of elderly subjects and specifically looked for an effect of statins on cognitive impairment, but no effect was seen. In spite of this, the relationship between cholesterol metabolism and Alzheimer’s disease continues to fascinate researchers and the lay public. Small studies, however, seem to document some benefit in subsets of patients with mild Alzheimer’s disease or vascular dementia ([320-322](#_ENREF_320)). The majority of researchers remain skeptical that a clinically significant benefit is present in these patients and for these outcomes. This conclusion is supported by a Cochrane Collaboration analysis ([323](#_ENREF_323)) and a systematic review ([324](#_ENREF_324)).

While prescribing statins, in a large number of patients in this age group a discussion will occur. Fear of statins is a clinical reality and the patient and even more often the patient’s family will raise objections to prescribing. We recommend that physicians periodically browse the internet to see what their patients are reading and to be able to respond promptly to unsupported objections.

**PCSK9 Inhibitors**

PCSK9 inhibitors achieved maximum efficacy when they are administered every two weeks. The two drugs used on the US market have a similar LDLc lowering and they have never been tested comparatively. In the package insert for alirocumab the reported percent decreases for LDLc, total cholesterol, non-HDLc and ApoB were respectively 58%, 36% 50% and 51% ([325](#_ENREF_325)) while for evolocumab they were 63%, 36%, 54% and 50% ([326](#_ENREF_326)). The LDLc lowering efficacy of alirocumab does not seem to depend on age with patients age over 75 years having similar efficacy compared to younger patients ([327](#_ENREF_327)). In all the trials reported the adverse events do not appear to be more frequent in the treated arm than in the placebo arm ([328](#_ENREF_328)).

The impact of the FDA labeling for possible cognitive impairment for statins determined the investigators for both drugs to investigate thoroughly the effect of these powerful cholesterol agents on cognitive function. The investigators of evolocumab undertook the EBBINGHAUS trial ([329](#_ENREF_329)). They enrolled 1204 patients with normal cognitive function from the Fourier trial and followed them for 19 months. There was no difference in raw score for the spatial working memory strategy index of executive function (primary end point), working memory, episodic memory, or psychomotor speed and there were no associations between LDLc levels and cognitive changes. The investigators of alirocumab reported that in 14 Phase 2 and 3 trials, rates of neurocognitive treatment emerging adverse events were similar in patients receiving alirocumab and controls when stratified by age and were not increased when LDLc was lower than 25 mg/dl ([330](#_ENREF_330)).

**Ezetimibe**

Ezetimibe is used mostly as an add-on therapy to statins. In monotherapy it will decrease the LDLc by 18% on average ([331](#_ENREF_331)) and in add-on to statins it will reduce the LDLc by an additional 15% ([297](#_ENREF_297)). There is no significant age-related efficacy. The drug has no significant adverse events when compared to placebo in clinical trials ([297](#_ENREF_297),[332](#_ENREF_332),[333](#_ENREF_333)).

**Bempedoic Acid**

Bempedoic acid was launched in 2020 as an add-on cholesterol lowering drug. It blocks a hepatic enzyme called adenosine triphosphate citrate lyase, which is involved in cholesterol synthesis. ([334](#_ENREF_334)). The drug is marketed in the US as monotherapy (NexletolR, 180mg bempedoic acid) and in combination with ezetimibe (NexlizetR, containing 180 mg of bempedoic acid and 10 mg of ezetimibe). In clinical trials, the monotherapy produced an average LDLc lowering of 23% ([335](#_ENREF_335)) and in combination with ezetimibe, as an add-on to statin therapy an average LDLc lowering of 36% ([336](#_ENREF_336)). As opposed to ezetimibe, bempedoic acid has adverse effects that may be significant in the elderly. In clinical trials against placebo, bempedoic acid reported 44% increase in adverse events leading to discontinuation ([335](#_ENREF_335)). The main adverse events were a 2.7-fold increase in the incidence of gout with a 0.74 mg/dl increase in serum uric acid and tendon rupture occurring in 0.5% treated patients. Both adverse events are more likely to occur in elderly patients but neither is frequent or threatening enough to prevent the drug from being used in patients over 75 years old.

**Bile Acid Binding Resins**

Bile acid binding resinsare, along with niacin, the oldest class of lipid lowering drugs on the market. The traditional drugs from this class have gastrointestinal side effects and drug interactions which make them extremely difficult to use in patients over age 75. More recently, a newer member of this class, Colesevelam, has appeared on the market. This drug used in maximum dose induces decreases in LDLc reported between 10 and 20% depending on the background medication ([337](#_ENREF_337)). The side effect profile includes gastrointestinal side effects but they are much more tolerable than that of traditional drugs from this class. Drug interaction profile specifies recommendation that Colesevelam should be administered four hours after verapamil, cyclosporine, warfarin, oral contraceptives, olmesartan, sulfonylureas and vitamins. The best time to recommend the use of this medication is with lunch. The drug has not been specifically studied in elderly patients but it may be used with supervision and monitoring. Colesevelam has been reported to improve glycemic control in patients with diabetes treated with oral agents ([338](#_ENREF_338)) or with insulin ([339](#_ENREF_339)).

**Fenofibrate**

Fenofibrate is used in conjunction with statins when TG are elevated. The TG lowering efficacy depends on baseline TG level with levels of less than 150 mg/dl, 150-<350 mg/dl, 350-499 mg/dl an over 500-1,500 mg/dl reporting TG lowering of 28.9%, 35.9%, 46.2% and 54.5% respectively ([340](#_ENREF_340)). The dose used depends on the brand name and is equivalent to 135 mg/day for TrilipixR but should be reduced in presence of diminished eGFR. No effect of age on efficacy has been reported but patients over age 75 have frequently diminished eGFR.

Fenofibrate has a large number of potential adverse effects. Myopathy has been reported in monotherapy and although there is no increased risk of myopathy through interaction with statins (as opposed to gemfibrozil) the risk is increased through interaction with colchicine. Another important interaction is the increase in INR in patients treated with warfarin. Elevation of creatinine occurs in the majority of patients treated and resolves with discontinuation of the drug. Elevation of liver function tests and in some cases, chronic active hepatitis may occur. Like other fibrates, fenofibrate increases the risk of cholelithiasis. Finally, an increase in the risk of deep vein thrombosis has been reported. A majority of these adverse events are likely to occur more frequently or be more serious in patients age over 75 years, therefore the drug should be used with caution and under supervision in this age group.

**Omega 3 Fatty Acids and Icosapent Ethyl**

These drugs are used as an add-on to statin therapy in high risk patients with hypertriglyceridemia. For the latter, the efficacy in term of TG reduction is 21.5% in patients with TG 200-500 mg/dl ([341](#_ENREF_341)) 33.1% for TG 500-750 mg/dl and 45.4% for TG 750-200 mg/dl ([342](#_ENREF_342)).

**SHOULD LIPID-LOWERING DRUGS BE PRESCRIBED FOR THE ELDERLY?**

**Secondary Prevention**

In presence of ASCVD, there is no age limitation for diagnostic ([343-345](#_ENREF_343)), or invasive procedures ([346-348](#_ENREF_346)) or cardiac rehabilitation ([349](#_ENREF_349)), therefore, there should be no limitations in prescribing statins. Secondary prevention guidelines advise lipid-lowering therapy regardless of age in the majority of older patients with ASCVD unless issues of frailty, comorbidity, and polypharmacy confound management ([2](#_ENREF_2),[350](#_ENREF_350)).

**Primary Prevention**

Conversely, in primary prevention, the Guideline on the Management of Blood Cholesterol ([2](#_ENREF_2)) recommends, for patients 75 years or older, a decision be made after a discussion considering risk, benefit and patient preferences. In cardiovascular risk prediction, age is an imperfect indicator of the presence of atherosclerosis. No guideline should use limits for management or prevention based on age alone. It is conceivable, however, that some patients older than age 75 years have too advanced atherosclerosis for events to be prevented by lipid lowering drug therapy. In addition, it is also conceivable that in the frail elderly, cholesterol negatively predicts cardiovascular risk and its further lowering might be an unwise intervention. In the current status, however, the burden of proof has shifted favoring the interventional approach. Elderly patients should not be denied lipid lowering drug therapy until proven that the recommendations should be limited to certain subgroups within this population.

Several factors should be weighed when considering initiating an elderly patient on a lipid management therapy for primary prevention of an event. The decision to initiate an intervention for reduction of cardiovascular risk is based on estimation of global risk, estimation of longevity of the patient and estimation of individual risk of the therapeutic intervention. Cardiovascular prevention through lipid intervention has different distinct stages:

* Evaluation of goals (global risk, longevity and addressing patient’s and family’s concerns).
* Choice of lipoprotein to target, and of its target level
* Choice of statin
* Choice of drugs to target additional or alternative targets

EVALUATION OF GOALS

The therapeutic intervention should not be denied based on age alone, but the decision to intervene should belong to the patient or to the patient’s advocate. The recommendation of the physician should be accompanied by a discussion with the patient or the decision-maker, for which the informed consent process should be documented. In patients who have cognitive impairment or terminal illnesses or poor quality of life, the option might be to withhold cardiovascular prevention therapy. In the majority of healthy elderly in this age group, preservation of the function appears to be the main desired purpose of preventive therapy. Some patients or families are capable to verbalize their concerns and the physician should be prepared to address the role of lipid intervention in the prevention of the specific risk. Does the intervention decrease the risk of stroke, of hospitalization, of nursing home admission, etc.? The discussion is similar to the informed consent process for an invasive procedure or clinical study. The physician makes a brief recommendation and outlines his opinion about risks and benefits. The patient or his decision-maker will question the decision or accept it.

CHOICE OF LIPOPROTEIN TO TARGET AND ITS TARGET LEVEL

The primary goal for cardiovascular prevention through lipid intervention is a reduction of atherogenic particles and the intervention should be initiated by prescribing a statin. In presence of hypertriglyceridemia irrespective of its level, statins should be prescribed targeting either non-HDLc or ApoB. Since statins have limited ability to reduce TG, residual hypertriglyceridemia should be targeted as a second step.

CHOICE OF STATIN

Choice of statin depends mostly on the percent difference between the current level of the particle targeted and the goal proposed. Most guidelines recommend that statin therapy produce at least a 30% decrease in LDLc and, consideration should be given to initiate treatment with a moderate statin dose in some patients who otherwise should be treated with high dose statins:

Characteristics predisposing individuals to statin adverse effects include:

* Multiple or serious comorbidities, including impaired renal or hepatic function.
* History of previous statin intolerance or muscle disorders.
* Unexplained ALT (alanine aminotransferase) elevations 2-3 times ULN (upper limit of normal).
* Concurrent use of drugs affecting statin metabolism.

These characteristics apply to all patients but have an increased prevalence in the elderly. Additional characteristics that may modify the decision to use higher statin intensities are not age related and include:

* History of hemorrhagic stroke.
* Asian ancestry.

CHOICE OF DRUGS TO TARGET ADDITIONAL OR ALTERNATIVE TARGETS

In patients who did not achieve the prespecified atherogenic particle goal with maximum tolerated statin dose, ezetimibe with or without bempedoic acid should be added. In patients with markedly elevated cholesterol levels in whom goals cannot be achieved with this strategy, a PCSK9 inhibitor should be recommended.

Treatment of residual hypertriglyceridemia should be undertaken, particularly in secondary prevention. Based on clinical trial evidence, the first line drug should be icosapent ethyl. Fenofibrate, although more effective has less convincing evidence of effectiveness for cardiovascular prevention when added to statin therapy. In secondary prevention when the clinical impression is that increased Lp(a) is a major contributor to the ASCVD events, a PCSK9 inhibitor should be considered.

DISCONTINUATION OF STATIN THERAPY

The current guidelines specify; “A counterpoint to the rationale for statin therapy in primary prevention for adults of older ages is the compelling rationale to discontinue therapy in older adults with severe age-related management complexities”. Same as statin prescribing, deprescribing should be recommended as part of a discussion with the patient and the patient’s family. The difficulty of such decision might be overestimated by the physicians. In a small study including patients with a median age of 78 years, 89% of participants reported that they would be willing to stop one or more of the patient’s regular medications if their doctor said it was possible and 95% agreed that they would be willing to have a statin deprescribed ([351](#_ENREF_351)). In a small randomized trial, discontinuation of statins with estimated survival of less than one year there was no significant differences in mortality between the active and control group and a better quality of life in the patients in whom the statin was discontinued ([352](#_ENREF_352),[353](#_ENREF_353)).

**EXAMPLES OF LIPID LOWERING DRUGS PRESCRIBING IN ELDERLY**

**Patient:** Age 79 in good physical shape no life-threatening comorbidity taking a statin in moderate dose

**Recommendation:** Evaluate mentally the drug interaction risk and if none continue the statin without discussing it.

**Patient:** Age 84 survived an acute coronary syndrome and was treated with primary stenting

**Recommendation:** Evaluate mentally the drug interaction risk and if none prescribe a high dose statin, if risk is high then initiate the statin at a moderate dose.

**Patient:** Age 79 in good physical shape, no life-threatening comorbidity, not taking a statin wants to know if he should

**Recommendation:** Evaluate mentally the drug interaction risk and if none prescribe a moderate dose statin.

**Patient:** The same patient, age 79 in good physical shape, no life-threatening comorbidity, now taking a statin, returns with his daughter who wants to know if he MUST take the statin

**Recommendation:** Consider a CACS

**Patient:** The same patient, age 79 in good physical shape, no life-threatening comorbidity, has a CACS = 0

**Recommendation:** May stop the statin.

**Patient:** The same patient, age 79 in good physical shape with a CACS = 0 is ready to stop the statin, but you find out from the daughter that he never quit smoking

**Recommendation:** Don’t stop the statin and consider going to a high dose.

**Patient:** Age 79 in good physical shape, taking a statin in low dose has a CACS=0 and “mild diabetes”.

**Recommendation:** Consider increasing the statin dose.

**Patient:** Age 81 in good physical shape, taking a statin in low dose, has extensive psoriasis.

**Recommendation:** Consider increasing the statin dose.

**Patient:** Age 79 has an acute coronary syndrome and now, three months later, has an ejection fraction of 30% and a ventricular defibrillator was implanted.

**Recommendation:** Evaluate mentally the drug interaction risk and if low prescribe a statin.

**Patient:** Age 79 with chronic obstructive pulmonary disease (COPD) on 24/7 oxygen therapy, taking a statin in moderate dose and had an acute coronary syndrome and now has orthopnea and anasarca.

**Recommendation:** Discussion for discontinuation of statin therapy.

**CONCLUSION**

The cardiovascular prevention clinical trial evidence for the patients in the older elderly group, that is in patients over age 75 years, is very limited and patients’ or patients’ family choice has a dominant role in the decision-making process. The role of the managing physician is to empower the patients and their relatives in order to make an informed decision. The current guideline will be updated as the medical knowledge progresses. For the time being, we believe that the guidelines should be seen in the spirit of evidence-based medicine. In 1996 Sackett, the founder of the [Oxford Centre for Evidence-Based Medicine](http://en.wikipedia.org/w/index.php?title=Oxford_Centre_for_Evidence-Based_Medicine&action=edit&redlink=1), wrote: “External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision.” ([354](#_ENREF_354)).

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