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

Updated September 21, 2020

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), 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) 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). 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). 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). Expansive vascular remodeling can result in increased irreversible arterial stiffness, particularly in calcified vessels and in fibrotic plaques (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). 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). 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. (9,10). 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).

High density lipoprotein cholesterol (HDLc) does not seem to vary with age in men and postmenopausal women (10). Menopause but not age has an impact on the concentration of HDLc and HDLc subfractions (16). Aging has, however, an effect on HDL function since the HDL collected from older subjects has diminished cholesterol efflux capacity (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).

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). These data were confirmed using a meal containing retynyl palmitate and squalene as markers of postprandial lipoprotein metabolism (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). The effect of age on postprandial lipoprotein metabolism is attenuated in elderly who are physically active (22). Walking solely during the postprandial phase had an attenuating effect only in some studies (23) but not in others (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). The pathophysiological mechanisms have been extensively reviewed (26-28). 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), 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..

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) 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) or weight changes (32) but changes in behavior, weight, medication or comorbidity cannot explain them completely (33,34). 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).

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). 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). 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). 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). 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). 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) (47,48). 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). 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). Inflammatory marker levels are positively correlated with the number of

features of the Fried phenotype (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).

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).

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). 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). 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). 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). 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). 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). 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).

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 (68,69).

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 (70,71). This association seems to be confined to the elderly with a low activity level, indicating that a functional deterioration may be associated (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). 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).

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). 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). 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). The association between low cholesterol with non-cardiovascular mortality in elderly populations was confirmed by numerous cohorts (78-83).

Longitudinally documented decreases in cholesterol concentration have been associated with increased cardiovascular mortality in the elderly (84). It is particularly obvious in patients with low activity level (72). The association of low cholesterol and mortality is weakened after a longer duration of follow-up (72,85). It is not present in patients treated with lipid lowering drugs (86) In some studies the authors reported that the association is weaker in women (87) or stated that low cholesterol in women is not associated with mortality but rather that high cholesterol is protective (88). Rate of cholesterol decline was associated with increased risk of cardiovascular mortality in a large Finnish cohort (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). In the Leiden 85-Plus study, in healthy patients over age 85 years, the Framingham score did not predict cardiovascular death (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). Sussman et al (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). The concept of "life-time risk of a coronary event" (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), 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). 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). 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). 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). In large real-world cohorts high TG were associated with an increased risk of myocardial infarction, stroke and revascularizations in statin treated patients (103,104). 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). In another study TG were associated with recurrent stroke with hazard ratios of opposite directionalities in younger and older patients (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 (107,108). 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). 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).

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). In the Honolulu Heart Study, low HDLc was a powerful predictor of non-hemorrhagic stroke (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). 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). 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).

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 (115,116) and in some patient groups with specific comorbid conditions (117,118).

Apolipoproteins

ApoB and Apolipoprotein A_1 (ApoA$_1$) 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). In 77-year-old men in the Uppsala Longitudinal Study, low ApoA$_1$ concentration was the best predictor of coronary death (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).

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). 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).

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) and cardiovascular mortality (124,125). This association is particularly striking in Latin Americans

and South Asians (126) and in statin treated patients (127). Lp(a) was shown to be a risk factor for coronary heart disease and stroke by epidemiologic studies (128) and by Mendelian Randomization (129) and genome-wide association studies (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). 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). 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). 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). 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). 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). 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). 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).

In exploring the pathophysiology of this association in elderly patients, Lp(a) is an independent determinant of aortic stiffness (138) and is associated with hypoechoic carotid lesions, which correspond histologically to lipid-rich, unstable plaques (139,140). 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) and severity of the calcific stenosis (142).

Paradoxically, however, centenarians have higher levels of Lp(a) when compared with younger elderly groups (143,144). 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) 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). Studies in monozygotic and dizygotic twins indicated that 48% of the observed variability in ABI values could be attributed to additive genetic effects (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). The evidence of inheritance of cerebrovascular disease risk pertains to thrombotic or

hemorrhagic stroke, but not thromboembolic stroke (147,148). Inheritance of stroke risk increases with the number of relatives affected (147) and might be attributable to the genetic predisposition to hypertension (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 (149,150). The offspring also seem to have better cognitive performance in middle age (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). 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). 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). 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). 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). Kidney Disease: Improving Global Outcomes (KDIGO) defines clinical CKD by an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m^2 or lower, or an albumin creatinine ratio (ACR) of 30 mg/g or higher (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) and this was maintained in the 2018 guideline (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). 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 m^2) without abnormal proteinuria does not seem to confer much of an adverse effect on mortality and remaining life expectancy in older adults (160). Delanaye et al (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 m^2 or lower. In a large community study of patients age over 75 years in the United Kingdom (162), there was a graded and independent increase in all-cause and cardiovascular mortality risk with declining eGFR below 45 ml/min/1.73 m^2 but not in the group with eGFR 45-60 ml/min/1.73 m^2

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). Presence of CKD in elderly patients is also associated with a significantly increased risk of stroke

(164), PAD (165) and hospitalizations (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). However, the relative mortality risk with moderate CKD decreases with age (168). The rate of decline of eGFR is also a predictor of heart failure, MI and PAD after adjustment for baseline renal function (169,170).These associations are gender dependent with women having a slower decline in GFR and a better patient and renal survival (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). Bansai et al (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). 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). 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 (176,177). 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). The risk of total mortality is even stronger when participants have other elevated inflammatory markers (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).

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). 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).

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). 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). 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), while low gait speed is also a marker of frailty (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). 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). 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). In the prospective Rotterdam Coronary Calcification Study, a markedly graded association was found between coronary calcification and stroke (average age 71 years) (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). 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). 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). In appropriately selected asymptomatic patients, the absence of CAC predicts excellent survival with a 10-year event rate of approximately 1% (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) 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). Progression of CAC is a powerful predictor of events in untreated patients (199) but not in patients treated with statins (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). 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). 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 (203,204). In patients over 80 years of age, low ABI is associated with an increased risk of stroke (205) and cardiovascular death (206). In older studies, addition of ABI to equations of prediction of cardiovascular risk resulted in improvement of the predictability of the model (207). More recent studies, using the net reclassification index (NRI) (208) have evaluated the ability of ABI to improve the classification of level of risk. Some studies showed a clinically significant improvement (209) but in other studies the improvement was modest or non-existent (185,210,211).

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). 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). 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 (217,218). In Chinese women older than 65 years, an increased risk of hemorrhagic stroke was noted when menopause occurred late (219). Similarly, in elderly American women who had late menopause, another study reported an increased risk of cardiovascular death (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). 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).

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 (225,226).

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). However, other studies in elderly groups have indicated problems with adherence to exercise regimens over time (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) 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). 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)

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). 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). 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). 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). 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). 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). 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). 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). In 65,000 Medicare patients surviving an acute MI, statin therapy was associated with decreased mortality only in patients younger than 80 years (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). 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). 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). 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). 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). 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). 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). 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). 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). A similar study reported on 1,278 pairs of propensity score matched patients free of ASCVD followed for 5.2 years (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). 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). 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). 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).

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 dose vs 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)

This is 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 study will 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

Ezetimibe has 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). 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). 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). 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 (259,260). 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).

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). 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). 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 (266,267).

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) 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). However, five of the six studies did not include patients age over 75 years and in the only one that did (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) 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). 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). This study included the clofibrate trials. Finally, a meta-analysis of two trials (274,275) 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).

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.(277,278). 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). A more recent meta-analysis reported that patients treated with niacin added to statin therapy show no additional benefit (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). 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). A thorough Cochrane analysis done in 2018 (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). 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). 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). 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). 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), 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) and the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidemias (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). Statins are classified in three groups (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 mg Pravastatin 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) 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). 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) 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). 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). 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). 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). 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)
- There is an age related decrease in hepatic blood flow and decrease in drug clearance (306)
- Aging maybe associated with changes in induction and inhibition of different Cyp-450 enzymes (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) .
- Frailty (but not aging per se) has been associated with diminished drug esterase and conjugation activity (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). 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). In the West of Scotland Coronary Prevention Study (WOSCOPS), investigators reported a decrease in the risk of incident diabetes in statin treated patients (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). Statin related risk of incident diabetes is more frequent in older patients (313) and with higher dose statin use (314). In women age 77-82 followed for over 10 years the incidence of diabetes was 5% (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), increased insulin resistance (317) or a statin-induced proinflammatory response (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). 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). 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) and a systematic review (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) while for evolocumab they were 63%, 36%, 54% and 50% (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). 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).

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). 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).

Ezetimibe

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

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). The drug is marketed in the US as monotherapy (Nexletol[R], 180mg bempedoic acid) and in combination with ezetimibe (Nexlizet[R], containing 180 mg of bempedoic

acid and 10 mg of ezetimibe). In clinical trials, the monotherapy produced an average LDLc lowering of 23% (335) and in combination with ezetimibe, as an add-on to statin therapy an average LDLc lowering of 36% (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). 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 resins are, 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). 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) or with insulin (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). The dose used depends on the brand name and is equivalent to 135 mg/day for Trilipix^R 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) 33.1% for TG 500-750 mg/dl and 45.4% for TG 750-200 mg/dl (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), or invasive procedures (346-348) or cardiac rehabilitation (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 (2,350).

Primary Prevention

Conversely, in primary prevention, the Guideline on the Management of Blood Cholesterol (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). 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 (352,353).

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, 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).

REFERENCES

1. LRC-CPPT. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984; 251:351-364

2. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019; 139:e1082-e1143

3. US-CENSUS-BUREAU. U.S. Census Bureau Projections Show a Slower Growing, Older, More Diverse Nation a Half Century from Now August 2012. https://www.census.gov/newsroom/releases/archives/population/cb12-243.html.

4. Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, Berger JS. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. J Am Coll Cardiol 2013; 61:1736-1743

5. Ehara S, Naruko T, Kobayashi Y, Kataoka T, Nakagawa M, Shirai N, Ishii H, Okuyama T, Oe H, Sugioka K, Hozumi T, Haze K, Yoshikawa J, Yoshiyama M, Ueda M. Comparison of clinical characteristics and arterial remodeling by intravascular ultrasonic imaging in three age groups (< or =55, 56 to 69 and > or =70 years) of Japanese patients with acute myocardial infarction. Am J Cardiol 2007; 100:1713-1717

6. Hasegawa T, Ehara S, Kobayashi Y, Kataoka T, Yamashita H, Nishioka H, Asawa K, Yamagishi H, Yoshiyama M, Takeuchi K, Yoshikawa J, Ueda M. Acute myocardial infarction: clinical characteristics and plaque morphology between expansive remodeling and constrictive remodeling by intravascular ultrasound. Am Heart J 2006; 151:332-337

7. Bureau UC. America's Health Ranking. wwwamericashealthrankingsorg/explore/senior/measure/poverty_sr/state/ALL 2020;

8. Capistrant BD, Moon JR, Berkman LF, Glymour MM. Current and long-term spousal caregiving and onset of cardiovascular disease. J Epidemiol Community Health 2012; 66:951-956

9. Loh TP, Ma S, Heng D, Khoo CM. Age-Related Changes in the Cardiometabolic Profiles in Singapore Resident Adult Population: Findings from the National Health Survey 2010. PLoS One 2016; 11:e0162102

10. Weijenberg MP, Feskens EJ, Kromhout D. Age-related changes in total and high-density-lipoprotein cholesterol in elderly Dutch men. Am J Public Health 1996; 86:798-803

11. Millar JS, Lichtenstein AH, Cuchel M, Dolnikowski GG, Hachey DL, Cohn JS, Schaefer EJ. Impact of age on the metabolism of VLDL, IDL, and LDL apolipoprotein B-100 in men. J Lipid Res 1995; 36:1155-1167

12. Batista MC, Welty FK, Diffenderfer MR, Sarnak MJ, Schaefer EJ, Lamon-Fava S, Asztalos BF, Dolnikowski GG, Brousseau ME, Marsh JB. Apolipoprotein A-I, B-100, and B-48 metabolism in subjects with chronic kidney disease, obesity, and the metabolic syndrome. Metabolism 2004; 53:1255-1261

13. Chan DC, Watts GF, Barrett PH. Comparison of intraperitoneal and posterior subcutaneous abdominal adipose tissue compartments as predictors of VLDL apolipoprotein B-100 kinetics in overweight/obese men. Diabetes Obes Metab 2003; 5:202-206

14. Pont F, Duvillard L, Florentin E, Gambert P, Verges B. Early kinetic abnormalities of apoB-containing lipoproteins in insulin-resistant women with abdominal obesity. Arterioscler Thromb Vasc Biol 2002; 22:1726-1732

15. Welty FK, Lichtenstein AH, Barrett PH, Dolnikowski GG, Schaefer EJ. Interrelationships between human apolipoprotein A-I and apolipoproteins B-48 and B-100 kinetics using stable isotopes. Arterioscler Thromb Vasc Biol 2004; 24:1703-1707

16. Anagnostis P, Stevenson JC, Crook D, Johnston DG, Godsland IF. Effects of menopause, gender and age on lipids and high-density lipoprotein cholesterol subfractions. Maturitas 2015; 81:62-68

17. Berrougui H, Isabelle M, Cloutier M, Grenier G, Khalil A. Age-related impairment of HDL-mediated cholesterol efflux. J Lipid Res 2007; 48:328-336

18. Gaw A, Murray HM, Brown EA, Group PS. Plasma lipoprotein(a) [Lp(a)] concentrations and cardiovascular events in the elderly: evidence from the prospective study of pravastatin in the elderly at risk (PROSPER). Atherosclerosis 2005; 180:381-388

19. Cohn JS, McNamara JR, Cohn SD, Ordovas JM, Schaefer EJ. Postprandial plasma lipoprotein changes in human subjects of different ages. J Lipid Res 1988; 29:469-479

20. Relas H, Gylling H, Rajaratnam RA, Miettinen TA. Postprandial retinyl palmitate and squalene metabolism is age dependent. J Gerontol A Biol Sci Med Sci 2000; 55:B515-521

21. Pinto LB, Wajngarten M, Silva EL, Vinagre CC, Maranhao RC. Plasma kinetics of a cholesterol-rich emulsion in young, middle-aged, and elderly subjects. Lipids 2001; 36:1307-1311

22. Emerson SR, Kurti SP, Emerson EM, Cull BJ, Casey K, Haub MD, Rosenkranz SK. Postprandial Metabolic Responses Differ by Age Group and Physical Activity Level. J Nutr Health Aging 2018; 22:145-153

23. Kashiwabara K, Kidokoro T, Yanaoka T, Burns SF, Stensel DJ, Miyashita M. Different Patterns of Walking and Postprandial Triglycerides in Older Women. Med Sci Sports Exerc 2018; 50:79-87

24. Diekmann C, Huber H, Preuss M, Preuss P, Predel HG, Stoffel-Wagner B, Fimmers R, Stehle P, Egert S. Moderate Postmeal Walking Has No Beneficial Effects Over Resting on Postprandial Lipemia, Glycemia, Insulinemia, and Selected Oxidative and Inflammatory Parameters in Older Adults with a Cardiovascular Disease Risk Phenotype: A Randomized Crossover Trial. The Journal of nutrition 2019; 149:1930-1941

25. Perez-Caballero AI, Alcala-Diaz JF, Perez-Martinez P, Garcia-Rios A, Delgado-Casado N, Marin C, Yubero-Serrano E, Camargo A, Caballero J, Malagon MM, Tinahones FJ, Perez-Jimenez F, Lopez-Miranda J, Delgado-Lista J. Lipid metabolism after an oral fat test meal is affected by age-associated features of metabolic syndrome, but not by age. Atherosclerosis 2013; 226:258-262

26. Katsanos CS. Clinical considerations and mechanistic determinants of postprandial lipemia in older adults. Adv Nutr 2014; 5:226-234

27. Liu HH, Li JJ. Aging and dyslipidemia: a review of potential mechanisms. Ageing Res Rev 2015; 19:43-52

28. Maranhao RC, Pala D, Freitas FR. Lipoprotein removal mechanisms and aging: implications for the cardiovascular health of the elderly. Curr Opin Endocrinol Diabetes Obes 2020; 27:104-109

29. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville MUSDoH. Standard Biochemistry Profile https://wwwncdcgov/Nchs/Nhanes/2017-2018/BIOPRO_Jhtm 2018-2019;

30. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, Kovesdy CP, Younessi H, Anker SD, Morley JE. Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care 2007; 10:433-442

31. Garry PJ, Hunt WC, Koehler KM, VanderJagt DJ, Vellas BJ. Longitudinal study of dietary intakes and plasma lipids in healthy elderly men and women. Am J Clin Nutr 1992; 55:682-688

32. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984-1994. Circulation 1997; 96:37-43

33. Truesdale KP, Stevens J, Cai J. Nine-year changes in cardiovascular disease risk factors with weight maintenance in the atherosclerosis risk in communities cohort. Am J Epidemiol 2007; 165:890-900

34. Wong MWK, Braidy N, Pickford R, Vafaee F, Crawford J, Muenchhoff J, Schofield P, Attia J, Brodaty H, Sachdev P, Poljak A. Plasma lipidome variation during the second half of the human lifespan is associated with age and sex but minimally with BMI. PLoS One 2019; 14:e0214141

35. Hopstock LA, Bonaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Lochen ML, Mathiesen EB, Njolstad I, Wilsgaard T. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905-1977 in the population-based Tromso Study 1979-2016. BMJ Open 2017; 7:e015001

36. NCOA. https://wwwncoaorg/ ACCESSED 2020;

37. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002; 287:356-359

38. Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. Diabetes Care 2003; 26:575-581

39. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among u.s. Adults. Diabetes Care 2004; 27:2444-2449

40. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care 2005; 28:2745-2749

41. Thomas GN, Tomlinson B, Hong AW, Hui SS. Age-related anthropometric remodelling resulting in increased and redistributed adiposity is associated with increases in the prevalence of cardiovascular risk factors in Chinese subjects. Diabetes Metab Res Rev 2006; 22:72-78

42. Hughes VA, Roubenoff R, Wood M, Frontera WR, Evans WJ, Fiatarone Singh MA. Anthropometric assessment of 10-y changes in body composition in the elderly. Am J Clin Nutr 2004; 80:475-482

43. Imbeault P, Prins JB, Stolic M, Russell AW, O'Moore-Sullivan T, Despres JP, Bouchard C, Tremblay A. Aging per se does not influence glucose homeostasis: in vivo and in vitro evidence. Diabetes Care 2003; 26:480-484

44. Tyroler HA, Ford CE. Serum cholesterol and coronary heart disease risk in female and older hypertensives. The experience under usual community care in the Hypertension Detection and Follow-up Program. Ann Epidemiol 1992; 2:155-160

45. Hunter GR, Weinsier RL, Gower BA, Wetzstein C. Age-related decrease in resting energy expenditure in sedentary white women: effects of regional differences in lean and fat mass. Am J Clin Nutr 2001; 73:333-337

46. Okoro CA, Zhong Y, Ford ES, Balluz LS, Strine TW, Mokdad AH. Association between the metabolic syndrome and its components and gait speed among U.S. adults aged 50 years and older: a cross-sectional analysis. BMC Public Health 2006; 6:282

47. Abbott RD, Curb JD, Rodriguez BL, Masaki KH, Yano K, Schatz IJ, Ross GW, Petrovitch H. Age-related changes in risk factor effects on the incidence of coronary heart disease. Ann Epidemiol 2002; 12:173-181

48. Curb JD, Abbott RD, Rodriguez BL, Masaki K, Popper J, Chen R, Petrovitch H, Blanchette P, Schatz I, Yano K. Prospective association between low and high total and low-density lipoprotein cholesterol and coronary heart disease in elderly men. J Am Geriatr Soc 2004; 52:1975-1980

49. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56:M146-156

50. Schalk BW, Visser M, Deeg DJ, Bouter LM. Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: the Longitudinal Aging Study Amsterdam. Age Ageing 2004; 33:266-272

51. Okamura T, Hayakawa T, Hozawa A, Kadowaki T, Murakami Y, Kita Y, Abbott RD, Okayama A, Ueshima H. Lower levels of serum albumin and total cholesterol associated with decline in activities of daily living and excess mortality in a 12-year cohort study of elderly Japanese. J Am Geriatr Soc 2008; 56:529-535

52. Reuben DB, Ix JH, Greendale GA, Seeman TE. The predictive value of combined hypoalbuminemia and hypocholesterolemia in high functioning community-dwelling older persons: MacArthur Studies of Successful Aging. J Am Geriatr Soc 1999; 47:402-406

53. Hubbard RE, O'Mahony MS, Savva GM, Calver BL, Woodhouse KW. Inflammation and frailty measures in older people. J Cell Mol Med 2009;

54. Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, Penninx B, Pahor M, Wallace R, Havlik RJ. Serum IL-6 level and the development of disability in older persons. J Am Geriatr Soc 1999; 47:639-646

55. Cappola AR, Xue QL, Ferrucci L, Guralnik JM, Volpato S, Fried LP. Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. J Clin Endocrinol Metab 2003; 88:2019-2025

56. Penninx BW, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, Nevitt M, Visser M, Harris T, Pahor M. Inflammatory markers and incident mobility limitation in the elderly. J Am Geriatr Soc 2004; 52:1105-1113

57. Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. Clin Endocrinol (Oxf) 2005; 63:403-411

58. Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med 2006; 119:526 e529-517

59. Stenholm S, Maggio M, Lauretani F, Bandinelli S, Ceda GP, Di Iorio A, Giallauria F, Guralnik JM, Ferrucci L. Anabolic and catabolic biomarkers as predictors of muscle strength decline: the InCHIANTI study. Rejuvenation Res 13:3-11

60. Figaro MK, Kritchevsky SB, Resnick HE, Shorr RI, Butler J, Shintani A, Penninx BW, Simonsick EM, Goodpaster BH, Newman AB, Schwartz AV, Harris TB. Diabetes, inflammation, and functional decline in older adults: findings from the Health, Aging and Body Composition (ABC) study. Diabetes Care 2006; 29:2039-2045

61. Alford SH, Divine G, Chao C, Habel LA, Janakiraman N, Wang Y, Feigelson HS, Scholes D, Roblin D, Epstein MM, Engel L, Havstad S, Wells K, Yood MU, Fortuny J, Johnson CC, Cancer Research Network Lymphoma Study G. Serum cholesterol trajectories in the 10 years prior to lymphoma diagnosis. Cancer Causes Control 2018; 29:143-156

62. Charlton J, Ravindrarajah R, Hamada S, Jackson SH, Gulliford MC. Trajectory of Total Cholesterol in the Last Years of Life Over Age 80 Years: Cohort Study of 99,758 Participants. J Gerontol A Biol Sci Med Sci 2018; 73:1083-1089

63. Jeong SM, Choi S, Kim K, Kim SM, Lee G, Son JS, Yun JM, Park SM. Association of change in total cholesterol level with mortality: A population-based study. PLoS One 2018; 13:e0196030

64. Lehtimaki T, Ojala P, Rontu R, Goebeler S, Karhunen PJ, Jylha M, Mattila K, Metso S, Jokela H, Nikkila M, Wuolijoki E, Hervonen A, Hurme M. Interleukin-6 modulates plasma cholesterol and C-reactive protein concentrations in nonagenarians. J Am Geriatr Soc 2005; 53:1552-1558

65. Hrnciarikova D, Hyspler R, Vyroubal P, Klemera P, Hronek M, Zadak Z. Serum lipids and neopterin in urine as new biomarkers of malnutrition and inflammation in the elderly. Nutrition 2009; 25:303-308

66. Cesari M, Onder G, Zamboni V, Capoluongo E, Russo A, Bernabei R, Pahor M, Landi F. C-reactive protein and lipid parameters in older persons aged 80 years and older. J Nutr Health Aging 2009; 13:587-593

67. Manolio TA, Cushman M, Gottdiener JS, Dobs A, Kuller LH, Kronmal RA, Group CHSCR. Predictors of falling cholesterol levels in older adults: the Cardiovascular Health Study. Ann Epidemiol 2004; 14:325-331

68. Tilvis RS, Valvanne JN, Strandberg TE, Miettinen TA. Prognostic significance of serum cholesterol, lathosterol, and sitosterol in old age; a 17-year population study. Ann Med 2011; 43:292-301

69. Sittiwet C, Simonen P, Gylling H, Strandberg TE. Mortality and Cholesterol Metabolism in Subjects Aged 75 Years and Older: The Helsinki Businessmen Study. J Am Geriatr Soc 2020; 68:281-287

70. Rudman D, Mattson DE, Feller AG, Nagraj HS. A mortality risk index for men in a Veterans Administration extended care facility. JPEN Journal of parenteral and enteral nutrition 1989; 13:189-195

71. Rudman D, Mattson DE, Nagraj HS, Feller AG, Jackson DL, Caindec N, Rudman IW. Prognostic significance of serum cholesterol in nursing home men. JPEN Journal of parenteral and enteral nutrition 1988; 12:155-158

72. Harris T, Feldman JJ, Kleinman JC, Ettinger WH, Jr., Makuc DM, Schatzkin AG. The low cholesterol-mortality association in a national cohort. J Clin Epidemiol 1992; 45:595-601

73. Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. Arch Intern Med 1993; 153:1065-1073

74. Smith GD, Shipley MJ, Marmot MG, Rose G. Plasma cholesterol concentration and mortality. The Whitehall Study. JAMA 1992; 267:70-76

75. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. Lancet 1997; 350:1119-1123

76. Iribarren C, Jacobs DR, Jr., Sidney S, Claxton AJ, Gross MD, Sadler M, Blackburn H. Serum total cholesterol and risk of hospitalization, and death from respiratory disease. Int J Epidemiol 1997; 26:1191-1202

77. Staessen J, Amery A, Birkenhager W, Bulpitt C, Clement D, de Leeuw P, Deruyttere M, De Schaepdryver A, Dollery C, Fagard R, et al. Is a high serum cholesterol level associated with longer survival in elderly hypertensives? J Hypertens 1990; 8:755-761

78. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. Lancet 2001; 358:351-355

79. Brescianini S, Maggi S, Farchi G, Mariotti S, Di Carlo A, Baldereschi M, Inzitari D. Low total cholesterol and

increased risk of dying: are low levels clinical warning signs in the elderly? Results from the Italian Longitudinal Study on Aging. J Am Geriatr Soc 2003; 51:991-996

80. Casiglia E, Mazza A, Tikhonoff V, Scarpa R, Schiavon L, Pessina AC. Total cholesterol and mortality in the elderly. J Intern Med 2003; 254:353-362

81. Schupf N, Costa R, Luchsinger J, Tang MX, Lee JH, Mayeux R. Relationship between plasma lipids and all-cause mortality in nondemented elderly. J Am Geriatr Soc 2005; 53:219-226

82. Tikhonoff V, Casiglia E, Mazza A, Scarpa R, Thijs L, Pessina AC, Staessen JA. Low-density lipoprotein cholesterol and mortality in older people. J Am Geriatr Soc 2005; 53:2159-2164

83. Spada RS, Toscano G, Cosentino FI, Iero I, Lanuzza B, Tripodi M, Ferri R. Low total cholesterol predicts mortality in the nondemented oldest old. Arch Gerontol Geriatr 2007; 44 Suppl 1:381-384

84. Pekkanen J, Nissinen A, Vartiainen E, Salonen JT, Punsar S, Karvonen MJ. Changes in serum cholesterol level and mortality: a 30-year follow-up. The Finnish cohorts of the seven countries study. Am J Epidemiol 1994; 139:155-165

85. Song YM, Sung J, Kim JS. Which cholesterol level is related to the lowest mortality in a population with low mean cholesterol level: a 6.4-year follow-up study of 482,472 Korean men. Am J Epidemiol 2000; 151:739-747

86. Liang Y, Vetrano DL, Qiu C. Serum total cholesterol and risk of cardiovascular and non-cardiovascular mortality in old age: a population-based study. BMC Geriatr 2017; 17:294

87. Takata Y, Ansai T, Soh I, Awano S, Nakamichi I, Akifusa S, Goto K, Yoshida A, Fujii H, Fujisawa R, Sonoki K. Serum total cholesterol concentration and 10-year mortality in an 85-year-old population. Clin Interv Aging 2014; 9:293-300

88. Maihofer AX, Shadyab AH, Wild RA, LaCroix AZ. Associations between Serum Levels of Cholesterol and Survival to Age 90 in Postmenopausal Women. J Am Geriatr Soc 2020; 68:288-296

89. Reinikainen J, Laatikainen T, Karvanen J, Tolonen H. Lifetime cumulative risk factors predict cardiovascular disease mortality in a 50-year follow-up study in Finland. Int J Epidemiol 2015; 44:108-116

90. Koller MT, Steyerberg EW, Wolbers M, Stijnen T, Bucher HC, Hunink MG, Witteman JC. Validity of the Framingham point scores in the elderly: results from the Rotterdam study. Am Heart J 2007; 154:87-93

91. de Ruijter W, Westendorp RG, Assendelft WJ, den Elzen WP, de Craen AJ, le Cessie S, Gussekloo J. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. BMJ 2009; 338:a3083

92. Anum EA, Adera T. Hypercholesterolemia and coronary heart disease in the elderly: a meta-analysis. Ann Epidemiol 2004; 14:705-721

93. Sussman JB, Wiitala WL, Zawistowski M, Hofer TP, Bentley D, Hayward RA. The Veterans Affairs Cardiac Risk Score: Recalibrating the Atherosclerotic Cardiovascular Disease Score for Applied Use. Medical care 2017; 55:864-870

94. Hakim AA, Curb JD, Burchfiel CM, Rodriguez BL, Sharp DS, Yano K, Abbott RD. Screening for coronary heart disease in elderly men based on current and past cholesterol levels. J Clin Epidemiol 1999; 52:1257-1265

95. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 2009; 119:3078-3084

96. Barrett-Connor E, Bergstrom J, Wright M, Kramer CK. Heart disease risk factors in midlife predict subclinical coronary atherosclerosis more than 25 years later in survivors without clinical heart disease: the Rancho Bernardo Study. J Am Geriatr Soc 2009; 57:1041-1044

97. Lloyd-Jones DM, Wilson PW, Larson MG, Leip E, Beiser A, D'Agostino RB, Cleeman JI, Levy D. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. Arch Intern Med 2003; 163:1966-1972

98. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults:. Circulation 2013; 129:S1-72

99. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP, Lloyd-Jones DM. Lifetime risks of cardiovascular disease. N Engl J Med 2012; 366:321-329

100. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet 2014; 384:626-635

101. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007; 115:450-458

102. Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, Woodward M. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation 2004; 110:2678-2686

103. Toth PP, Fazio S, Wong ND, Hull M, Nichols GA. Risk of cardiovascular events in patients with hypertriglyceridaemia: A review of real-world evidence. Diabetes Obes Metab 2020; 22:279-289

104. Nichols GA, Philip S, Reynolds K, Granowitz CB, Fazio S. Increased Cardiovascular Risk in Hypertriglyceridemic Patients With Statin-Controlled LDL Cholesterol. J Clin Endocrinol Metab 2018; 103:3019-3027

105. Lv YB, Mao C, Gao X, Yin ZX, Kraus VB, Yuan JQ, Zhang J, Luo JS, Zeng Y, Shi XM. Triglycerides Paradox Among the Oldest Old: "The Lower the Better?". J Am Geriatr Soc 2019; 67:741-748

106. Eun MY, Seo WK, Lee J, Kim M, Kim J, Kim JH, Oh K, Koh SB. Age-dependent predictors for recurrent stroke: the paradoxical role of triglycerides. Eur Neurol 2013; 69:171-178

107. Barter P. HDL: a recipe for longevity. Atheroscler Suppl 2004; 5:25-31

108. Arai Y, Hirose N. Aging and HDL metabolism in elderly people more than 100 years old. J Atheroscler Thromb 2004; 11:246-252

109. Cheung KS, Lau BH. Successful aging among Chinese near-centenarians and centenarians in Hong Kong: a multidimensional and interdisciplinary approach. Aging Ment Health 2016; 20:1314-1326

110. Zimetti F, Freitas WM, Campos AM, Daher M, Adorni MP, Bernini F, Sposito AC, Zanotti I, Brazilian Study on Healthy A. Cholesterol efflux capacity does not associate with coronary calcium, plaque vulnerability, and telomere length in healthy octogenarians. J Lipid Res 2018; 59:714-721

111. Psaty BM, Anderson M, Kronmal RA, Tracy RP, Orchard T, Fried LP, Lumley T, Robbins J, Burke G, Newman AB, Furberg CD. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: The Cardiovascular Health Study. J Am Geriatr Soc 2004; 52:1639-1647

112. Curb JD, Abbott RD, Rodriguez BL, Masaki KH, Chen R, Popper JS, Petrovitch H, Ross GW, Schatz IJ, Belleau GC, Yano K. High density lipoprotein cholesterol and the risk of stroke in elderly men: the Honolulu heart program. Am J Epidemiol 2004; 160:150-157

113. Zuliani G, Cherubini A, Atti AR, Ble A, Vavalle C, Di Todaro F, Benedetti C, Volpato S, Marinescu MG, Senin U, Fellin R. Low cholesterol levels are associated with short-term mortality in older patients with ischemic stroke. J Gerontol A Biol Sci Med Sci 2004; 59:293-297

114. Packard CJ, Ford I, Robertson M, Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG. Plasma lipoproteins and apolipoproteins as predictors of cardiovascular risk and treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Circulation 2005; 112:3058-3065

115. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. Eur Heart J 2017; 38:2478-2486

116. Ko DT, Alter DA, Guo H, Koh M, Lau G, Austin PC, Booth GL, Hogg W, Jackevicius CA, Lee DS, Wijeysundera HC, Wilkins JT, Tu JV. High-Density Lipoprotein Cholesterol and Cause-Specific Mortality in Individuals Without Previous Cardiovascular Conditions: The CANHEART Study. J Am Coll Cardiol 2016; 68:2073-2083

117. Costacou T, Evans RW, Orchard TJ. High-density lipoprotein cholesterol in diabetes: is higher always better? J Clin Lipidol 2011; 5:387-394

118. Moradi H, Streja E, Kashyap ML, Vaziri ND, Fonarow GC, Kalantar-Zadeh K. Elevated high-density lipoprotein cholesterol and cardiovascular mortality in maintenance hemodialysis patients. Nephrol Dial Transplant 2014; 29:1554-1562

119. Bruno G, Merletti F, Biggeri A, Bargero G, Prina-Cerai S, Pagano G, Cavallo-Perin P. Effect of age on the association of non-high-density-lipoprotein cholesterol and apolipoprotein B with cardiovascular mortality in a Mediterranean population with type 2 diabetes: the Casale Monferrato study. Diabetologia 2006; 49:937-944

120. Florvall G, Basu S, Larsson A. Apolipoprotein A1 is a stronger prognostic marker than are HDL and LDL cholesterol for cardiovascular disease and mortality in elderly men. J Gerontol A Biol Sci Med Sci 2006; 61:1262-1266

121. Wolters FJ, Yang Q, Biggs ML, Jakobsdottir J, Li S, Evans DS, Bis JC, Harris TB, Vasan RS, Zilhao NR, Ghanbari M, Ikram MA, Launer L, Psaty BM, Tranah GJ, Kulminski AM, Gudnason V, Seshadri S, investigators EC. The impact of APOE genotype on survival: Results of 38,537 participants from six population-based cohorts (E2-CHARGE). PLoS One 2019; 14:e0219668

122. Mooijaart SP, Berbee JF, van Heemst D, Havekes LM, de Craen AJ, Slagboom PE, Rensen PC, Westendorp RG. ApoE plasma levels and risk of cardiovascular mortality in old age. PLoS Med 2006; 3:e176

123. Waldeyer C, Makarova N, Zeller T, Schnabel RB, Brunner FJ, Jorgensen T, Linneberg A, Niiranen T, Salomaa V, Jousilahti P, Yarnell J, Ferrario MM, Veronesi G, Brambilla P, Signorini SG, Iacoviello L, Costanzo S, Giampaoli S, Palmieri L, Meisinger C, Thorand B, Kee F, Koenig W, Ojeda F, Kontto J, Landmesser U, Kuulasmaa K, Blankenberg S. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur Heart J 2017; 38:2490-2498

124. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. Eur Heart J 2019; 40:2760-2770

125. Langsted A, Nordestgaard BG. Lipoprotein(a): is it more, less or equal to LDL as a causal factor for cardiovascular disease and mortality? Curr Opin Lipidol 2020; 31:125-131

126. Pare G, Caku A, McQueen M, Anand SS, Enas E, Clarke R, Boffa MB, Koschinsky M, Wang X, Yusuf S, Investigators I. Lipoprotein(a) Levels and the Risk of Myocardial Infarction Among 7 Ethnic Groups. Circulation 2019; 139:1472-1482

127. Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, Schwartz GG, Olsson AG, Colhoun HM, Kronenberg F, Drechsler C, Wanner C, Mora S, Lesogor A, Tsimikas S. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. Lancet 2018; 392:1311-1320

128. Emerging Risk Factors C, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009; 302:412-423

129. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. J Am Coll Cardiol 2013; 61:1146-1156

130. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M, Consortium P. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 2009; 361:2518-2528

131. Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Chirico M, Frisardi V, Cacciapaglia M, Vendemiale G, Capurso A, Panza F. All-cause mortality and competing risks of fatal and nonfatal vascular events in the Italian longitudinal study on aging: impact of lipoprotein(a). Rejuvenation Res 2009; 12:395-402

132. D'Angelo A, Ruotolo G, Garancini P, Sampietro F, Mazzola G, Calori G. Lipoprotein(a), fibrinogen and vascular mortality in an elderly northern Italian population. Haematologica 2006; 91:1613-1620

133. Ariyo AA, Thach C, Tracy R. Lp(a) lipoprotein, vascular disease, and mortality in the elderly. N Engl J Med 2003; 349:2108-2115

134. Zhao Y, Delaney JA, Quek RG, Gardin JM, Hirsch CH, Gandra SR, Wong ND. Cardiovascular Disease, Mortality Risk, and Healthcare Costs by Lipoprotein(a) Levels According to Low-density Lipoprotein Cholesterol Levels in Older High-risk Adults. Clin Cardiol 2016; 39:413-420

135. Boden-Albala B, Kargman DE, Lin IF, Paik MC, Sacco RL, Berglund L. Increased stroke risk and lipoprotein(a) in a multiethnic community: the Northern Manhattan Stroke Study. Cerebrovascular diseases (Basel, Switzerland) 2010; 30:237-243

136. Milionis HJ, Filippatos TD, Loukas T, Bairaktari ET, Tselepis AD, Elisaf MS. Serum lipoprotein(a) levels and apolipoprotein(a) isoform size and risk for first-ever acute ischaemic nonembolic stroke in elderly individuals. Atherosclerosis 2006; 187:170-176

137. Volpato S, Vigna GB, McDermott MM, Cavalieri M, Maraldi C, Lauretani F, Bandinelli S, Zuliani G, Guralnik JM, Fellin R, Ferrucci L. Lipoprotein(a), inflammation, and peripheral arterial disease in a community-based sample of older men

and women (the InCHIANTI study). Am J Cardiol 2010; 105:1825-1830

138. Wakabayashi I, Masuda H. Lipoprotein (a) as a determinant of arterial stiffness in elderly patients with type 2 diabetes mellitus. Clinica chimica acta; international journal of clinical chemistry 2006; 373:127-131

139. Iwamoto T, Fukuda S, Shimizu S, Takasaki M. Long-term effects of lipoprotein(a) on carotid atherosclerosis in elderly Japanese. J Gerontol A Biol Sci Med Sci 2004; 59:62-67

140. Iwamoto T, Miyaji H, Shinozaki K, Koyama S, Takasaki M. Changes in carotid atherosclerosis patterns detected by ultrasonography in Japanese elderly patients with aortic aneurysm. J Atheroscler Thromb 2003; 10:13-18

141. Zheng KH, Tsimikas S, Pawade T, Kroon J, Jenkins WSA, Doris MK, White AC, Timmers N, Hjortnaes J, Rogers MA, Aikawa E, Arsenault BJ, Witztum JL, Newby DE, Koschinsky ML, Fayad ZA, Stroes ESG, Boekholdt SM, Dweck MR. Lipoprotein(a) and Oxidized Phospholipids Promote Valve Calcification in Patients With Aortic Stenosis. J Am Coll Cardiol 2019; 73:2150-2162

142. Liu SL, Rozi R, Shi HW, Gao Y, Guo YL, Tang YD, Li JJ, Wu NQ. Association of serum lipoprotein(a) level with the severity and prognosis of calcific aortic valve stenosis: a Chinese cohort study. J Geriatr Cardiol 2020; 17:133-140

143. Thillet J, Doucet C, Chapman J, Herbeth B, Cohen D, Faure-Delanef L. Elevated lipoprotein(a) levels and small apo(a) isoforms are compatible with longevity: evidence from a large population of French centenarians. Atherosclerosis 1998; 136:389-394

144. Arai Y, Hirose N, Nakazawa S, Yamamura K, Shimizu K, Takayama M, Ebihara Y, Osono Y, Homma S. Lipoprotein metabolism in Japanese centenarians: effects of apolipoprotein E polymorphism and nutritional status. J Am Geriatr Soc 2001; 49:1434-1441

145. Wassel CL, Loomba R, Ix JH, Allison MA, Denenberg JO, Criqui MH. Family history of peripheral artery disease is associated with prevalence and severity of peripheral artery disease: the San Diego population study. J Am Coll Cardiol 2011; 58:1386-1392

146. Carmelli D, Fabsitz RR, Swan GE, Reed T, Miller B, Wolf PA. Contribution of genetic and environmental influences to ankle-brachial blood pressure index in the NHLBI Twin Study. National Heart, Lung, and Blood Institute. Am J Epidemiol 2000; 151:452-458

147. Flossmann E, Schulz UG, Rothwell PM. Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke. Stroke 2004; 35:212-227

148. Schulz UG, Flossmann E, Rothwell PM. Heritability of ischemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies. Stroke 2004; 35:819-824

149. Atzmon G, Schechter C, Greiner W, Davidson D, Rennert G, Barzilai N. Clinical phenotype of families with longevity. J Am Geriatr Soc 2004; 52:274-277

150. Sebastiani P, Sun FX, Andersen SL, Lee JH, Wojczynski MK, Sanders JL, Yashin A, Newman AB, Perls TT. Families Enriched for Exceptional Longevity also have Increased Health-Span: Findings from the Long Life Family Study. Frontiers in public health 2013; 1:38

151. Stijntjes M, de Craen AJ, van Heemst D, Meskers CG, van Buchem MA, Westendorp RG, Slagboom PE, Maier AB. Familial longevity is marked by better cognitive performance at middle age: the Leiden Longevity Study. PLoS One 2013; 8:e57962

152. Westendorp RG, van Heemst D, Rozing MP, Frolich M, Mooijaart SP, Blauw GJ, Beekman M, Heijmans BT, de Craen AJ, Slagboom PE, Leiden Longevity Study G. Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: The Leiden Longevity Study. J Am Geriatr Soc 2009; 57:1634-1637

153. Van daele CM, De Meyer T, De Buyzere ML, Gillebert TC, Denil SL, Bekaert S, Chirinos JA, Segers P, De Backer GG, De Bacquer D, Rietzschel ER, Asklepios I. Addition of a novel, protective family history category allows better profiling of cardiovascular risk and atherosclerotic burden in the general population. The Asklepios Study. PLoS One 2013; 8:e63185

154. Revelas M, Thalamuthu A, Oldmeadow C, Evans TJ, Armstrong NJ, Kwok JB, Brodaty H, Schofield PR, Scott RJ, Sachdev PS, Attia JR, Mather KA. Review and meta-analysis of genetic polymorphisms associated with exceptional human longevity. Mech Ageing Dev 2018; 175:24-34

155. Sebastiani P, Bae H, Sun FX, Andersen SL, Daw EW, Malovini A, Kojima T, Hirose N, Schupf N, Puca A, Perls TT. Meta-analysis of genetic variants associated with human exceptional longevity. Aging (Albany NY) 2013; 5:653-661

156. Centers for Disease Control and Prevention. National Chronic Kidney Disease Fact Sheet: General Information and National Estimates on Chronic Kidney Disease in the United States, 2010. Atlanta, GA: U.S. Department of Health and Human Services, CDC. Atlanta, GA: U.S. Department of Health and Human Services, CDC;2010.

157. Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group M. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014; 85:1303-1309

158. Writing C, Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, Jr., DePalma SM, Minissian MB, Orringer CE, Smith SC, Jr. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2016; 68:92-125

159. Glassock RJ, Winearls C. Ageing and the glomerular filtration rate: truths and consequences. Trans Am Clin Climatol Assoc 2009; 120:419-428

160. Glassock RJ, Rule AD. Aging and the Kidneys: Anatomy, Physiology and Consequences for Defining Chronic Kidney Disease. Nephron 2016; 134:25-29

161. Delanaye P, Glassock RJ, Pottel H, Rule AD. An Age-Calibrated Definition of Chronic Kidney Disease: Rationale and Benefits. Clin Biochem Rev 2016; 37:17-26

162. Roderick PJ, Atkins RJ, Smeeth L, Mylne A, Nitsch DD, Hubbard RB, Bulpitt CJ, Fletcher AE. CKD and mortality risk in older people: a community-based population study in the United Kingdom. Am J Kidney Dis 2009; 53:950-960

163. Tonelli M, Jose P, Curhan G, Sacks F, Braunwald E, Pfeffer M. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. Bmj 2006; 332:1426

164. Chen YC, Su YC, Lee CC, Huang YS, Hwang SJ. Chronic kidney disease itself is a causal risk factor for stroke beyond traditional cardiovascular risk factors: a nationwide cohort study in Taiwan. PLoS One 2012; 7:e36332

165. Yap YS, Chuang HY, Chien CM, Tai YK. Relationship between peripheral artery disease and combined albuminuria and low estimated glomerular filtration rate among elderly patients with type 2 diabetes mellitus. Diab Vasc Dis Res 2014; 11:41-47

166. Nitsch D, Nonyane BA, Smeeth L, Bulpitt CJ, Roderick PJ, Fletcher A. CKD and hospitalization in the elderly: a community-based cohort study in the United Kingdom. Am J Kidney Dis 2011; 57:664-672

167. Odden MC, Shlipak MG, Whitson HE, Katz R, Kearney PM, defilippi C, Shastri S, Sarnak MJ, Siscovick DS, Cushman M, Psaty BM, Newman AB. Risk factors for cardiovascular disease across the spectrum of older age: the Cardiovascular Health Study. Atherosclerosis 2014; 237:336-342

168. Raymond NT, Zehnder D, Smith SC, Stinson JA, Lehnert H, Higgins RM. Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. Nephrol Dial Transplant 2007; 22:3214-3220

169. Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, Newman AB, Sarnak MJ. Rapid kidney function decline and mortality risk in older adults. Arch Intern Med 2008; 168:2212-2218

170. Shlipak MG, Katz R, Kestenbaum B, Siscovick D, Fried L, Newman A, Rifkin D, Sarnak MJ. Rapid decline of kidney function increases cardiovascular risk in the elderly. J Am Soc Nephrol 2009; 20:2625-2630

171. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int 2006; 69:375-382

172. Cao JJ, Biggs ML, Barzilay J, Konen J, Psaty BM, Kuller L, Bleyer AJ, Olson J, Wexler J, Summerson J, Cushman M. Cardiovascular and mortality risk prediction and stratification using urinary albumin excretion in older adults ages 68-102: the Cardiovascular Health Study. Atherosclerosis 2008; 197:806-813

173. Bansal N, Katz R, De Boer IH, Peralta CA, Fried LF, Siscovick DS, Rifkin DE, Hirsch C, Cummings SR, Harris TB, Kritchevsky SB, Sarnak MJ, Shlipak MG, Ix JH. Development and validation of a model to predict 5-year risk of death without ESRD among older adults with CKD. Clin J Am Soc Nephrol 2015; 10:363-371

174. Zoller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurol 2012; 12:41

175. Zoller B, Li X, Sundquist J, Sundquist K. Risk of subsequent coronary heart disease in patients hospitalized

for immune-mediated diseases: a nationwide follow-up study from Sweden. PLoS One 2012; 7:e33442

176. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med 2006; 145:21-29

177. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation 2008; 118:2243-2251, 2244p following 2251

178. Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, Polak JF, Tracy RP. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation 2005; 112:25-31

179. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006; 355:2631-2639

180. Cao JJ, Thach C, Manolio TA, Psaty BM, Kuller LH, Chaves PH, Polak JF, Sutton-Tyrrell K, Herrington DM, Price TR, Cushman M. C-reactive protein, carotid intima-media thickness, and incidence of ischemic stroke in the elderly: the Cardiovascular Health Study. Circulation 2003; 108:166-170

181. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU, Lindemans J, Hofman A, Steyerberg EW, van der Lugt A, van den Meiracker AH, Witteman JC. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med 2012; 156:438-444

182. Melander O, Newton-Cheh C, Almgren P, Hedblad B, Berglund G, Engstrom G, Persson M, Smith JG, Magnusson M, Christensson A, Struck J, Morgenthaler NG, Bergmann A, Pencina MJ, Wang TJ. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA 2009; 302:49-57

183. Shah T, Casas JP, Cooper JA, Tzoulaki I, Sofat R, McCormack V, Smeeth L, Deanfield JE, Lowe GD, Rumley A, Fowkes FG, Humphries SE, Hingorani AD. Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts. Int J Epidemiol 2009; 38:217-231

184. Wilson PW, Pencina M, Jacques P, Selhub J, D'Agostino R, Sr., O'Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. Circ Cardiovasc Qual Outcomes 2008; 1:92-97

185. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 2012; 308:788-795

186. Raggi P, Gongora MC, Gopal A, Callister TQ, Budoff M, Shaw LJ. Coronary artery calcium to predict all-cause mortality in elderly men and women. J Am Coll Cardiol 2008; 52:17-23

187. Rodondi N, Taylor BC, Bauer DC, Lui LY, Vogt MT, Fink HA, Browner WS, Cummings SR, Ensrud KE. Association between aortic calcification and total and cardiovascular mortality in older women. J Intern Med 2007; 261:238-244

188. Inzitari M, Naydeck BL, Newman AB. Coronary artery calcium and physical function in older adults: the Cardiovascular Health Study. J Gerontol A Biol Sci Med Sci 2008; 63:1112-1118

189. Blaha M, Budoff, MJ, Defilippis, AP, Rivera, JJ, Blankstein, R, O'Leary, DH, Lima, J, Blumenthal, RS, Nasir, K. Association between hsCRP2, Coronary Artery Calcium, and Adverse Events - Implications for the JUPITER Population: Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2010; 122:A12825

190. Kuller LH, Lopez OL, Mackey RH, Rosano C, Edmundowicz D, Becker JT, Newman AB. Subclinical Cardiovascular Disease and Death, Dementia, and Coronary Heart Disease in Patients 80+ Years. J Am Coll Cardiol 2016; 67:1013-1022

191. Newman AB, Naydeck BL, Ives DG, Boudreau RM, Sutton-Tyrrell K, O'Leary DH, Kuller LH. Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcomes in adults 70 to 99 years old. Am J Cardiol 2008; 101:186-192

192. Vliegenthart R, Hollander M, Breteler MM, van der Kuip DA, Hofman A, Oudkerk M, Witteman JC. Stroke is associated with coronary calcification as detected by electron-beam CT: the Rotterdam Coronary Calcification Study. Stroke 2002; 33:462-465

193. Hunt ME, O'Malley PG, Vernalis MN, Feuerstein IM, Taylor AJ. C-reactive protein is not associated with the presence or extent of calcified subclinical atherosclerosis. Am Heart J 2001; 141:206-210

194. Jenny NS, Brown ER, Detrano R, Folsom AR, Saad MF, Shea S, Szklo M, Herrington DM, Jacobs DR, Jr. Associations of inflammatory markers with coronary artery calcification: results from the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 209:226-229

195. Kubo T, Matsuo Y, Hayashi Y, Yamano T, Tanimoto T, Ino Y, Kitabata H, Takarada S, Hirata K, Tanaka A, Nakamura N, Mizukoshi M, Imanishi T, Akasaka T. High-sensitivity C-reactive protein and plaque composition in patients with stable angina pectoris: a virtual histology intravascular ultrasound study. Coron Artery Dis 2009; 20:531-535

196. Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, Callister T, Raggi P, Blumenthal RS, Nasir K. Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging 2009; 2:692-700

197. Parker MS, Hui FK, Camacho MA, Chung JK, Broga DW, Sethi NN. Female breast radiation exposure during CT pulmonary angiography. AJR Am J Roentgenol 2005; 185:1228-1233

198. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007; 49:1860-1870

199. Budoff MJ, Nasir K, McClelland RL, Detrano R, Wong N, Blumenthal RS, Kondos G, Kronmal RA. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2009; 53:345-352

200. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, Tuzcu EM, Nissen SE. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol 2015; 65:1273-1282

201. Gupta A, Lau E, Varshney R, Hulten EA, Cheezum M, Bittencourt MS, Blaha MJ, Wong ND, Blumenthal RS, Budoff MJ, Umscheid CA, Nasir K, Blankstein R. The Identification of Calcified Coronary Plaque Is Associated With Initiation and Continuation of Pharmacological and Lifestyle Preventive Therapies: A Systematic Review and Meta-Analysis. JACC Cardiovasc Imaging 2017; 10:833-842

202. Hong JC, Blankstein R, Shaw LJ, Padula WV, Arrieta A, Fialkow JA, Blumenthal RS, Blaha MJ, Krumholz HM, Nasir K. Implications of Coronary Artery Calcium Testing for Treatment Decisions Among Statin Candidates According to the ACC/AHA Cholesterol Management Guidelines: A Cost-Effectiveness Analysis. JACC Cardiovasc Imaging 2017; 10:938-952

203. Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. Arterioscler Thromb Vasc Biol 2005; 25:1463-1469

204. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, Fowkes FG, Hiatt WR, Jonsson B, Lacroix P, Marin B, McDermott MM, Norgren L, Pande RL, Preux PM, Stoffers HE, Treat-Jacobson D, American Heart Association Council on Peripheral Vascular D, Council on E, Prevention, Council on Clinical C, Council on Cardiovascular N, Council on Cardiovascular R, Intervention, Council on Cardiovascular S, Anesthesia. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation 2012; 126:2890-2909

205. Gronewold J, Hermann DM, Lehmann N, Kroger K, Lauterbach K, Berger K, Weimar C, Kalsch HI, Moebus S, Jockel KH, Bauer M, Erbel R, Heinz Nixdorf Recall Study Investigative G. Ankle-brachial index predicts stroke in the general population in addition to classical risk factors. Atherosclerosis 2014; 233:545-550

206. Ankle Brachial Index C, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K, Fowkes FG, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodriguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronek A, Hiatt WR, Hamman R, Resnick HE, Guralnik J, McDermott MM. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008; 300:197-208

207. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation 2004; 110:3075-3080

208. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Statistics in medicine 2008; 27:157-172; discussion 207-112

209. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, Ix JH, Burke GL, Liu K, Shea S. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2010; 56:1506-1512

210. Murphy TP, Dhangana R, Pencina MJ, D'Agostino RB, Sr. Ankle-brachial index and cardiovascular risk prediction: an analysis of 11,594 individuals with 10-year follow-up. Atherosclerosis 2012; 220:160-167

211. Lin JS, Olson CM, Johnson ES, Whitlock EP. The ankle-brachial index for peripheral artery disease screening and cardiovascular disease prediction among asymptomatic adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2013; 159:333-341

212. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. Stroke 2009; 40:1044-1049

213. Roeters van Lennep JE, Heida KY, Bots ML, Hoek A, collaborators of the Dutch Multidisciplinary Guideline Development Group on Cardiovascular Risk Management after Reproductive D. Cardiovascular disease risk in women with premature ovarian insufficiency: A systematic review and meta-analysis. European journal of preventive cardiology 2016; 23:178-186

214. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. JAMA Cardiol 2016; 1:767-776

215. Shen L, Song L, Liu B, Li H, Zheng X, Zhang L, Yuan J, Liang Y, Wang Y. Effects of early age at natural menopause on coronary heart disease and stroke in Chinese women. Int J Cardiol 2017; 241:6-11

216. Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, Brunner EJ, Kuh D, Hardy R, Avis NE, Gold EB, Derby CA, Matthews KA, Cade JE, Greenwood DC, Demakakos P, Brown DE, Sievert LL, Anderson D, Hayashi K, Lee JS, Mizunuma H, Tillin T, Simonsen MK, Adami HO, Weiderpass E, Mishra GD. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Health 2019; 4:e553-e564

217. Velez MP, Alvarado BE, Rosendaal N, da Camara SM, Belanger E, Richardson H, Pirkle CM. Age at natural

menopause and physical functioning in postmenopausal women: the Canadian Longitudinal Study on Aging. Menopause 2019; 26:958-965

218. Velez MP, Rosendaal N, Alvarado B, da Camara S, Belanger E, Pirkle C. Age at natural menopause and physical function in older women from Albania, Brazil, Colombia and Canada: A life-course perspective. Maturitas 2019; 122:22-30

219. Choi SH, Lee SM, Kim Y, Choi NK, Cho YJ, Park BJ. Natural menopause and risk of stroke in elderly women. Journal of Korean medical science 2005; 20:1053-1058

220. Tom SE, Cooper R, Wallace RB, Guralnik JM. Type and timing of menopause and later life mortality among women in the Iowa Established Populations for theEpidemiological Study of the Elderly (EPESE) cohort. J Womens Health (Larchmt) 2012; 21:10-16

221. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. High diet quality is associated with a lower risk of cardiovascular disease and all-cause mortality in older men. The Journal of nutrition 2014; 144:673-680

222. Sijtsma FP, Soedamah-Muthu SS, de Hoon SE, Jacobs DR, Jr., Kromhout D. Healthy eating and survival among elderly men with and without cardiovascular-metabolic diseases. Nutrition, metabolism, and cardiovascular diseases : NMCD 2015; 25:1117-1124

223. van Lee L, Geelen A, Kiefte-de Jong JC, Witteman JC, Hofman A, Vonk N, Jankovic N, Hooft van Huysduynen EJ, de Vries JH, van 't Veer P, Franco OH, Feskens EJ. Adherence to the Dutch dietary guidelines is inversely associated with 20-year mortality in a large prospective cohort study. European journal of clinical nutrition 2016; 70:262-268

224. Talegawkar SA, Bandinelli S, Bandeen-Roche K, Chen P, Milaneschi Y, Tanaka T, Semba RD, Guralnik JM, Ferrucci L. A higher adherence to a Mediterranean-style diet is inversely associated with the development of frailty in community-dwelling elderly men and women. The Journal of nutrition 2012; 142:2161-2166

225. Gellert C, Schottker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. Arch Intern Med 2012; 172:837-844

226. Muezzinler A, Mons U, Gellert C, Schottker B, Jansen E, Kee F, O'Doherty MG, Kuulasmaa K, Freedman ND, Abnet CC, Wolk A, Hakansson N, Orsini N, Wilsgaard T, Bueno-de-Mesquita B, van der Schouw YT, Peeters PH, de Groot

LC, Peters A, Orfanos P, Linneberg A, Pisinger C, Tamosiunas A, Baceviciene M, Luksiene D, Bernotiene G, Jousilahti P, Petterson-Kymmer U, Jansson JH, Soderberg S, Eriksson S, Jankovic N, Sanchez MJ, Veronesi G, Sans S, Drygas W, Trichopoulou A, Boffetta P, Brenner H. Smoking and All-cause Mortality in Older Adults: Results From the CHANCES Consortium. Am J Prev Med 2015; 49:e53-63

227. Soares-Miranda L, Siscovick DS, Psaty BM, Longstreth WT, Jr., Mozaffarian D. Physical Activity and Risk of Coronary Heart Disease and Stroke in Older Adults: The Cardiovascular Health Study. Circulation 2016; 133:147-155

228. Picorelli AM, Pereira LS, Pereira DS, Felicio D, Sherrington C. Adherence to exercise programs for older people is influenced by program characteristics and personal factors: a systematic review. J Physiother 2014; 60:151-156

229. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Fito M, Gea A, Hernan MA, Martinez-Gonzalez MA, Investigators PS. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 2018; 378:e34

230. Oreopoulos A, Kalantar-Zadeh K, Sharma AM, Fonarow GC. The obesity paradox in the elderly: potential mechanisms and clinical implications. Clin Geriatr Med 2009; 25:643-659, viii

231. Sun Y, Xie G, Patel A, Li S, Zhao W, Yang X, Wu T, Li M, Li X, Du X, Hu R, Huo Y, Hu D, Gao RL, Wu Y. Prescription of statins at discharge and 1-year risk of major clinical outcomes among acute coronary syndromes patients with extremely low LDL-cholesterol in clinical pathways for acute coronary syndromes studies. Clin Cardiol 2018; 41:1192-1200

232. Lee KH, Jeong MH, Kim HM, Ahn Y, Kim JH, Chae SC, Kim YJ, Hur SH, Seong IW, Hong TJ, Choi DH, Cho MC, Kim CJ, Seung KB, Chung WS, Jang YS, Rha SW, Bae JH, Cho JG, Park SJ, Investigators K. Benefit of early statin therapy in patients with acute myocardial infarction who have extremely low low-density lipoprotein cholesterol. J Am Coll Cardiol 2011; 58:1664-1671

233. Piao ZH, Jin L, Kim JH, Ahn Y, Kim YJ, Cho MC, Kim CJ, Kim HS, Liu B, Jeong MH, Other Korea Acute Myocardial Infarction Registry I. Benefits of Statin Therapy in Patients With Acute Myocardial Infarction With Serum Low-Density Lipoprotein Cholesterol </= 50 mg/dl. Am J Cardiol 2017; 120:174-180

234. Cholesterol Treatment Trialists C. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 2019; 393:407-415

235. Allen Maycock CA, Muhlestein JB, Horne BD, Carlquist JF, Bair TL, Pearson RR, Li Q, Anderson JL, Intermountain Heart Collaborative S. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. J Am Coll Cardiol 2002; 40:1777-1785

236. Cooke CA, Kirkland SA, Sketris IS, Cox J. The impact of statins on health services utilization and mortality in older adults discharged from hospital with ischemic heart disease: a cohort study. BMC Health Serv Res 2009; 9:198

237. Gransbo K, Melander O, Wallentin L, Lindback J, Stenestrand U, Carlsson J, Nilsson J. Cardiovascular and cancer mortality in very elderly post-myocardial infarction patients receiving statin treatment. J Am Coll Cardiol 2010; 55:1362-1369

238. Eaton CB, Lapane KL, Murphy JB, Hume AL. Effect of statin (HMG-Co-A-Reductase Inhibitor) use on 1-year mortality and hospitalization rates in older patients with cardiovascular disease living in nursing homes. J Am Geriatr Soc 2002; 50:1389-1395

239. Foley TR, Singh GD, Kokkinidis DG, Choy HK, Pham T, Amsterdam EA, Rutledge JC, Waldo SW, Armstrong EJ, Laird JR. High-Intensity Statin Therapy Is Associated With Improved Survival in Patients With Peripheral Artery Disease. Journal of the American Heart Association 2017; 6

240. Rothschild DP, Novak E, Rich MW. Effect of Statin Therapy on Mortality in Older Adults Hospitalized with Coronary Artery Disease: A Propensity-Adjusted Analysis. J Am Geriatr Soc 2016; 64:1475-1479

241. Foody JM, Rathore SS, Galusha D, Masoudi FA, Havranek EP, Radford MJ, Krumholz HM. Hydroxymethylglutaryl-CoA reductase inhibitors in older persons with acute myocardial infarction: evidence for an age-statin interaction. J Am Geriatr Soc 2006; 54:421-430

242. Ble A, Hughes PM, Delgado J, Masoli JA, Bowman K, Zirk-Sadowski J, Mujica Mota RE, Henley WE, Melzer D. Safety and Effectiveness of Statins for Prevention of Recurrent Myocardial Infarction in 12 156 Typical Older Patients: A

Quasi-Experimental Study. J Gerontol A Biol Sci Med Sci 2017; 72:243-250

243. Olafsdottir E, Aspelund T, Sigurdsson G, Thorsson B, Eiriksdottir G, Harris TB, Launer LJ, Benediktsson R, Gudnason V. Effects of statin medication on mortality risk associated with type 2 diabetes in older persons: the population-based AGES-Reykjavik Study. BMJ Open 2011; 1:e000132

244. Fung CSC, Wan EYF, Chan AKC, Lam CLK. Statin use reduces cardiovascular events and all-cause mortality amongst Chinese patients with type 2 diabetes mellitus: a 5-year cohort study. BMC Cardiovasc Disord 2017; 17:166

245. Hayashi T, Kubota K, Kawashima S, Sone H, Watanabe H, Ohrui T, Yokote K, Takemoto M, Araki A, Noda M, Noto H, Sakuma I, Yoshizumi M, Ina K, Nomura H, Japan CDMg. Efficacy of HMG-CoA reductase inhibitors in the prevention of cerebrovascular attack in 1016 patients older than 75 years among 4014 type 2 diabetic individuals. Int J Cardiol 2014; 177:860-866

246. Pilotto A, Panza F, Copetti M, Simonato M, Sancarlo D, Gallina P, Strandberg T, Investigators MAP. Statin Treatment and Mortality in Community-Dwelling Frail Older Patients with Diabetes Mellitus: A Retrospective Observational Study. PLoS One 2015; 10:e0130946

247. Clua-Espuny JL, Gonzalez-Henares MA, Queralt-Tomas MLL, Campo-Tamayo W, Muria-Subirats E, Panisello-Tafalla A, Lucas-Noll J. Mortality and Cardiovascular Complications in Older Complex Chronic Patients with Type 2 Diabetes. BioMed research international 2017; 2017:6078498

248. Ramos R, Comas-Cufi M, Marti-Lluch R, Ballo E, Ponjoan A, Alves-Cabratosa L, Blanch J, Marrugat J, Elosua R, Grau M, Elosua-Bayes M, Garcia-Ortiz L, Garcia-Gil M. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. BMJ 2018; 362:k3359

249. Orkaby AR, Gaziano JM, Djousse L, Driver JA. Statins for Primary Prevention of Cardiovascular Events and Mortality in Older Men. J Am Geriatr Soc 2017; 65:2362-2368

250. Strandberg TE, Pitkala KH, Tilvis RS. Statin treatment is associated with clearly reduced mortality risk of cardiovascular patients aged 75 years and older. J Gerontol A Biol Sci Med Sci 2008; 63:213-214; author reply 214

251. Kim K, Lee CJ, Shim CY, Kim JS, Kim BK, Park S, Chang HJ, Hong GR, Ko YG, Kang SM, Choi D, Ha JW, Hong MK,

Jang Y, Lee SH. Statin and clinical outcomes of primary prevention in individuals aged >75years: The SCOPE-75 study. Atherosclerosis 2019; 284:31-36

252. Galindo-Ocana J, Bernabeu-Wittel M, Formiga F, Fuertes-Martin A, Baron-Franco B, Murcia-Zaragoza JM, Moreno-Gavino L, Ollero-Baturone M, researchers PP. Effects of renin-angiotensin blockers/inhibitors and statins on mortality and functional impairment in polypathological patients. Eur J Intern Med 2012; 23:179-184

253. Luotola K, Jyvakorpi S, Urtamo A, Pitkala KH, Kivimaki M, Strandberg TE. Statin treatment, phenotypic frailty and mortality among community-dwelling octogenarian men: the HBS cohort. Age Ageing 2020; 49:258-263

254. Gnjidic D, Le Couteur DG, Blyth FM, Travison T, Rogers K, Naganathan V, Cumming RG, Waite L, Seibel MJ, Handelsman DJ, McLachlan AJ, Hilmer SN. Statin use and clinical outcomes in older men: a prospective population-based study. BMJ Open 2013; 3

255. Jacobs JM, Cohen A, Ein-Mor E, Stessman J. Cholesterol, statins, and longevity from age 70 to 90 years. J Am Med Dir Assoc 2013; 14:883-888

256. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, Investigators I-I. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372:2387-2397

257. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS, Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; 376:1713-1722

258. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM, Committees OO, Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med 2018; 379:2097-2107

259. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or

Atherosclerotic Cardiovascular Disease. JAMA 2016; 316:743-753

260. Arrieta A, Page TF, Veledar E, Nasir K. Economic Evaluation of PCSK9 Inhibitors in Reducing Cardiovascular Risk from Health System and Private Payer Perspectives. PLoS One 2017; 12:e0169761

261. Avalere. xxxhttps://avalerecom/insights/affordable-patient-access-to-pcsk9-inhibitors-remains-challenging-across-part-d-plans-in-2020 2020;

262. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R, Investigators S. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377:2181-2192

263. Wanner C, Krane V, Ruf G, Marz W, Ritz E. Rationale and design of a trial improving outcome of type 2 diabetics on hemodialysis. Die Deutsche Diabetes Dialyse Studie Investigators. Kidney Int Suppl 1999; 71:S222-226

264. Wanner C, Krane V, Marz W, Olschewski M, Asmus HG, Kramer W, Kuhn KW, Kutemeyer H, Mann JF, Ruf G, Ritz E. Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): demographic and baseline characteristics. Kidney Blood Press Res 2004; 27:259-266

265. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009; 360:1395-1407

266. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janosi A, Kamensky G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007; 357:2248-2261

267. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372:1231-1239

268. Nordestgaard BG, Tybjaerg-Hansen A. Genetic determinants of LDL, lipoprotein(a), triglyceride-rich lipoproteins and HDL: concordance and discordance with cardiovascular disease risk. Curr Opin Lipidol 2011; 22:113-122

269. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis 2011; 217:492-498

270. Group AS, Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Jr., Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010; 362:1563-1574

271. Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-Gonzalez I, Briel M. Fibrates for primary prevention of cardiovascular disease events. Cochrane Database Syst Rev 2016; 11:CD009753

272. Wang D, Liu B, Tao W, Hao Z, Liu M. Fibrates for secondary prevention of cardiovascular disease and stroke. Cochrane Database Syst Rev 2015:CD009580

273. Zhou YH, Ye XF, Yu FF, Zhang X, Qin YY, Lu J, He J. Lipid management in the prevention of stroke: a meta-analysis of fibrates for stroke prevention. BMC Neurol 2013; 13:1

274. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999; 341:410-418

275. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795

people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366:1849-1861

276. Jun M, Zhu B, Tonelli M, Jardine MJ, Patel A, Neal B, Liyanage T, Keech A, Cass A, Perkovic V. Effects of fibrates in kidney disease: a systematic review and meta-analysis. J Am Coll Cardiol 2012; 60:2061-2071

277. Investigators A-H, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011; 365:2255-2267

278. Group HTC, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014; 371:203-212

279. Schandelmaier S, Briel M, Saccilotto R, Olu KK, Arpagaus A, Hemkens LG, Nordmann AJ. Niacin for primary and secondary prevention of cardiovascular events. Cochrane Database Syst Rev 2017; 6:CD009744

280. D'Andrea E, Hey SP, Ramirez CL, Kesselheim AS. Assessment of the Role of Niacin in Managing Cardiovascular Disease Outcomes: A Systematic Review and Meta-analysis. JAMA Netw Open 2019; 2:e192224

281. Goldie C, Taylor AJ, Nguyen P, McCoy C, Zhao XQ, Preiss D. Niacin therapy and the risk of new-onset diabetes: a meta-analysis of randomised controlled trials. Heart 2016; 102:198-203

282. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik M, Steinbeck G, Del Castillo U, Sack R, Worth H, Katus H, Spitzer W, Sabin G, Senges J. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation 122:2152-2159

283. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 363:2015-2026

284. Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ 341:c6273

285. Investigators OT, Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, Riddle MC, Ryden LE, Yusuf S. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012; 367:309-318

286. Einvik G, Klemsdal TO, Sandvik L, Hjerkinn EM. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. Eur J Cardiovasc Prev Rehabil 2010; 17:588-592

287. Risk, Prevention Study Collaborative G, Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, Longoni P, Marzona I, Milani V, Silletta MG, Tognoni G, Marchioli R. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med 2013; 368:1800-1808

288. Writing Group for the ARG, Bonds DE, Harrington M, Worrall BB, Bertoni AG, Eaton CB, Hsia J, Robinson J, Clemons TE, Fine LJ, Chew EY. Effect of long-chain omega-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA internal medicine 2014; 174:763-771

289. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KH, Summerbell CD, Worthington HV, Song F, Hooper L. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev 2020; 3:CD003177

290. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P, Chew EY, Bosch J, Collins R, Lewington S, Armitage J, Clarke R, Omega-3 Treatment Trialists C. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77917 Individuals. JAMA Cardiol 2018; 3:225-234

291. Popoff F, Balaciano G, Bardach A, Comande D, Irazola V, Catalano HN, Izcovich A. Omega 3 fatty acid supplementation after myocardial infarction: a systematic review and meta-analysis. BMC Cardiovasc Disord 2019; 19:136

292. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372:1223-1230

293. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS):

a randomised open-label, blinded endpoint analysis. Lancet 2007; 369:1090-1098

294. Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, Matsuzawa Y, Sasaki J, Oikawa S, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke 2008; 39:2052-2058

295. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, Group ESCSD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41:111-188

296. Streja L, Packard CJ, Shepherd J, Cobbe S, Ford I, Group W. Factors affecting low-density lipoprotein and high-density lipoprotein cholesterol response to pravastatin in the West Of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol 2002; 90:731-736

297. Morrone D, Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, Shah AK, Tershakovec AM. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis 2012; 223:251-261

298. Robinson JG, Booth B. Statin use and lipid levels in older adults: National Health and Nutrition Examination Survey, 2001 to 2006. J Clin Lipidol 2010; 4:483-490

299. Patel J, Superko HR, Martin SS, Blumenthal RS, Christopher-Stine L. Genetic and immunologic susceptibility to statin-related myopathy. Atherosclerosis 2015; 240:260-271

300. Lee E, Ryan S, Birmingham B, Zalikowski J, March R, Ambrose H, Moore R, Lee C, Chen Y, Schneck D. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005; 78:330-341

301. He Y, Li X, Gasevic D, Brunt E, McLachlan F, Millenson M, Timofeeva M, Ioannidis JPA, Campbell H, Theodoratou E. Statins and Multiple Noncardiovascular Outcomes: Umbrella Review of Meta-analyses of Observational Studies and Randomized Controlled Trials. Ann Intern Med 2018; 169:543-553

302. Iwere RB, Hewitt J. Myopathy in older people receiving statin therapy: a systematic review and meta-analysis. Br J Clin Pharmacol 2015; 80:363-371

303. Schech S, Graham D, Staffa J, Andrade SE, La Grenade L, Burgess M, Blough D, Stergachis A, Chan KA, Platt R, Shatin D. Risk factors for statin-associated rhabdomyolysis. Pharmacoepidemiol Drug Saf 2007; 16:352-358

304. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004; 292:2585-2590

305. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41

306. Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, James OF. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology 1989; 9:297-301

307. Kinirons MT, O'Mahony MS. Drug metabolism and ageing. Br J Clin Pharmacol 2004; 57:540-544

308. Gupta S. P-glycoprotein expression and regulation. Age-related changes and potential effects on drug therapy. Drugs Aging 1995; 7:19-29

309. Williams FM, Wynne H, Woodhouse KW, Rawlins MD. Plasma aspirin esterase: the influence of old age and frailty. Age Ageing 1989; 18:39-42

310. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359:2195-2207

311. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care 2009; 32:1924-1929

312. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001; 103:357-362

313. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375:735-742

314. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011; 305:2556-2564

315. Jones M, Tett S, Peeters GM, Mishra GD, Dobson A. New-Onset Diabetes After Statin Exposure in Elderly Women: The Australian Longitudinal Study on Women's Health. Drugs Aging 2017; 34:203-209

316. Sadighara M, Amirsheardost Z, Minaiyan M, Hajhashemi V, Naserzadeh P, Salimi A, Seydi E, Pourahmad J. Toxicity of Atorvastatin on Pancreas Mitochondria: A Justification for Increased Risk of Diabetes Mellitus. Basic Clin Pharmacol Toxicol 2017; 120:131-137

317. Kain V, Kapadia B, Misra P, Saxena U. Simvastatin may induce insulin resistance through a novel fatty acid mediated cholesterol independent mechanism. Sci Rep 2015; 5:13823

318. Henriksbo BD, Schertzer JD. Is immunity a mechanism contributing to statin-induced diabetes? Adipocyte 2015; 4:232-238

319. FDA. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. https://wwwfdagov/drugs/drug-safety-and-availability/fda-drug-safety-communication-important-safety-label-changes-cholesterol-lowering-statin-drugs#sa 2012;

320. Sparks DL, Connor DJ, Sabbagh MN, Petersen RB, Lopez J, Browne P. Circulating cholesterol levels, apolipoprotein E genotype and dementia severity influence the benefit of atorvastatin treatment in Alzheimer's disease: results of the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. Acta Neurol Scand Suppl 2006; 185:3-7

321. Sparks DL, Sabbagh M, Connor D, Soares H, Lopez J, Stankovic G, Johnson-Traver S, Ziolkowski C, Browne P. Statin therapy in Alzheimer's disease. Acta Neurol Scand Suppl 2006; 185:78-86

322. Zhou B, Teramukai S, Fukushima M. Prevention and treatment of dementia or Alzheimer's disease by statins: a meta-analysis. Dement Geriatr Cogn Disord 2007; 23:194-201

323. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2009:CD003160

324. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE, Heidenreich PA, Rader DJ, deGoma EM. Statins and cognitive function: a systematic review. Ann Intern Med 2013; 159:688-697

325. Regeneron. Prescribing Information. https://wwwregeneroncom/sites/default/files/Praluent_PIpdf 2020;

326. Amgen. Repatha Prescribing information. https://wwwpiamgencom/~/media/amgen/repositorysites/pi-amgen-com/repatha/repatha_pi_hcp_englishpdf 2019;

327. Raal FJ, Tuomilehto J, Sposito AC, Fonseca FA, Averna M, Farnier M, Santos RD, Ferdinand KC, Wright RS, Navarese EP, Lerch DM, Louie MJ, Lee LV, Letierce A, Robinson JG. Treatment effect of alirocumab according to age group, smoking status, and hypertension: Pooled analysis from 10 randomized ODYSSEY studies. J Clin Lipidol 2019; 13:735-743

328. Zhang XL, Zhu QQ, Zhu L, Chen JZ, Chen QH, Li GN, Xie J, Kang LN, Xu B. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med 2015; 13:123

329. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Robinson JG, Honarpour N, Wasserman SM, Ott BR, Investigators E. Cognitive Function in a Randomized Trial of Evolocumab. N Engl J Med 2017; 377:633-643

330. Harvey PD, Sabbagh MN, Harrison JE, Ginsberg HN, Chapman MJ, Manvelian G, Moryusef A, Mandel J, Farnier M. No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized Phase 2 and 3 controlled trials: a meta-analysis of individual patient data. Eur Heart J 2018; 39:374-381

331. Merck. Ezetimibe Package Insert. https://wwwmerckcom/product/usa/pi_circulars/z/zetia/zetia_pipdf 2013;

332. Ose L, Shah A, Davies MJ, Rotonda J, Maccubbin D, Tribble D, Veltri E, Mitchel Y. Consistency of lipid-altering effects of ezetimibe/simvastatin across gender, race, age, baseline low density lipoprotein cholesterol levels, and coronary heart disease status: results of a pooled retrospective analysis. Curr Med Res Opin 2006; 22:823-835

333. Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. Cochrane Database Syst Rev 2018; 11:CD012502

334. Esperion. Package Insert. https://piesperioncom/nexletol/nexletol-pipdf 2020;

335. Dai L, Zuo Y, You Q, Zeng H, Cao S. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: A systematic review and meta-analysis of randomized controlled trials. European journal of preventive cardiology 2020:2047487320930585

336. Ballantyne CM, Laufs U, Ray KK, Leiter LA, Bays HE, Goldberg AC, Stroes ES, MacDougall D, Zhao X, Catapano AL. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. European journal of preventive cardiology 2020; 27:593-603

337. Daiichi. Welchol Package Insert. https://dsicom/prescribing-information-portlet/getDocument?product=WC&inline=true 2020;

338. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. Diabetes Care 2008; 31:1479-1484

339. Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. Arch Intern Med 2008; 168:1531-1540

340. AbbVie. Trilipix Package insert. https://wwwrxabbviecom/pdf/trilipix_pipdf 2018;

341. Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, Soni PN. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol 2012; 110:984-992

342. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol 2011; 108:682-690

343. Gurunathan S, Ahmed A, Pabla J, Karogiannis N, Hua A, Young G, Nalin Shah B, Senior R. The clinical efficacy and long-term prognostic value of stress echocardiography in octogenarians. Heart 2017; 103:517-523

344. Nudi F, Biondi-Zoccai G, Schillaci O, di Belardino N, Versaci F, Nudi A, Pinto A, Neri G, Procaccini E, Frati G, Iskandrian AE. Prognostic accuracy of myocardial perfusion imaging in octogenarians. J Nucl Cardiol 2018; 25:1342-1349

345. Katsikis A, Theodorakos A, Manira V, Papaioannou S, Kolovou G, Voudris V, Koutelou M. Long-term prognostic implications of myocardial perfusion imaging in octogenarians: an all-comer, cohort study. Eur J Nucl Med Mol Imaging 2017; 44:1547-1558

346. Couture EL, Farand P, Nguyen M, Allard C, Wells GA, Mansour S, Rinfret S, Afilalo J, Eisenberg M, Montigny M, Kouz S, Afilalo M, Lauzon C, Dery JP, L'Allier P, Schampaert E, Tardif JC, Huynh T. Impact of an invasive strategy in the elderly hospitalized with acute coronary syndrome with emphasis on the nonagenarians. Catheter Cardiovasc Interv 2018; 92:E441-E448

347. Khan MR, Kayani WT, Ahmad W, Manan M, Hira RS, Hamzeh I, Jneid H, Virani SS, Kleiman N, Lakkis N, Alam M. Effect of increasing age on percutaneous coronary intervention vs coronary artery bypass grafting in older adults with unprotected left main coronary artery disease: A meta-analysis and meta-regression. Clin Cardiol 2019; 42:1071-1078

348. Lee SO, Lee H, Cho YH, Jeong DS, Lee YT, Kim WS. Comparison of Off-Pump Coronary Artery Bypass between Octogenarians and Septuagenarians: A Propensity Score Analysis. Korean J Thorac Cardiovasc Surg 2019; 52:155-161

349. Mehta H, Sacrinty M, Johnson D, St Clair M, Paladenech C, Robinson K. Comparison of usefulness of secondary prevention of coronary disease in patients <80 versus >/=80 years of age. Am J Cardiol 2013; 112:1099-1103

350. Fleg JL, Forman DE, Berra K, Bittner V, Blumenthal JA, Chen MA, Cheng S, Kitzman DW, Maurer MS, Rich MW, Shen WK, Williams MA, Zieman SJ, American Heart Association Committees on Older P, Exercise Cardiac R, Prevention of the Council on Clinical Cardiology CoC, Stroke Nursing CoL, Cardiometabolic H. Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association. Circulation 2013; 128:2422-2446

351. Qi K, Reeve E, Hilmer SN, Pearson SA, Matthews S, Gnjidic D. Older peoples' attitudes regarding polypharmacy, statin use and willingness to have statins deprescribed in Australia. Int J Clin Pharm 2015; 37:949-957

352. Kutner JS, Abernethy AP. Coding Error Resulting in Change in Secondary Outcome Scores in Trial of Safety and Benefit of Discontinuing Statin Therapy Among Terminally Ill Patients. JAMA internal medicine 2019; 179:126

353. Kutner JS, Blatchford PJ, Taylor DH, Jr., Ritchie CS, Bull JH, Fairclough DL, Hanson LC, LeBlanc TW, Samsa GP, Wolf S, Aziz NM, Currow DC, Ferrell B, Wagner-Johnston N, Zafar SY, Cleary JF, Dev S, Goode PS, Kamal AH, Kassner C, Kvale EA, McCallum JG, Ogunseitan AB, Pantilat SZ, Portenoy RK, Prince-Paul M, Sloan JA, Swetz KM, Von Gunten CF, Abernethy AP. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA internal medicine 2015; 175:691-700

354. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312:71-72