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PERSPECTIVE

# Dyslipidemia and Cardiovascular Prevention in the Elderly: A Balance between Benefits and Risks of Statin Treatment in a Specific Population

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**Abstract:** ***Introduction*:** Atherosclerotic Cardiovascular Diseases (CVD) are among the most relevant causes of morbidity and mortality worldwide, especially in aged people. Statins are one of the leading pharmacological interventions against atherosclerosis and are widely used to reduce the risk of occurring coronary artery diseases and related outcomes in both primary and secondary prevention. The management of chronic diseases is improved considerably over time, leading to an increase in life expectancy despite heavier comorbidity-related burdens in the elderly.

***Aims*:** The paper focused on the role of statins in the management of atherosclerosis and related burdens in elderly patients.

***Results*:** Statins are essential in reducing the risk of CVD in secondary and primary prevention, particularly in high-risk individuals. Guidelines encourage using specific algorithms with age-specific cut-offs to assess individual cardiovascular risk irrespective of baseline age, as the expansion of life expectancy produces favorable effects of statin treatment in those over 70.

***Discussion*:** Besides the estimation of baseline CV risk, a specific age-related assessment is also necessary before prescribing statin treatment in aged people focusing on frailty, potential pharmacological interactions due to polypharmacotherapy, cognitive impairment, and background chronic comorbidities, such as diabetes mellitus. Before starting statin therapy, an accurate choice of type and dose of statins is needed as potential adverse events are more prevalent with high-dose than low-to-moderate-dose regimens and with lipophile than hydrophile statins (*e.g.*, potential implication on intra-cerebral cholesterol metabolism).

***Conclusion*:** Despite possible adverse events, elderly patients should receive statins, when appropriate, to avoid the first occurrence of recurrent cardiovascular events and related burdens.

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## 1. INTRODUCTION

Cardiovascular Diseases (CVD) are among the most relevant causes of morbidity and mortality worldwide. The chances of suffering a cardiovascular event increase considerably among men over 65 years of age and women over 75 [1, 2]. Myocardial infarction and stroke are in first place among CVD, leading to poor quality of life and mortality excess [1].

"Elderly" individuals are aged more than 65 years old, while those over 75 years are considered "old people" and those above 90 years are "lifelong age" [3]. Over 80% of cardiovascular deaths occur in the elderly [4-6]. In 2015, people over 65 were 617 million, representing 8.5% of the global population (7.3 billion). In 2030 this percentage will increase to 12% (1 billion) worldwide [4, 7], and in Europe, it will rise to 25%, which will be the highest compared to the other continents [7, 8]. Therefore, the number of patients with established CVD is expected to increase remarkably in the next few years, and now every effort to prevent CVD is crucial and will significantly influence public health policies [4]. Statins represent one of the most effective pharmacological treatments against atherosclerosis (Table **1**). Statins have been shown to reduce stroke and myocardial infarction risks in every age group [1, 9].

However, elderly patients have a shorter life expectancy, with comorbidity-related burdens heavier than younger people; therefore, statins might have less beneficial effects. That is the reason why the pros and cons of statin treatment must be weighed accurately in elderly patients, especially in those who need high-dose treatment [1].

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**Table 1. Summary of the main characteristics of statins currently available for treating hypercholesterolemia.**

| Statin | Origin | Solubility | Low Intensity* | Moderate Intensity* | High Intensity* |
|---|---|---|---|---|---|
| Lovastatin | Natural, modified | Lipophilic | 10-20 mg | 40-80 mg | - |
| Pravastatin | Natural, modified | Hydrophilic | 10-20 mg | 40-80 mg | - |
| Simvastatin | Natural, modified | Lipophilic | 10 mg | 20-40 mg | - |
| Fluvastatin | Fully synthetic | Hydrophilic | 20-40 mg | 80 mg | - |
| Atorvastatin | Fully synthetic | Lipophilic | 5 mg | 10-20 mg | 40-80 mg |
| Rosuvastatin | Fully synthetic | Hydrophilic | | 5-10 mg | 20-40 mg |

**Note:** *The intensity of a statin regimen refers to the percentage of LDL-c decline from baseline once the treatment has started: low intensity = <30%, moderate intensity = 30-49%, high intensity = ≥ 50% [41, 42].

## 2. PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS

While lipid-lowering agents for secondary prevention are recommended by the most recent guidelines with a good level of evidence, the theme of the primary prevention of CVD is still a dilemma in the elderly [6]. According to the 2019 ESC/EAS Guidelines for the management of dyslipidemias, and the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice, the choice of starting a lipid-lowering agent must be evaluated according to a personalized risk profile. Easy-to-use calculator tools could summarize the risk that is expressed as a 10-year or lifelong probability of occurring cardiovascular events in patients with a negative personal history of previous CVD. The SCORE2 risk tables guide the risk evaluation in patients <70, estimating the 10-year fatal and non-fatal cardiovascular disease risk (class I recommendation, evidence level A). The tables for those over 70 years are called the SCORE2-OP (SCORE2 - Older Person). In this age group, the decision to start a lipid-lowering agent should be considered only in patients at high risk (class of recommendation IIb, level of evidence B) [10].

Other European and American guidelines on dyslipidemia support a "patient-based" approach in the elderly [6, 11]. No RCT about statin therapy for primary prevention in elderly patients has been completed so far, and current evidence is provided by observational studies, subgroup analyses, and metanalyses [12].

The PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease) trial, published in 2002, was one of the first studies to assess the benefits of statins for primary prevention in the elderly. Before that, it was assumed that low LDL-cholesterol levels were associated with a higher mortality rate and increased risk of dementia. Among 5,840 patients aged 70-82 years with high background cardiovascular risk, with or without pre-existing cardiovascular diseases, were randomized to receive pravastatin 40 mg per day or the placebo. The primary endpoint was a composite of coronary death, non-fatal myocardial infarction, and stroke. After 3.2 years of follow-up, treatment with pravastatin showed a 15% reduction of the primary endpoint. These data supported the use of pravastatin, especially for its safety and tolerability [13, 14]. However, it did not significantly reduce the primary outcome in patients without previous cardiovascular disease [12].

In a posthoc analysis of the ALLHAT-LLT trial (Lipid-Lowering Trial component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), the results of primary prevention with Pravastatin 40 mg per day vs. usual care were compared between two groups of patients: 65-74 and over 75 years. In 2,867 participants (average age 71 years), no significant differences were found in the risk of cardiovascular events or mortality between the two groups. On the other hand, a slight but not statistically significant increase in all-cause mortality (primary endpoint) was highlighted in the arm of participants >75 years assuming statins (HR 1.34, CI 0.98-1.84) [12, 15].

The JUPITER trial (Justification for the use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), published in 2008, aimed to assess treatment with rosuvastatin 20 mg per day *vs*. placebo in 17,802 patients without cardiovascular disease, with LDL-cholesterol levels <130 mg/dL and CRP levels >2 mg/L. Inflammation is crucial in atherogenesis and atherosclerosis, and statins lower both LDL and CRP levels. In patients treated with rosuvastatin, there was a 47% reduction of the primary endpoint, composite of non-fatal myocardial infarction and stroke, and cardiovascular death) [16].

In 2016, the HOPE-3 trial (Heart Outcomes Prevention Evaluation) was designed to evaluate rosuvastatin 10 mg per day vs. placebo in 12,705 patients without cardiovascular disease, at intermediate cardiovascular risk (defined as about 1% annual risk of cardiovascular events). The statin led to a 24% reduction of the primary endpoint, similar to those found in the JUPITER trial [17].

One year later, Ridker *et al*. conducted a meta-analysis to assess the efficacy of statins on age-specific outcomes from these two trials. In patients over 70 years without established CVD, cardiovascular morbidity and mortality risk was diminished by 26% in those assuming statin therapy. In conclusion, the authors highlighted that data supported the prescription of statins for the primary prevention of cardiovascular events and related burdens in the elderly. Despite these findings, some uncertainties about possible adverse effects and other treatment-related concerns remain, including hemorrhagic stroke, cognitive decline, pharmacological interactions, adherence to therapy, quality of life, and cost-to-benefit ratio. Even though those trials involved many patients, only a few were above 80 years old [18].

A meta-analysis of 10 observational studies showed that statin therapy in patients ≥ 65 years without established CVD was associated with a reduction in 14%, 20%, and 15% of all-cause mortality, cardiovascular mortality, and stroke, respectively. The reduction of all-cause mortality risk also appears relevant in people over 75 years, but only in those with Diabetes Mellitus (DM). According to the GRADE system, however, the quality of evidence is low, leading to a real need for well-designed clinical trials [4]. The updated recommendation suggests that statin treatment in primary prevention should be considered in high-risk adults aged 40 to 75 years, while the evidence is limited in those over 75 [19]. Currently, only two RCTs are specifically assessing the benefits of treatment with statins in this setting, namely the STAREE (STAtin Therapy for Reducing Events in the Elderly), NCT02099123 (estimated study competition date on December 2025) and the PREVENTABLE (Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults), NCT04262206 (estimated study competition date on December 2026). Both trials aim to evaluate the effects of atorvastatin (20 and 40 mg/day in the STAREE and PREVENTABLE, respectively) versus placebo in people ≥70 and ≥ 75 years, respectively.

## 3. SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS

A recent meta-analysis evaluated the results of 28 Randomized Clinical Trials (RCTs) about treatment with statins. The participants were divided into 6 age groups (< 55 years, 56-60 years, 61-65 years, 66-70 years, 71-75 years, and >75 years). Among around 187 thousand participants, 14,483 (8%) were more than 75 years old. Globally, the treatment with statins determined a decrease in Major Adverse Cardiovascular Events (MACEs) of 21% (Risk Ratio or RR 0.79, CI 95% 0.77-0.81, $p$ <0.01) for every 1.0 mmol/L (40 mg/dL) reduction of LDL-cholesterol levels. The authors observed a decline in the risk of MACEs in every age group. Even if the benefit appeared slightly lower in the elderly, this trend has not reached statistical significance ($p$-value 0.06).

While analyzing coronary events, statins led to a 24% reduction of risk (RR 0.76, CI 95% 0.73-0.79, $p$<0.01) for every 1.0 mmol/L reduction of Low-Density Lipoprotein (LDL)-cholesterol levels. Again, the decrease appeared to be lower ($p$ = 0.009) in the elderly. The risk of coronary revascularization procedures decreased by 25% (RR 0.75, CI 95% 0.73-0.78) for every 1.0 mmol/L reduction of LDL-cholesterol levels, without any relevant differences across the different groups of age ($p$ trend 0.6). There was no difference among the groups for stroke risk reduction, which was 16% (RR 0.84, CI 95% 0.80-0.89, $p$ trend 0.7).

Considering only patients with pre-existing cardiovascular disease (the ones in secondary prevention), the risk reduction of MACEs was similar in all the age groups ($p$ trend 0.2). On the other hand, considering the ones without cardiovascular diseases (primary prevention), the risk reduction appeared to be lower in the elderly compared to the young people ($p$ trend 0.05). Eventually, this study identified a 12% reduction (RR 0.88, CI 95% 0.85-0.91) of cardiovascular mortality for every 1.0 mmol/L reduction of LDL-cholesterol levels. This reduction was lower in the elderly ($p$ trend 0.004), but only excluding patients with heart failure or dialysis. Treatment with statins did not affect mortality due to non-cardiovascular causes, cancer incidence, and all-cause mortality. The authors concluded that statins significantly reduced the risk of cardiovascular events in every age group, but benefits appeared less evident in patients over 75 years, especially in primary cardiovascular prevention [20].

In the SAGE (Study Assessing Goals in the Elderly), 893 outpatients with established coronary artery disease were randomized to receive moderate versus intensive statin treatment (pravastatin 40 mg/day *vs*. atorvastatin 80 mg/day). Atorvastatin-treated patients experienced more substantial LDL cholesterol reduction than pravastatin-treated ones. A slight but not-significant reduction in the risk of acute cardiovascular events (RR 0.71; 95% CI 0.46-1.09) and a significantly more relevant decrease in all-cause mortality (HR 0.33; 95% CI 0.13-0.83; $p$=0.014) were observed [21].

Ischemic stroke is one of the leading causes of inability and mortality in the elderly. In the SPARCL (Stroke Prevention by Aggressive Reduction of Cholesterol Levels) trial, 4,731 patients were included, randomized (1:1) to receive atorvastatin 80 mg/day or placebo, and followed up for five years. Patients had a previous history of stroke or transient ischemic attack but no evidence of coronary artery disease. The LDL cholesterol levels in the atorvastatin group decreased by around 61 mg/dL, corresponding to a decrease of 53% from baseline, and were unchanged in the placebo group. This effect was accompanied by a 5-year absolute reduction in risk of fatal or non-fatal stroke by 2.2%, mostly due to ischemic etiology. The risk of major cardiovascular events was reduced by 3.5% after five years of treatment, while no difference in the overall mortality rate was observed between the two groups [22]. The authors also observed that the number of hemorrhagic strokes was higher in patients randomized to receive atorvastatin 80 mg/day (55 events) than in those on pravastatin (33 events). A recently published meta-analysis of 11 RCTs with 20,163 patients (67% men, mean age 65 years) followed up for 4 years confirmed the above-mentioned results. More precisely, high-intensity statin-based therapy compared to low-intensity statin-based therapy produced a relevant reduction in the risk of cardiovascular events, including ischemic but not hemorrhagic stroke, in patients with any evidence of atherosclerosis (RR 0.79; 95% CI, 0.69-0.91, $p$ <0.001) but not in those without this condition [23].

The most recent guidelines of the European Society of Cardiology about treating dyslipidemia are based on the result of this meta-analysis. In patients with established CVD (secondary prevention), the lipid-lowering treatment with a statin is always recommended irrespective of baseline age (class of recommendation I, level of evidence A) [6].

## 4. SPECIFIC CONSIDERATIONS FOR THE USE OF STATIN FOR THE ELDERLY

### 4.1. Frailty

The evidence about possible benefits and potential risks of lipid-lowering agents in primary prevention is limited, not only because older age groups are scarcely represented in clinical trials but also because there is a lack of information regarding the functional and frailty status of participants.

Frailty is a clinical syndrome characterized by a decline in functional status and an increase in vulnerability affecting aged people [11]. Individuals with frailty have an increased risk of mortality and are more prone to develop a complete dependence on caregivers to carry out activities of daily living [24]. In geriatric care, chronological age could be considerably different from biological age, and the individual performance status of older patients is usually included in a wide range of clinical variability. Therefore, it seems arbitrary to use the chronological age as the only or best-established cut-off in clinical trials and routine practice, with this statement being particularly true for statin treatment [11].

### 4.2. Side Effects and Drug Interactions

Generally, drugs are cleared more slowly in the elderly than in adult patients. The glomerular filtration rate declines over time, and the same occurs at the liver levels, where a reduction in oxidizing and conjugating enzymes blunts the metabolism and elimination of drugs and their derivatives.

Consequently, plasmatic concentrations of drugs could be longer in aged people. Clinicians frequently compensate for this effect by avoiding prescriptions or prescribing low-dose therapy in the elderly, particularly when drugs with a narrow therapeutic range are used.

Furthermore, polytherapy is a common finding in elderly individuals as there is an actual need to treat more than one comorbidity leading to an increased risk of drug interactions. Statins do not escape these general rules. Except for rosuvastatin, the plasma concentration of all statins is moderately increased in elderly patients [25]. Aside from pravastatin and rosuvastatin, all available statins are metabolized by the hepatic P450 cytochrome system. The plasmatic concentration of statins may rise when other drugs compete with the cytochrome P450 system, increasing the risk of adverse effects, such as myositis and rhabdomyolysis. The same can occur with certain foods containing cytochrome isoenzyme inhibitors, such as grapefruit juice [26].

The risk of developing severe statin-related muscle injury, such as rhabdomyolysis, is around 0.1%. Due to the rarity of the side effect, its predisposing factors are not well-defined. Advanced age may be considered a potential risk factor, as elderly patients appear to be more vulnerable to muscle injury. Hypothyroidism, pre-existing muscle diseases, renal insufficiency, the initiation of concomitant therapies interfering with statin metabolism, female gender, diabetes mellitus, and ethnicity (particularly for Asians) are other possible precipitating factors [25, 27, 28].

As seen previously, large randomized cardiovascular outcome clinical trials evaluated patients ≥ 65 years of age (including those over 70 and 80) for 3 to 5 years of treatment. Based on these data, statins appeared safe in the elderly, even if the risk of myopathy and rhabdomyolysis seemed to be double compared to that observed in the younger patients. In any case, this remains a rare adverse event. In deciding whether to initiate (or not) a lipid-lowering therapy in older patients, clinicians should consider this risk, including potential drug interactions, priorities of care, and patient preferences [25].

### 4.3. Diabetes Mellitus

In recent scientific literature, a correlation between statins and the incidence of diabetes mellitus has emerged. In the JUPITER clinical trial, the prevalence of new-onset DM was slightly higher in the statin group compared to the placebo group (3% *vs*. 2.4%). The glycated hemoglobin (HbA1c) values were higher in the statin group than in the placebo after 24 months of treatment, but the difference was clinically irrelevant [13, 16].

Furthermore, a meta-analysis of 13 clinical trials, including 91,140 participants, showed that statin therapy was associated with a 9% increased risk of incident type 2 DM, corresponding to one new case of DM for every 255 patients treated for four years with statins. Most importantly, the risk of newly diagnosed type 2 DM was higher in older participants [13, 29].

The CORALL study (Compare the Effect of Rosuvastatin with Atorvastatin on Apo B/Apo A-1 Ratio in Patients with Type 2 Diabetes Mellitus and Dyslipidaemia) evaluated the effect of high-dose statins on glycemic control in patients with background DM. Patients were randomized to receive rosuvastatin 10 mg or atorvastatin 20 mg, and treatment was titrated progressively to 40 and 80 mg, respectively, with a global length of observation of 12 weeks. Patients on high-dose statin regimens experienced a slight deterioration of glucose control in both groups: HbA1c values increased from 7.4% to 7.7% in the atorvastatin group and 7.6% to 7.9% in the rosuvastatin group [13, 30].

Although statins increased the incidence of DM and worsened glycemic control in patients with established DM before starting statin treatment, no data showed that statins worsened cardiovascular outcomes [13, 31]. On the contrary, DM is an independent risk factor for cardiovascular events, and LDL cholesterol is the primary target of lipid-lowering agents in patients with DM. Clinical trials conducted specifically in patients with type 2 DM and subgroup analyses of the leading clinical trials involving patients with DM who were assuming statins demonstrated significant benefit of statin therapy in preventing cardiovascular events. According to a meta-analysis of 14 clinical trials, statin therapy reduced the 5-year incidence of major cardiovascular events by 23% on every 1 mmol/L of LDL reduction, regardless of baseline LDL value [6, 32]. Furthermore, people with type 2 DM have a decreased relative risk of major cardiovascular events of the same magnitude as non-diabetic individuals. As the absolute risk of cardiovascular events is more elevated in DM than in non-diabetes, the absolute benefit of lipid-lowering therapy will be more significant for patients with DM, with an overall reduction in the number needed to treat. Therefore, statin therapy is the first-line treatment to reduce LDL cholesterol and cardiovascular risk in patients with DM [6, 32, 33].

In conclusion, statin therapy causes only a modest increase in the risk of new-onset DM, especially in patients with multiple risk factors. Nevertheless, the risk of developing statin-induced DM (0.2% per year in major clinical trials) and the risk of worsening glucose control in individuals with established DM are clinically irrelevant [1, 32]. On the other hand, the clinical benefits of statin treatment in reducing background cardiovascular risk in all patients, including those with

DM, are relevant. The prescription of statins should be encouraged even in individuals at high risk of developing DM or with pre-existing or newly diagnosed DM [1, 34].

The precise relationship between lipid profile and mortality in elderly and type 2 DM patients is unclear. The ZODIAC-13 (Zwolle Outpatient Diabetes project Integrating Available Care) study aimed to understand the relationship between lipid profile and mortality in elderly patients with type 2 DM over a 10-year follow-up. In 1998, 881 patients with type 2 DM aged >60 were included in the study. The cohort was split into two groups: patients aged 60-75 years and over 75 years. Higher plasma lipid values did not correlate with or increase all-cause and cardiovascular mortality in patients >75 years old. However, the outcome changed when stratifying patients by disease duration. In patients with DM duration greater than eight years, higher plasma lipid values were associated with increased cardiovascular mortality [35].

Lastly, a relevant reduction in the all-cause mortality risk was observed in patients with DM on statins; this result underlines the potential of this class of drugs in elderly patients with DM in primary prevention.

### 4.4. Cognitive Impairment and Dementia

Cognitive impairment and dementia are not-infrequent findings in the elderly, as life expectancy increases over time. Mild cognitive impairment is a symptomatic phase of predementia in which patients exhibit only slightly reduced cognitive functions that do not significantly affect their routine activities. It is estimated that 10 to 20% of patients older than 65 may have a mild cognitive impairment [36]. The prevalence of dementia in patients over 65 years is 5 to 10%, according to epidemiological data, and it rises to 30% in over 80 years old. The incidence rate is similar between the genders, with an annual rate of around 0.1% at age 60-64 to 8.6% at age 95 [37].

Genetic factors, chronic comorbidities, lifestyle, and education are the leading determinant of cognitive function over time. Degenerative neurologic disorders (such as Alzheimer's Disease), CVD, and metabolic diseases represent the most common causes of cognitive decline and dementia [36, 38, 39].

Burdens related to cognitive decline are relevant in terms of social, medical, and economic perspectives, with a real need to diagnose and treat it precociously. Brain training, regular physical exercise, a healthy lifestyle, and adequate treatment of cardio-metabolic risk factors, including dyslipidemia, are the basic goals in preventing dementia [1].

The risk of dementia increases alongside LDL levels, and lowering serum cholesterol concentration with statins reduces this risk. However, some concern about statin handling in the elderly is due to the concept that lower levels of LDL cholesterol could affect lipid metabolism in the brain with potentially detrimental consequences in terms of neurotransmission. From this point of view, neurocognitive outcomes of statins may be attributable to both cholesterol and non-cholesterol-dependent effects, as recently reviewed [40]. More precisely, statins may modulate neuroinflammation, oxidative stress, apoptosis, synaptic plasticity, and the blood-brain barrier permeability, resulting in either protective or detrimental consequences. The precise effect of statins on cognition remains to be determined as the results of clinical trials are equivocal (improvement or not-improvement). However, some reflections could be considered regarding the chemical composition of statins, daily dose, and duration of treatment. Lipophilic (including atorvastatin, simvastatin, and lovastatin) than hydrophilic (such as rosuvastatin and pravastatin) statins are more prone to cross the blood-brain barriers as no-specific carries are required to mediate the transition, and they negatively affect the cholesterol metabolism in the brain Table **1** [40-42]. Low-dose compared to high-dose statin therapy may be associated with better cognitive outcomes, but its clinical efficacy should be addressed based on individualized therapeutic targets for optimal lipid management. Lastly, potential cognitive improvements may require several months (6-12) to be observed. Therefore, specific trials are needed.

## CONCLUSION

The progressive increase in life expectancy leads to a rise in elder and comorbid patients. The prevention of CVD and its related sequelae should be considered an important endpoint in elderly patients, and statins remain the gold standard of treatment for hypercholesterolemia and cardiovascular protection.

Secondary cardiovascular prevention improves the quality of life and reduces the number of recurrent cardiovascular events and mortality rates in patients over 70 years old. Primary prevention improves the quality of life and may also reduce the mortality rate in patients over 70 years, especially those with DM.

The benefits increase when intensive over moderate statin treatment is prescribed. However, caution should be considered in elderly individuals, as side effects of statin are more frequently observed in them than in younger people, because of the multiple associated comorbidities and frailty, due to potential drug interactions and possible detrimental cognitive outcomes.

Despite possible side effects, elderly patients should receive statins to avoid cardiovascular events, such as myocardial infarction or stroke. The essential goal of statin therapy is to prevent a first or recurrent cardiovascular event, which may considerably improve morbidity and mortality in older people.

## AUTHORS' CONTRIBUTIONS

V.F. conceived the perspective; V.F., A.B., S.B., and G.C. drafted the original manuscript; D.T., D.Tr., G.L., and V.T. read and implemented the text in a second drafting, and also provided additional sections and references. V.T. and G.P. read the final version and the manuscript and provided further conclusive feedback. All the authors read the text, approved the final version of the paper, and agreed to the journal submission.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| CVD | = | Cardiovascular Diseases |
| DM | = | Diabetes Mellitus |
| LDL | = | Low-Density Lipoprotein |

MACEs = Major Adverse Cardiovascular Events

RCTs = Randomized Clinical Trials

RR = Risk Ratio

## CONFLICT OF INTEREST

The authors deny any compelling financial interest related to the paper.

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## REFERENCES

[1] Horodinschi, R.N.; Stanescu, A.M.A.; Bratu, O.G.; Pantea. S., A.; Radavoi, D.G.; Diaconu, C.C. Treatment with statins in elderly patients. *Medicina,* **2019**, *55*(11), 721. http://dx.doi.org/10.3390/medicina55110721 PMID: 31671689

[2] Robinson, J.G.; Bakris, G.; Torner, J.; Stone, N.J.; Wallace, R. Is it time for a cardiovascular primary prevention trial in the elderly? *Stroke,* **2007**, *38*(2), 441-450. http://dx.doi.org/10.1161/01.STR.0000254602.58896.d2 PMID: 17194877

[3] Cybulski, M.; Krajewska-Kułak, E.; Sowa, P.; Orzechowska, M.; Van Damme-Ostapowicz, K.; Rozwadowska, E.; Guzowski, A. Elderly peoples' perception of young people - A preliminary study. *Iran. J. Public Health,* **2013**, *42*(10), 1099-1105. PMID: 26060617

[4] Awad, K.; Mohammed, M.; Zaki, M.M.; Abushouk, A.I.; Lip, G.Y.H.; Blaha, M.J.; Lavie, C.J.; Toth, P.P.; Jukema, J.W.; Sattar, N.; Banach, M. Association of statin use in older people primary prevention group with risk of cardiovascular events and mortality: A systematic review and meta-analysis of observational studies. *BMC Med.,* **2021**, *19*(1), 139. http://dx.doi.org/10.1186/s12916-021-02009-1 PMID: 34154589

[5] Benjamin, E.J.; Blaha, M.J.; Chiuve, S.E.; Cushman, M.; Das, S.R.; Deo, R.; de Ferranti, S.D.; Floyd, J.; Fornage, M.; Gillespie, C.; Isasi, C.R.; Jiménez, M.C.; Jordan, L.C.; Judd, S.E.; Lackland, D.; Lichtman, J.H.; Lisabeth, L.; Liu, S.; Longenecker, C.T.; Mackey, R.H.; Matsushita, K.; Mozaffarian, D.; Mussolino, M.E.; Nasir, K.; Neumar, R.W.; Palaniappan, L.; Pandey, D.K.; Thiagarajan, R.R.; Reeves, M.J.; Ritchey, M.; Rodriguez, C.J.; Roth, G.A.; Rosamond, W.D.; Sasson, C.; Towfighi, A.; Tsao, C.W.; Turner, M.B.; Virani, S.S.; Voeks, J.H.; Willey, J.Z.; Wilkins, J.T.; Wu, J.H.Y.; Alger, H.M.; Wong, S.S.; Muntner, P. Heart disease and stroke statistics—2017 update: A report from the American Heart Association. *Circulation,* **2017**, *135*(10), e146-e603. http://dx.doi.org/10.1161/CIR.0000000000000485 PMID: 28122885

[6] Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; Graham, I.M.; Halliday, A.; Landmesser, U.; Mihaylova, B.; Pedersen, T.R.; Riccardi, G.; Richter, D.J.; Sabatine, M.S.; Taskinen, M.R.; Tokgozoglu, L.; Wiklund, O.; Mueller, C.; Drexel, H.; Aboyans, V.; Corsini, A.; Doehner, W.; Farnier, M.; Gigante, B.; Kayikcioglu, M.; Krstacic, G.; Lambrinou, E.; Lewis, B.S.; Masip, J.; Moulin, P.; Petersen, S.; Petronio, A.S.; Piepoli, M.F.; Pintó, X.; Räber, L.; Ray, K.K.; Reiner, Ž.; Riesen, W.F.; Roffi, M.; Schmid, J-P.; Shlyakhto, E.; Simpson, I.A.; Stroes, E.; Sudano, I.; Tselepis, A.D.; Viigimaa, M.; Vindis, C.; Vonbank, A.; Vrablik, M.; Vrsalovic, M.; Zamorano, J.L.; Collet, J-P.; Koskinas, K.C.; Casula, M.; Badimon, L.; John Chapman, M.; De Backer, G.G.; Delgado, V.; Ference, B.A.; Graham, I.M.; Halliday, A.; Landmesser, U.; Mihaylova, B.; Pedersen, T.R.; Riccardi, G.; Richter, D.J.; Sabatine, M.S.; Taskinen, M-R.; Tokgozoglu, L.; Wiklund, O.; Windecker, S.; Aboyans, V.; Baigent, C.; Collet, J-P.; Dean, V.; Delgado, V.; Fitzsimons, D.; Gale, C.P.; Grobbee, D.; Halvorsen, S.; Hindricks, G.; Iung, B.; Jüni, P.; Katus, H.A.; Landmesser, U.; Leclercq, C.; Lettino, M.; Lewis, B.S.; Merkely, B.; Mueller, C.; Petersen, S.; Petronio, A.S.; Richter, D.J.; Roffi, M.; Shlyakhto, E.; Simpson, I.A.; Sousa-Uva, M.; Touyz, R.M.; Nibouche, D.; Zelveian, P.H.; Siostrzonek, P.; Najafov, R.; van de Borne, P.; Pojskic, B.; Postadzhiyan, A.; Kypris, L.; Špinar, J.; Larsen, M.L.; Eldin, H.S.; Viigimaa, M.; Strandberg, T.E.; Ferrières, J.; Agladze, R.; Laufs, U.; Rallidis, L.; Bajnok, L.; Gudjónsson, T.; Maher, V.; Henkin, Y.; Gulizia, M.M.; Mussagaliyeva, A.; Bajraktari, G.; Kerimkulova, A.; Latkovskis, G.; Hamoui, O.; Slapikas, R.; Visser, L.; Dingli, P.; Ivanov, V.; Boskovic, A.; Nazzi, M.; Visseren, F.; Mitevska, I.; Retterstøl, K.; Jankowski, P.; Fontes-Carvalho, R.; Gaita, D.; Ezhov, M.; Foscoli, M.; Giga, V.; Pella, D.; Fras, Z.; de Isla, L.P.; Hagström, E.; Lehmann, R.; Abid, L.; Ozdogan, O.; Mitchenko, O.; Patel, R.S. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur. Heart J.,* **2020**, *41*(1), 111-188. http://dx.doi.org/10.1093/eurheartj/ehz455 PMID: 31504418

[7] Ferrucci, L.; Giallauria, F.; Guralnik, J.M. Epidemiology of aging. *Radiol. Clin. North Am.,* **2008**, *46*(4), 643-652. http://dx.doi.org/10.1016/j.rcl.2008.07.005 PMID: 18922285

[8] Dicker, D.; Nguyen, G.; Abate, D.; Abate, K.H.; Abay, S.M.; Abbafati, C.; Abbasi, N.; Abbastabar, H.; Abd-Allah, F.; Abdela, J.; Abdelalim, A.; Abdel-Rahman, O.; Abdi, A.; Abdollahpour, I.; Abdulkader, R.S.; Abdurahman, A.A.; Abebe, H.T.; Abebe, M.; Abebe, Z.; Abebo, T.A.; Aboyans, V.; Abraha, H.N.; Abrham, A.R.; Abu-Raddad, L.J.; Abu-Rmeileh, N.M.E.; Accrombessi, M.M.K.; Acharya, P.; Adebayo, O.M.; Adedeji, I.A.; Adedoyin, R.A.; Adekanmbi, V.; Adetokunboh, O.O.; Adhena, B.M.; Adhikari, T.B.; Adib, M.G.; Adou, A.K.; Adsuar, J.C.; Afarideh, M.; Afshin, A.; Agarwal, G.; Aggarwal, R.; Aghayan, S.A.; Agrawal, S.; Agrawal, A.; Ahmadi, M.; Ahmadi, A.; Ahmadieh, H.; Ahmed, M.L.C.; Ahmed, S.; Ahmed, M.B.; Aichour, A.N.; Aichour, I.; Aichour, M.T.E.; Akanda, A.S.; Akbari, M.E.; Akibu, M.; Akinyemi, R.O.; Akinyemiju, T.; Akseer, N.; Alahdab, F.; Al-Aly, Z.; Alam, K.; Alebel, A.; Aleman, A.V.; Alene, K.A.; Al-Eyadhy, A.; Ali, R.; Alijanzadeh, M.; Alizadeh-Navaei, R.; Aljunid, S.M.; Alkerwi, A.; Alla, F.; Allebeck, P.; Allen, C.A.; Alonso, J.; Al-Raddadi, R.M.; Alsharif, U.; Altirkawi, K.; Alvis-Guzman, N.; Amare, A.T.; Amini, E.; Ammar, W.; Amoako, Y.A.; Anber, N.H.; Andrei, C.L.; Androudi, S.; Animut, M.D.; Anjomshoa, M.; Anlay, D.Z.; Ansari, H.; Ansariadi, A.; Ansha, M.G.; Antonio, C.A.T.; Appiah, S.C.Y.; Aremu, O.; Areri, H.A.; Ärnlöv, J.; Arora, M.; Artaman, A.; Aryal, K.K.; Asadi-Lari, M.; Asayesh, H.; Asfaw, E.T.; Asgedom, S.W.; Assadi, R.; Ataro, Z.; Atey, T.M.M.; Athari, S.S.; Atique, S.; Atre, S.R.; Atteraya, M.S.; Attia, E.F.; Ausloos, M.; Avila-Burgos, L.; Avokpaho, E.F.G.A.; Awasthi, A.; Awuah, B.; Ayala Quintanilla, B.P.; Ayele, H.T.; Ayele, Y.; Ayer, R.; Ayuk, T.B.; Azzopardi, P.S.; Azzopardi-Muscat, N.; Badali, H.; Badawi, A.; Balakrishnan, K.; Bali, A.G.; Banach, M.; Banstola, A.; Barac, A.; Barboza, M.A.; Barquera, S.; Barrero, L.H.; Basaleem, H.; Bassat, Q.; Basu, A.; Basu, S.; Baune, B.T.; Bazargan-Hejazi, S.; Bedi, N.; Beghi, E.; Behzadifar, M.; Behzadifar, M.; Béjot, Y.; Bekele, B.B.; Belachew, A.B.; Belay, A.G.; Belay, E.; Belay, S.A.; Belay, Y.A.; Bell, M.L.; Bello, A.K.; Bennett, D.A.; Bensenor, I.M.; Berhane, A.; Berman, A.E.; Bernabe, E.; Bernstein, R.S.; Bertolacci, G.J.; Beuran, M.; Beyranvand, T.; Bhala, N.; Bhatia, E.; Bhatt, S.; Bhattarai, S.; Bhaumik, S.; Bhutta, Z.A.; Biadgo, B.; Bijani, A.; Bikbov, B.; Bililign, N.; Bin Sayeed, M.S.; Birlik, S.M.; Birungi, C.; Bisanzio, D.; Biswas, T.; Bjørge, T.; Bleyer, A.; Basara, B.B.; Bose, D.; Bosetti, C.; Boufous, S.; Bourne, R.; Brady, O.J.; Bragazzi, N.L.; Brant, L.C.; Brazinova, A.; Breitborde, N.J.K.; Brenner, H.; Britton, G.; Brugha, T.; Burke, K.E.; Busse, R.; Butt, Z.A.; Cahuana-Hurtado, L.; Callender, C.S.K.H.; Campos-Nonato, I.R.; Campuzano Rincon, J.C.; Cano, J.; Car, M.; Cárdenas, R.; Carreras, G.; Carrero, J.J.; Carter, A.; Carvalho, F.; Castañeda-Orjuela, C.A.; Castillo Rivas, J.; Castro, F.; Catalá-López, F.; Çavlin, A.; Cerin, E.; Chaiah, Y.; Champs, A.P.; Chang, H-Y.; Chang, J-C.; Chattopadhyay, A.; Chaturvedi, P.; Chen, W.; Chiang, P.P-C.; Chimed-Ochir, O.; Chin, K.L.; Chisumpa, V.H.; Chitheer, A.; Choi, J-Y.J.; Christensen, H.; Christopher, D.J.; Chung, S-C.; Cicuttini, F.M.; Ciobanu, L.G.; Cirillo, M.; Claro, R.M.; Cohen, A.J.; Collado-Mateo, D.; Constantin, M-M.; Conti, S.; Cooper, C.; Cooper, L.T.; Cortesi, P.A.; Cortinovis, M.; Cousin, E.; Criqui, M.H.; Cromwell, E.A.; Crowe, C.S.; Crump, J.A.; Cucu, A.; Cunningham, M.; Daba, A.K.; Dachew, B.A.; Dadi, A.F.; Dandona, L.; Dandona, R.;

Dang, A.K.; Dargan, P.I.; Daryani, A.; Das, S.K.; Das Gupta, R.; das Neves, J.; Dasa, T.T.; Dash, A.P.; Weaver, N.D.; Davitoiu, D.V.; Davletov, K.; Dayama, A.; Courten, B.; De la Hoz, F.P.; De leo, D.; De Neve, J-W.; Degefa, M.G.; Degenhardt, L.; Degfie, T.T.; Deiparine, S.; Dellavalle, R.P.; Demoz, G.T.; Demtsu, B.B.; Denova-Gutiérrez, E.; Deribe, K.; Dervenis, N.; Des Jarlais, D.C.; Dessie, G.A.; Dey, S.; Dharmaratne, S.D.; Dhimal, M.; Ding, E.L.; Djalalinia, S.; Doku, D.T.; Dolan, K.A.; Donnelly, C.A.; Dorsey, E.R.; Douwes-Schultz, D.; Doyle, K.E.; Drake, T.M.; Driscoll, T.R.; Dubey, M.; Dubljanin, E.; Duken, E.E.; Duncan, B.B.; Duraes, A.R.; Ebrahimi, H.; Ebrahimpour, S.; Edessa, D.; Edvardsson, D.; Eggen, A.E.; El Bcheraoui, C.; El Sayed Zaki, M.; Elfaramawi, M.; El-Khatib, Z.; Ellingsen, C.L.; Elyazar, I.R.F.; Enayati, A.; Endries, A.Y.Y.; Er, B.; Ermakov, S.P.; Eshrati, B.; Eskandarieh, S.; Esmaeili, R.; Esteghamati, A.; Esteghamati, S.; Fakhar, M.; Fakhim, H.; Farag, T.; Faramarzi, M.; Fareed, M.; Farhadi, F.; Farid, T.A.; Farinha, C.S.S.; Farioli, A.; Faro, A.; Farvid, M.S.; Farzadfar, F.; Farzaei, M.H.; Fazeli, M.S.; Feigin, V.L.; Feigl, A.B.; Feizy, F.; Fentahun, N.; Fereshtehnejad, S-M.; Fernandes, E.; Fernandes, J.C.; Feyissa, G.T.; Fijabi, D.O.; Filip, I.; Finegold, S.; Fischer, F.; Flor, L.S.; Foigt, N.A.; Ford, J.A.; Foreman, K.J.; Fornari, C.; Frank, T.D.; Franklin, R.C.; Fukumoto, T.; Fuller, J.E.; Fullman, N.; Fürst, T.; Furtado, J.M.; Futran, N.D.; Galan, A.; Gallus, S.; Gambashidze, K.; Gamkrelidze, A.; Gankpe, F.G.; Garcia-Basteiro, A.L.; Garcia-Gordillo, M.A.; Gebre, T.; Gebre, A.K.; Gebregergs, G.B.; Gebrehiwot, T.T.; Gebremedhin, A.T.; Gelano, T.F.; Gelaw, Y.A.; Geleijnse, J.M.; Genova-Maleras, R.; Gessner, B.D.; Getachew, S.; Gething, P.W.; Gezae, K.E.; Ghadami, M.R.; Ghadimi, R.; Ghasemi Falavarjani, K.; Ghasemi-Kasman, M.; Ghiasvand, H.; Ghimire, M.; Ghoshal, A.G.; Gill, P.S.; Gill, T.K.; Gillum, R.F.; Giussani, G.; Goenka, S.; Goli, S.; Gomez, R.S.; Gomez-Cabrera, M.C.; Gómez-Dantés, H.; Gona, P.N.; Goodridge, A.; Gopalani, S.V.; Goto, A.; Goulart, A.C.; Goulart, B.N.G.; Grada, A.; Grosso, G.; Gugnani, H.C.; Guimaraes, A.L.S.; Guo, Y.; Gupta, P.C.; Gupta, R.; Gupta, R.; Gupta, T.; Gyawali, B.; Haagsma, J.A.; Hachinski, V.; Hafezi-Nejad, N.; Hagos, T.B.; Hailegiyorgis, T.T.; Hailu, G.B.; Haj-Mirzaian, A.; Haj-Mirzaian, A.; Hamadeh, R.R.; Hamidi, S.; Handal, A.J.; Hankey, G.J.; Harb, H.L.; Harikrishnan, S.; Haririan, H.; Haro, J.M.; Hasan, M.; Hassankhani, H.; Hassen, H.Y.; Havmoeller, R.; Hay, R.J.; Hay, S.I.; He, Y.; Hedayatizadeh-Omran, A.; Hegazy, M.I.; Heibati, B.; Heidari, M.; Hendrie, D.; Henok, A.; Henry, N.J.; Heredia-Pi, I.; Herteliu, C.; Heydarpour, F.; Heydarpour, P.; Heydarpour, S.; Hibstu, D.T.; Hoek, H.W.; Hole, M.K.; Homaie Rad, E.; Hoogar, P.; Horino, M.; Hosgood, H.D.; Hosseini, S.M.; Hosseinzadeh, M.; Hostiuc, S.; Hostiuc, M.; Hotez, P.J.; Hoy, D.G.; Hsairi, M.; Htet, A.S.; Hu, G.; Huang, J.J.; Husseini, A.; Hussen, M.M.; Hutfless, S.; Iburg, K.M.; Igumbor, E.U.; Ikeda, C.T.; Ilesanmi, O.S.; Iqbal, U.; Irvani, S.S.N.; Isehunwa, O.O.; Islam, S.M.S.; Islami, F.; Jahangiry, L.; Jahanmehr, N.; Jain, R.; Jain, S.K.; Jakovljevic, M.; James, S.L.; Javanbakht, M.; Jayaraman, S.; Jayatilleke, A.U.; Jee, S.H.; Jeemon, P.; Jha, R.P.; Jha, V.; Ji, J.S.; Johnson, S.C.; Jonas, J.B.; Joshi, A.; Jozwiak, J.J.; Jungari, S.B.; Jürisson, M.; K, M.; Kabir, Z.; Kadel, R.; Kahsay, A.; Kahssay, M.; Kalani, R.; Kapil, U.; Karami, M.; Karami M., B.; Karch, A.; Karema, C.; Karimi, N.; Karimi, S.M.; Karimi-Sari, H.; Kasaeian, A.; Kassa, G.M.; Kassa, T.D.; Kassa, Z.Y.; Kassebaum, N.J.; Katibeh, M.; Katikireddi, S.V.; Kaul, A.; Kawakami, N.; Kazemeini, H.; Kazemi, Z.; Karyani, A.K.; K C, P.; Kebede, S.; Keiyoro, P.N.; Kemp, G.R.; Kengne, A.P.; Keren, A.; Kereselidze, M.; Khader, Y.S.; Khafaie, M.A.; Khajavi, A.; Khalid, N.; Khalil, I.A.; Khan, E.A.; Khan, G.; Khan, M.S.; Khan, M.A.; Khang, Y-H.; Khanna, T.; Khater, M.M.; Khatony, A.; Khazaie, H.; Khoja, A.T.; Khosravi, A.; Khosravi, M.H.; Khubchandani, J.; Kiadaliri, A.A.; Kibret, G.D.D.; Kim, C.; Kim, D.; Kim, J.Y.; Kim, Y-E.; Kimokoti, R.W.; Kinfu, Y.; Kinra, S.; Kisa, A.; Kissimova-Skarbek, K.; Kissoon, N.; Kivimäki, M.; Kleber, M.E.; Knibbs, L.D.; Knudsen, A.K.S.; Kochhar, S.; Kokubo, Y.; Kolola, T.; Kopec, J.A.; Kosek, M.N.; Kosen, S.; Koul, P.A.; Koyanagi, A.; Kravchenko, M.A.; Krishan, K.; Krishnaswami, S.; Kuate Defo, B.; Kucuk Bicer, B.; Kudom, A.A.; Kuipers, E.J.; Kulikoff, X.R.; Kumar, G.A.; Kumar, M.; Kumar, P.; Kumsa, F.A.; Kutz, M.J.; Lad, S.D.; Lafranconi, A.; Lal, D.K.; Lalloo, R.; Lam, H.; Lami, F.H.; Lan, Q.; Langan, S.M.; Lansingh, V.C.; Lansky, S.; Larson, H.J.; Laryea, D.O.; Lassi, Z.S.; Latifi, A.; Lavados, P.M.; Laxmaiah, A.; Lazarus, J.V.; Lebedev, G.; Lee, P.H.; Leigh, J.; Leshargie, C.T.; Leta, S.; Levi, M.; Li, S.; Li, Y.; Li, X.; Liang, J.; Liang, X.; Liben, M.L.; Lim, L-L.; Lim, S.S.; Limenih, M.A.; Linn, S.; Liu, S.; Liu, Y.; Lodha, R.; Logroscino, G.; Lonsdale, C.; Lorch, S.A.; Lorkowski, S.; Lotufo, P.A.; Lozano, R.; Lucas, T.C.D.; Lunevicius, R.; Lyons, R.A.; Ma, S.; Mabika, C.; Macarayan, E.R.K.; Mackay, M.T.; Maddison, E.R.; Maddison, R.; Madotto, F.; Magdy Abd El Razek, H.; Magdy Abd El Razek, M.; Maghavani, D.P.; Majdan, M.; Majdzadeh, R.; Majeed, A.; Malekzadeh, R.; Malik, M.A.; Malta, D.C.; Mamun, A.A.; Manamo, W.A.; Manda, A-L.; Mansournia, M.A.; Mantovani, L.G.; Mapoma, C.C.; Marami, D.; Maravilla, J.C.; Marcenes, W.; Marina, S.; Martinez-Raga, J.; Martins, S.C.O.; Martins-Melo, F.R.; März, W.; Marzan, M.B.; Mashamba-Thompson, T.P.; Masiye, F.; Massenburg, B.B.; Maulik, P.K.; Mazidi, M.; McGrath, J.J.; McKee, M.; Mehata, S.; Mehendale, S.M.; Mehndiratta, M.M.; Mehrotra, R.; Mehta, K.M.; Mehta, V.; Mekonen, T.; Mekonnen, T.C.; Meles, H.G.; Meles, K.G.; Melese, A.; Melku, M.; Memiah, P.T.N.; Memish, Z.A.; Mendoza, W.; Mengistu, D.T.; Mengistu, G.; Mensah, G.A.; Mereta, S.T.; Meretoja, A.; Meretoja, T.J.; Mestrovic, T.; Mezgebe, H.B.; Miangotar, Y.; Miazgowski, B.; Miazgowski, T.; Miller, T.R.; Mini, G.K.; Mirica, A.; Mirrakhimov, E.M.; Misganaw, A.T.; Moazen, B.; Moges, N.A.; Mohammad, K.A.; Mohammadi, M.; Mohammadifard, N.; Mohammadi-Khanaposhtani, M.; Mohammadnia-Afrouzi, M.; Mohammed, S.; Mohammed, M.A.; Mohan, V.; Mokdad, A.H.; Molokhia, M.; Monasta, L.; Moradi, G.; Moradi, M.; Moradi-Lakeh, M.; Moradinazar, M.; Moraga, P.; Morawska, L.; Moreno Velásquez, I.; Morgado-da-Costa, J.; Morrison, S.D.; Mosapour, A.; Moschos, M.M.; Mousavi, S.M.; Muche, A.A.; Muchie, K.F.; Mueller, U.O.; Mukhopadhyay, S.; Mullany, E.C.; Muller, K.; Murhekar, M.; Murphy, T.B.; Murthy, G.V.S.; Murthy, S.; Musa, J.; Musa, K.I.; Mustafa, G.; Muthupandian, S.; Nachega, J.B.; Nagel, G.; Naghavi, M.; Naheed, A.; Nahvijou, A.; Naik, G.; Nair, S.; Najafi, F.; Nangia, V.; Nansseu, J.R.; Nascimento, B.R.; Nawaz, H.; Ncama, B.P.; Neamati, N.; Negoi, I.; Negoi, R.I.; Neupane, S.; Newton, C.R.J.; Ngalesoni, F.N.; Ngunjiri, J.W.; Nguyen, H.T.; Nguyen, H.T.; Nguyen, L.H.; Nguyen, M.; Nguyen, T.H.; Ningrum, D.N.A.; Nirayo, Y.L.; Nisar, M.I.; Nixon, M.R.; Nolutshungu, N.; Nomura, S.; Norheim, O.F.; Noroozi, M.; Norrving, B.; Noubiap, J.J.; Nouri, H.R.; Nourollahpour Shiadeh, M.; Nowroozi, M.R.; Nsoesie, E.O.; Nyasulu, P.S.; Ofori-Asenso, R.; Ogah, O.S.; Ogbo, F.A.; Oh, I-H.; Okoro, A.; Oladimeji, O.; Olagunju, A.T.; Olagunju, T.O.; Olivares, P.R.; Olusanya, B.O.; Olusanya, J.O.; Ong, S.K.; Opio, J.N.; Oren, E.; Ortiz, J.R.; Ortiz, A.; Ota, E.; Otstavnov, S.S.; Øverland, S.; Owolabi, M.O.; Oyekale, A.S.; P A, M.; Pacella, R.; Pakhale, S.; Pakhare, A.P.; Pana, A.; Panda, B.K.; Panda-Jonas, S.; Pandey, A.R.; Pandian, J.D.; Parisi, A.; Park, E-K.; Parry, C.D.H.; Parsian, H.; Patel, S.; Patle, A.; Patten, S.B.; Patton, G.C.; Paudel, D.; Pearce, N.; Peprah, E.K.; Pereira, A.; Pereira, D.M.; Perez, K.M.; Perico, N.; Pervaiz, A.; Pesudovs, K.; Petri, W.A.; Petzold, M.; Phillips, M.R.; Pigott, D.M.; Pillay, J.D.; Pirsaheb, M.; Pishgar, F.; Plass, D.; Polinder, S.; Pond, C.D.; Popova, S.; Postma, M.J.; Pourmalek, F.; Pourshams, A.; Poustchi, H.; Prabhakaran, D.; Prakash, V.; Prakash, S.; Prasad, N.; Qorbani, M.; Quistberg, D.A.; Radfar, A.; Rafay, A.; Rafiei, A.; Rahim, F.; Rahimi, K.; Rahimi-Movaghar, A.; Rahimi-Movaghar, V.; Rahman, M.; Rahman, M.H.U.; Rahman, M.A.; Rahman, S.; Rai, R.K.; Rajati, F.; Rajsic, S.; Raju, S.B.; Ram, U.; Ranabhat, C.L.; Ranjan, P.; Ranta, A.; Rasella, D.; Rawaf, D.L.; Rawaf, S.; Ray, S.E.; Razo-García, C.; Rego, M.A.S.; Rehm, J.; Reiner, R.C.; Reinig, N.; Reis, C.; Remuzzi, G.; Renzaho, A.M.N.; Resnikoff, S.; Rezaei, S.; Rezaeian, S.; Rezai, M.S.; Riahi, S.M.; Ribeiro, A.L.P.; Riojas, H.; Rios-Blancas, M.J.; Roba, K.T.; Robinson, S.R.; Roever, L.; Ronfani, L.; Roshandel, G.; Roshchin, D.O.; Rostami, A.; Rothenbacher, D.; Rubagotti, E.; Ruhago, G.M.; Saadat, S.; Sabde, Y.D.; Sachdev, P.S.; Saddik, B.; Sadeghi, E.; Moghaddam, S.S.; Safari, H.; Safari, Y.; Safari-Faramani, R.; Safdarian, M.; Safi, S.; Safiri, S.; Sagar, R.; Sahebkar, A.; Sahraian, M.A.; Sajadi, H.S.; Salahshoor, M.R.; Salam, N.; Salama, J.S.; Salamati, P.; Saldanha, R.F.; Salimi, Y.; Salimzadeh, H.; Salz, I.; Sambala, E.Z.; Samy, A.M.; Sanabria, J.; Sanchez-Niño, M.D.; Santos, I.S.; Santos, J.V.; Santric Milicevic, M.M.; Sao Jose, B.P.; Sardana, M.; Sarker, A.R.; Sarrafzadegan, N.; Sartorius, B.; Sarvi, S.; Sathian, B.; Satpathy, M.; Savic, M.; Sawant, A.R.; Sawhney, M.; Saxena, S.; Sayyah, M.; Scaria, V.; Schaeffner, E.; Schelonka, K.; Schmidt, M.I.; Schneider, I.J.C.; Schöttker, B.; Schutte, A.E.; Schwebel, D.C.; Schwendicke, F.; Scott, J.G.; Sekerija, M.; Sepanlou, S.G.; Serván-Mori, E.; Shabaninejad, H.; Shackelford, K.A.; Shafieesabet, A.; Shaheen, A.A.; Shaikh, M.A.; Shakir, R.A.; Shams-Beyranvand, M.; Shamsi, M.B.; Shamsizadeh, M.; Sharafi, H.; Sharafi, K.; Sharif, M.; Sharif-Alhoseini, M.; Sharma, M.; Sharma, J.; Sharma, R.; She, J.; Sheikh, A.;

Sheth, K.N.; Shi, P.; Shibuya, K.; Shifa, G.T.; Shiferaw, M.S.; Shigematsu, M.; Shiri, R.; Shirkoohi, R.; Shiue, I.; Shokraneh, F.; Shrime, M.G.; Shukla, S.R.; Si, S.; Siabani, S.; Siddiqi, T.J.; Sigfusdottir, I.D.; Sigurvinsdottir, R.; Silpakit, N.; Silva, D.A.S.; Silva, J.P.; Silveira, D.G.A.; Singam, N.S.V.; Singh, J.A.; Singh, V.; Sinha, A.P.; Sinha, D.N.; Sitas, F.; Skirbekk, V.; Sliwa, K.; Soares Filho, A.M.; Sobaih, B.H.; Sobhani, S.; Soofi, M.; Soriano, J.B.; Soyiri, I.N.; Sposato, L.A.; Sreeramareddy, C.T.; Srinivasan, V.; Srivastava, R.K.; Starodubov, V.I.; Stathopoulou, V.; Steel, N.; Stein, D.J.; Steiner, C.; Stewart, L.G.; Stokes, M.A.; Sudaryanto, A.; Sufiyan, M.B.; Sulo, G.; Sunguya, B.F.; Sur, P.J.; Sutradhar, I.; Sykes, B.L.; Sylaja, P.N.; Sylte, D.O.; Szoeke, C.E.I.; Tabarés-Seisdedos, R.; Tabuchi, T.; Tadakamadla, S.K.; Takahashi, K.; Tandon, N.; Tassew, A.A.; Tassew, S.G.; Tavakkoli, M.; Taveira, N.; Tawye, N.Y.; Tehrani-Banihashemi, A.; Tekalign, T.G.; Tekle, M.G.; Temesgen, H.; Temsah, M-H.; Temsah, O.; Terkawi, A.S.; Teshale, M.Y.; Tessema, B.; Teweldemedhin, M.; Thakur, J.S.; Thankappan, K.R.; Thirunavukkarasu, S.; Thomas, L.A.; Thomas, N.; Thrift, A.G.; Tilahun, B.; To, Q.G.; Tobe-Gai, R.; Tonelli, M.; Topor-Madry, R.; Topouzis, F.; Torre, A.E.; Tortajada-Girbés, M.; Tovani-Palone, M.R.; Towbin, J.A.; Tran, B.X.; Tran, K.B.; Tripathi, S.; Tripathy, S.P.; Truelsen, T.C.; Truong, N.T.; Tsadik, A.G.; Tsilimparis, N.; Tudor Car, L.; Tuzcu, E.M.; Tyrovolas, S.; Ukwaja, K.N.; Ullah, I.; Usman, M.S.; Uthman, O.A.; Uzun, S.B.; Vaduganathan, M.; Vaezi, A.; Vaidya, G.; Valdez, P.R.; Varavikova, E.; Varughese, S.; Vasankari, T.J.; Vasconcelos, A.M.N.; Venketasubramanian, N.; Vidavalur, R.; Villafaina, S.; Violante, F.S.; Vladimirov, S.K.; Vlassov, V.; Vollset, S.E.; Vos, T.; Vosoughi, K.; Vujcic, I.S.; Wagner, G.R.; Wagnew, F.W.S.; Waheed, Y.; Wang, Y.; Wang, Y-P.; Wassie, M.M.; Weiderpass, E.; Weintraub, R.G.; Weiss, D.J.; Weiss, J.; Weldegebreal, F.; Weldegwergs, K.G.; Werdecker, A.; Westerman, R.; Whiteford, H.A.; Widecka, J.; Widecka, K.; Wijeratne, T.; Winkler, A.S.; Wiysonge, C.S.; Wolfe, C.D.A.; Wondemagegn, S.A.; Wu, S.; Wyper, G.M.A.; Xu, G.; Yadav, R.; Yakob, B.; Yamada, T.; Yan, L.L.; Yano, Y.; Yaseri, M.; Yasin, Y.J.; Ye, P.; Yearwood, J.A.; Yentür, G.K.; Yeshaneh, A.; Yimer, E.M.; Yip, P.; Yisma, E.; Yonemoto, N.; Yoon, S-J.; York, H.W.; Yotebieng, M.; Younis, M.Z.; Yousefifard, M.; Yu, C.; Zachariah, G.; Zadnik, V.; Zafar, S.; Zaidi, Z.; Zaman, S.B.; Zamani, M.; Zare, Z.; Zeeb, H.; Zeleke, M.M.; Zenebe, Z.M.; Zerfu, T.A.; Zhang, K.; Zhang, X.; Zhou, M.; Zhu, J.; Zodpey, S.; Zucker, I.; Zuhlke, L.J.J.; Lopez, A.D.; Gakidou, E.; Murray, C.J.L. Global, regional, and national age-sex-specific mortality and life expectancy, 1950–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet,* **2018**, *392*(10159), 1684-1735.
http://dx.doi.org/10.1016/S0140-6736(18)31891-9
PMID: 30496102

[9] Hughes, S. Statin benefits in the elderly: New meta-analysis. *Medscape,* **2019**.

[10] Visseren, F.L.J.; Mach, F.; Smulders, Y.M.; Carballo, D.; Koskinas, K.C.; Bäck, M.; Benetos, A.; Biffi, A.; Boavida, J.M.; Capodanno, D.; Cosyns, B.; Crawford, C.; Davos, C.H.; Desormais, I.; Di Angelantonio, E.; Franco, O.H.; Halvorsen, S.; Hobbs, F.D.R.; Hollander, M.; Jankowska, E.A.; Michal, M.; Sacco, S.; Sattar, N.; Tokgozoglu, L.; Tonstad, S.; Tsioufis, K.P.; van Dis, I.; van Gelder, I.C.; Wanner, C.; Williams, B.; De Backer, G.; Regitz-Zagrosek, V.; Aamodt, A.H.; Abdelhamid, M.; Aboyans, V.; Albus, C.; Asteggiano, R.; Bäck, M.; Borger, M.A.; Brotons, C.; Čelutkienė, J.; Cifkova, R.; Cikes, M.; Cosentino, F.; Dagres, N.; De Backer, T.; De Bacquer, D.; Delgado, V.; Den Ruijter, H.; Dendale, P.; Drexel, H.; Falk, V.; Fauchier, L.; Ference, B.A.; Ferrières, J.; Ferrini, M.; Fisher, M.; Fliser, D.; Fras, Z.; Gaita, D.; Giampaoli, S.; Gielen, S.; Graham, I.; Jennings, C.; Jorgensen, T.; Kautzky-Willer, A.; Kavousi, M.; Koenig, W.; Konradi, A.; Kotecha, D.; Landmesser, U.; Lettino, M.; Lewis, B.S.; Linhart, A.; Løchen, M-L.; Makrilakis, K.; Mancia, G.; Marques-Vidal, P.; McEvoy, J.W.; McGreavy, P.; Merkely, B.; Neubeck, L.; Nielsen, J.C.; Perk, J.; Petersen, S.E.; Petronio, A.S.; Piepoli, M.; Pogosova, N.G.; Prescott, E.I.B.; Ray, K.K.; Reiner, Z.; Richter, D.J.; Rydén, L.; Shlyakhto, E.; Sitges, M.; Sousa-Uva, M.; Sudano, I.; Tiberi, M.; Touyz, R.M.; Ungar, A.; Verschuren, W.M.M.; Wiklund, O.; Wood, D.; Zamorano, J.L.; Smulders, Y.M.; Carballo, D.; Koskinas, K.C.; Bäck, M.; Benetos, A.; Biffi, A.; Boavida, J-M.; Capodanno, D.; Cosyns, B.; Crawford, C.A.; Davos, C.H.; Desormais, I.; Di Angelantonio, E.; Franco Duran, O.H.; Halvorsen, S.; Richard, H., F.D.; Hollander, M.; Jankowska, E.A.; Michal, M.; Sacco, S.; Sattar, N.; Tokgozoglu, L.; Tonstad, S.; Tsioufis, K.P.; Dis, I.; van Gelder, I.C.; Wanner, C.; Williams, B. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.,* **2021**, *42*(34), 3227-3337.
http://dx.doi.org/10.1093/eurheartj/ehab484 PMID: 34458905

[11] Stoll, F.; Eidam, A.; Bauer, J.M.; Haefeli, W.E. Management of dyslipidaemia in the elderly. *J. Cardiol. Pract.,* **2020**, *19*(5).

[12] Singh, S.; Zieman, S.; Go, A.S.; Fortmann, S.P.; Wenger, N.K.; Fleg, J.L.; Radziszewska, B.; Stone, N.J.; Zoungas, S.; Gurwitz, J.H. Statins for primary prevention in older adults-moving toward evidence-based decision-making. *J. Am. Geriatr. Soc.,* **2018**, *66*(11), 2188-2196.
http://dx.doi.org/10.1111/jgs.15449 PMID: 30277567

[13] Wilmot, K.A.; Khan, A.; Krishnan, S.; Eapen, D.J.; Sperling, L. Statins in the elderly: A patient-focused approach. *Clin. Cardiol.,* **2015**, *38*(1), 56-61.
http://dx.doi.org/10.1002/clc.22338 PMID: 25336290

[14] Shepherd, J.; Blauw, G.J.; Murphy, M.B.; Bollen, E.L.E.M.; Buckley, B.M.; Cobbe, S.M.; Ford, I.; Gaw, A.; Hyland, M.; Jukema, J.W.; Kamper, A.M.; Macfarlane, P.W.; Meinders, A.E.; Norrie, J.; Packard, C.J.; Perry, I.J.; Stott, D.J.; Sweeney, B.J.; Twomey, G.; Westendorp, R.G.J. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. *Lancet,* **2002**, *360*(9346), 1623-1630.
http://dx.doi.org/10.1016/S0140-6736(02)11600-X PMID: 12457784

[15] Han, B.H.; Sutin, D.; Williamson, J.D.; Davis, B.R.; Piller, L.B.; Pervin, H.; Pressel, S.L.; Blaum, C.S. Effect of statin treatment *vs* usual care on primary cardiovascular prevention among older adults. *JAMA Intern. Med.,* **2017**, *177*(7), 955-965.
http://dx.doi.org/10.1001/jamainternmed.2017.1442
PMID: 28531241

[16] Ridker, P.M.; Danielson, E.; Fonseca, F.A.H.; Genest, J.; Gotto, A.M., Jr; Kastelein, J.J.P.; Koenig, W.; Libby, P.; Lorenzatti, A.J.; MacFadyen, J.G.; Nordestgaard, B.G.; Shepherd, J.; Willerson, J.T.; Glynn, R.J. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.,* **2008**, *359*(21), 2195-2207.
http://dx.doi.org/10.1056/NEJMoa0807646
PMID: 18997196

[17] Yusuf, S.; Bosch, J.; Dagenais, G.; Zhu, J.; Xavier, D.; Liu, L.; Pais, P.; López-Jaramillo, P.; Leiter, L.A.; Dans, A.; Avezum, A.; Piegas, L.S.; Parkhomenko, A.; Keltai, K.; Keltai, M.; Sliwa, K.; Peters, R.J.G.; Held, C.; Chazova, I.; Yusoff, K.; Lewis, B.S.; Jansky, P.; Khunti, K.; Toff, W.D.; Reid, C.M.; Varigos, J.; Sanchez-Vallejo, G.; McKelvie, R.; Pogue, J.; Jung, H.; Gao, P.; Diaz, R.; Lonn, E. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N. Engl. J. Med.,* **2016**, *374*(21), 2021-2031.
http://dx.doi.org/10.1056/NEJMoa1600176 PMID: 27040132

[18] Ridker, P.M.; Lonn, E.; Paynter, N.P.; Glynn, R.; Yusuf, S. Primary prevention with statin therapy in the elderly. *Circulation,* **2017**, *135*(20), 1979-1981.
http://dx.doi.org/10.1161/CIRCULATIONAHA.117.028271
PMID: 28385949

[19] Mangione, C.M.; Barry, M.J.; Nicholson, W.K.; Cabana, M.; Chelmow, D.; Coker, T.R.; Davis, E.M.; Donahue, K.E.; Jaén, C.R.; Kubik, M.; Li, L.; Ogedegbe, G.; Pbert, L.; Ruiz, J.M.; Stevermer, J.; Wong, J.B. Statin use for the primary prevention of cardiovascular disease in adults. *JAMA,* **2022**, *328*(8), 746-753.
http://dx.doi.org/10.1001/jama.2022.13044 PMID: 35997723

[20] Efficacy and safety of statin therapy in older people: A meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet,* **2019**, *393*(10170), 407-415.
http://dx.doi.org/10.1016/S0140-6736(18)31942-1 PMID: 30712900

[21] Deedwania, P.; Stone, P.H.; Bairey Merz, C.N.; Cosin-Aguilar, J.; Koylan, N.; Luo, D.; Ouyang, P.; Piotrowicz, R.; Schenck-Gustafsson, K.; Sellier, P.; Stein, J.H.; Thompson, P.L.; Tzivoni, D. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: Results of the Study Assessing Goals in the Elderly (SAGE). *Circulation,* **2007**, *115*(6), 700-707.
http://dx.doi.org/10.1161/CIRCULATIONAHA.106.654756
PMID: 17283260

[22] Amarenco, P.; Bogousslavsky, J.; Callahan, A., III; Goldstein, L.B.; Hennerici, M.; Rudolph, A.E.; Sillesen, H.; Simunovic, L.; Szarek, M.; Welch, K.M.; Zivin, J.A. High-dose atorvastatin after stroke or transient ischemic attack. *N. Engl. J. Med.,* **2006**, *355*(6), 549-559.

http://dx.doi.org/10.1056/NEJMoa061894 PMID: 16899775

[23] Lee, M.; Cheng, C.Y.; Wu, Y.L.; Lee, J.D.; Hsu, C.Y.; Ovbiagele, B. Association between intensity of low-density lipoprotein cholesterol reduction with statin-based therapies and secondary stroke prevention. *JAMA Neurol.,* **2022**, *79*(4), 349-358. http://dx.doi.org/10.1001/jamaneurol.2021.5578 PMID: 35188949

[24] Morley, J.E.; Vellas, B.; Abellan van Kan, G.; Anker, S.D.; Bauer, J.M.; Bernabei, R.; Cesari, M.; Chumlea, W.C.; Doehner, W.; Evans, J.; Fried, L.P.; Guralnik, J.M.; Katz, P.R.; Malmstrom, T.K.; McCarter, R.J.; Gutierrez Robledo, L.M.; Rockwood, K.; von Haehling, S.; Vandewoude, M.F.; Walston, J. Frailty consensus: A call to action. *J. Am. Med. Dir. Assoc.,* **2013**, *14*(6), 392-397. http://dx.doi.org/10.1016/j.jamda.2013.03.022 PMID: 23764209

[25] Newman, C.B.; Preiss, D.; Tobert, J.A.; Jacobson, T.A.; Page, R.L., II; Goldstein, L.B.; Chin, C.; Tannock, L.R.; Miller, M.; Raghuveer, G.; Duell, P.B.; Brinton, E.A.; Pollak, A.; Braun, L.T.; Welty, F.K. Statin safety and associated adverse events: A scientific statement from the American Heart Association. *Arterioscler. Thromb. Vasc. Biol.,* **2019**, *39*(2), e38-e81. http://dx.doi.org/10.1161/ATV.0000000000000073 PMID: 30580575

[26] Hong, S.; Li, Q.C.; Jun, X. Treatment of dyslipidemia in the elderly. *J. Geriatr. Cardiol.,* **2011**, *8*(1), 55-64. http://dx.doi.org/10.3724/SP.J.1263.2011.00055 PMID: 22783285

[27] Link, E.; Parish, S.; Armitage, J.; Bowman, L.; Heath, S.; Matsuda, F.; Gut, I.; Lathrop, M.; Collins, R. SLCO1B1 variants and statin-induced myopathy - A genomewide study. *N. Engl. J. Med.,* **2008**, *359*(8), 789-799. http://dx.doi.org/10.1056/NEJMoa0801936 PMID: 18650507

[28] Schech, S.; Graham, D.; Staffa, J.; Andrade, S.E.; Grenade, L.L.; Burgess, M.; Blough, D.; Stergachis, A.; Chan, K.A.; Platt, R.; Shatin, D. Risk factors for statin-associated rhabdomyolysis. *Pharmacoepidemiol. Drug Saf.,* **2007**, *16*(3), 352-358. http://dx.doi.org/10.1002/pds.1287 PMID: 16892458

[29] Sattar, N.; Preiss, D.; Murray, H.M.; Welsh, P.; Buckley, B.M.; de Craen, A.J.M.; Seshasai, S.R.K.; McMurray, J.J.; Freeman, D.J.; Jukema, J.W.; Macfarlane, P.W.; Packard, C.J.; Stott, D.J.; Westendorp, R.G.; Shepherd, J.; Davis, B.R.; Pressel, S.L.; Marchioli, R.; Marfisi, R.M.; Maggioni, A.P.; Tavazzi, L.; Tognoni, G.; Kjekshus, J.; Pedersen, T.R.; Cook, T.J.; Gotto, A.M.; Clearfield, M.B.; Downs, J.R.; Nakamura, H.; Ohashi, Y.; Mizuno, K.; Ray, K.K.; Ford, I. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. *Lancet,* **2010**, *375*(9716), 735-742. http://dx.doi.org/10.1016/S0140-6736(09)61965-6 PMID: 20167359

[30] Simsek, S.; Schalkwijk, C.G.; Wolffenbuttel, B.H.R. Effects of rosuvastatin and atorvastatin on glycaemic control in Type 2 diabetes-the CORALL study. *Diabet. Med.,* **2012**, *29*(5), 628-631. http://dx.doi.org/10.1111/j.1464-5491.2011.03553.x PMID: 22151023

[31] Lloyd-Jones, D.M.; Leip, E.P.; Larson, M.G.; D'Agostino, R.B.; Beiser, A.; Wilson, P.W.F.; Wolf, P.A.; Levy, D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation,* **2006**, *113*(6), 791-798. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.548206 PMID: 16461820

[32] Kearney, P.M.; Blackwell, L.; Collins, R.; Keech, A.; Simes, J.; Peto, R.; Armitage, J.; Baigent, C. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: A meta-analysis. *Lancet,* **2008**, *371*(9607), 117-125. http://dx.doi.org/10.1016/S0140-6736(08)60104-X PMID: 18191683

[33] American Diabetes Association 9. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes-2018. Diabetes Care,* **2018**, *41*(1), S86-S104. PMID: 29222380

[34] Collins, R.; Armitage, J.; Parish, S.; Sleigh, P.; Peto, R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. *Lancet,* **2003**, *361*(9374), 2005-2016. http://dx.doi.org/10.1016/S0140-6736(03)13636-7 PMID: 12814710

[35] van Hateren, K.J.J.; Landman, G.W.D.; Kleefstra, N.; Logtenberg, S.J.J.; Groenier, K.H.; Kamper, A.M.; Houweling, S.T.; Bilo, H.J.G. The lipid profile and mortality risk in elderly type 2 diabetic patients: A ten-year follow-up study (ZODIAC-13). *PLoS One,* **2009**, *4*(12), e8464. http://dx.doi.org/10.1371/journal.pone.0008464 PMID: 20041116

[36] Langa, K.M.; Levine, D.A. The diagnosis and management of mild cognitive impairment: A clinical review. *JAMA,* **2014**, *312*(23), 2551-2561. http://dx.doi.org/10.1001/jama.2014.13806 PMID: 25514304

[37] Hugo, J.; Ganguli, M. Dementia and cognitive impairment: Epidemiology, diagnosis, and treatment. *Clin. Geriatr. Med.,* **2014**, *30*(3), 421-442. http://dx.doi.org/10.1016/j.cger.2014.04.001 PMID: 25037289

[38] Peracino, A.; Pecorelli, S. The epidemiology of cognitive impairment in the aging population: Implications for hearing loss. *Audiol. Neurotol.,* **2016**, *21*(1), 3-9. http://dx.doi.org/10.1159/000448346 PMID: 27806351

[39] Qin, J.; He, Z.; Wu, L.; Wang, W.; Lin, Q.; Lin, Y.; Zheng, L. Prevalence of mild cognitive impairment in patients with hypertension: A systematic review and meta-analysis. *Hypertens. Res.,* **2021**, *44*(10), 1251-1260. http://dx.doi.org/10.1038/s41440-021-00704-3 PMID: 34285378

[40] Jamshidnejad-Tosaramandani, T.; Kashanian, S.; Al-Sabri, M.H.; Kročianová, D.; Clemensson, L.E.; Gentreau, M.; Schiöth, H.B. Statins and cognition: Modifying factors and possible underlying mechanisms. *Front. Aging Neurosci.,* **2022**, *14*, 968039. http://dx.doi.org/10.3389/fnagi.2022.968039 PMID: 36046494

[41] Patel, M.; Kothari, C. Critical review of statins: A bio-analytical perspective for therapeutic drug monitoring, *TrAC Trends in Analytical Chemistry,* **2017**, *86*, 206-21. https://doi.org/10.1016/j.trac.2016.10.011

[42] Writing Committee; Lloyd-Jones, D.M.; Morris, P.B.; Ballantyne, C.M.; Birtcher, K.K.; Covington, A.M.; DePalma, S.M.; Minissian, M.B.; Orringer, C.E.; Smith, S.C. Jr, Waring, A.A.; Wilkins, J.T. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the american college of cardiology solution set oversight committee. *J. Am Coll Cardiol*. **2022**, *80*(14), 1366-418. doi: 10.1016/j.jacc.2022.07.006