European Heart Journal Supplements (2021) **23** (Supplement E), E109–E111
The Heart of the Matter
doi:10.1093/eurheartj/suab103

ESC
European Society
of Cardiology

Statins and age: is there a limit beyond which primary prevention is futile?

Gian Piero Perna*

Cardiologia Emodinamica e UTIC, Dipartimento Scienze Cardiovascolari, A.O.U. Ospedali Riuniti di Ancona, Ancona, Italy

KEYWORDS
Statin;
Primary prevention;
Advanced age

Hypercholesterolaemic patients at an advanced age (>75 years) with and without known cardiovascular disease are at higher cardiovascular risk than younger subjects, and the frequency of vascular events in this group of the patient increases with increasing age. However, in clinical practice, these subjects are undertreated for various reasons: conservative cultural attitude, fear of side effects, doubts about efficacy, lack of specific trials. Two recent meta-analyses have shown that the use of lipid-lowering drugs is as safe and effective in this age group as in younger subjects. Subjects aged >75 years in primary prevention are poorly represented in trials but should be considered for treatment in daily clinical practice, because, in the risk assessment (SCORE algorithm), they are very often classified as intermediate or high risk but can also be reclassified at increased risk if an additional assessment step with clinical markers (diabetes and reduced glomerular filtrate) or cardiovascular imaging is used for the detection of subclinical atherosclerosis. Greater attention to treatment methods and monitoring of possible side effects is recommended, but the only limit to the treatment is its 'futility' in the fragile patient.

Introduction

The world population of advanced age (>65 years) is continuously and progressively increasing. Since the absolute risk of cardiovascular disease is higher above the age of 65, mortality from cardiovascular causes is very high and in turn increasing in this age group. In particular, the proportion of patients hospitalized and treated for acute coronary syndrome has increased exponentially in recent years for patients aged >75 years.[1]

The greater risk of coronary and cardiovascular events in the elderly population is linked to several factors: the higher frequency of diabetes, untreated hypercholesterolaemia, arterial hypertension, and sub-clinical atherosclerotic disease.[1]

However, the use of statins and lipid-lowering drugs, despite being effective in the prevention of events, shows a clear trend of reduction with increasing age, an expression of less patient's adherence to the treatments prescribed but also of a lower degree of medical prescriptions.

It is possible that this lower use of lipid-lowering therapy in the 'real world' is due to several reasons:

- Fear of side effects related to comorbidities or potential drug interactions or changes in pharmacokinetics;
- The uncertainty about the efficacy and safety of lipid-lowering drugs in patients aged >75, often excluded from large trials by study protocol;
- A 'conservative *a priori*' cultural approach in the cardiovascular prevention treatment of the elderly population, particularly in the absence of a known cardiovascular disease.

For these reasons, many clinicians are actually unwilling—at present—to initiate primary cardiovascular prevention treatment with statins in elderly subjects without clear evidence of disease.

*Corresponding author. Email: perna54@yahoo.it

The current state of knowledge

In 2019 the CTT Trialist's Collaboration Group published a meta-analysis of 28 trials with statins in which 14 483 patients aged >75 were analysed (equal to 8% of all patients included) in which it was highlighted that the beneficial effect of statins (21% reduction in vascular events for every millimole reduction in LDL cholesterol) was independent of age and was also present in patients aged >75 years, albeit with less evidence in over 75 with no known cardiovascular disease.[2]

The European guidelines on the treatment of dyslipidaemia have incorporated this information, recommending statin treatment of all patients with known cardiovascular disease, regardless of age, and the initiation of primary prevention statin treatment in patients aged between 65 and 75 years (Class IA), while they recommend carefully evaluating treatment in primary prevention after the age of 75 (Class IIB). In addition, for all patients >65 years of age, a 'personalized' treatment is recommended starting at low doses in patients with reduced renal filtrate and with potentially interfering concomitant treatments and subsequent dose increase or integration of other lipid-lowering agents to achieve of the target.

More recently, two interesting studies have been published that show how good LDL cholesterol control reduces cardiovascular events even in old age (>75 years) and therefore should also be considered in these patients.

The Copenhagen General Population Study[3] is a large cohort study that included 91 161 non-diabetic subjects with no evidence of cardiovascular disease, who were therefore not treated with statins at the time of baseline assessment. In this population, the risk of coronary events at 8 years was higher in older subjects (70–100 years) compared to younger subjects (50–70 years), and in particular, it was 2.5/1000 above the 80 years, 1/1000 between 70 and 79 years, 0.8/1000 between 50 and 69 years. Furthermore, the risk of events was directly related to cholesterol levels and increased by 1.34 times for every millimole of LDL cholesterol. Using an LDL reduction model with a medium-intensity statin, the number of patients to be treated to avoid an event in this population was lower in patients> 80 years of age (80) than estimated for subjects with aged between 50 and 59 years (439).

The meta-analysis by Gencer *et al.*[4] concerns 21 442 patients aged >75 years included in trials with statins, ezetimibe, and PCSK9; the population analysed made up 8.8% of all patients treated (244 090). Regardless of the treatment implemented, the reduction of LDL cholesterol by 1 mmol/L reduces the risk of cardiovascular events by 26% in patients aged >75 years [RR 0.74, confidence interval (CI) 0.61–0.89], with no significant difference compared to younger subjects (RR 0.85, CI 0.78–0.92). It is interesting to note that in subjects aged> 75 years all components of the composite endpoint are significantly reduced: myocardial infarction—20%, cardiovascular death—15%, myocardial revascularization—20%, stroke—27%. Unfortunately, in this meta-analysis most of the patients had a known cardiovascular disease, so the data—however interesting—cannot be extrapolated to 'pure' primary prevention.

The only specific trial for primary prevention treatment is still 'ongoing' in Australia [STAtin therapy for Reducing Events in Elderly (STAREE)]. The study, started in 2014, evaluates the efficacy of Atorvastatin 40 mg on a composite endpoint (death, fatal, and non-fatal cardiovascular events, development of dementia, or disability). The completion of enrolment is scheduled for December 2022.

Reasonable certainties

LDL cholesterol levels are closely related to the frequency of events, at any age.

In old age (after 75 years), the frequency of cardiovascular events is higher and increases with increasing cholesterol levels and the worsening of the risk profile.[5]

Statins and non-statin lipid-lowering treatments are effective in reducing events, their effectiveness is directly proportional to the level of risk, and is independent of age.

Furthermore, statins are safe at any age when considering the potential drug interactions in case of comorbidities.

The effectiveness of lipid-lowering treatments—and in particular statins—is now certified in the secondary prevention of events even after the age of 75 and beyond.

The opportunity for treatment with statins in primary prevention after the age of 75 continues to represent an area of uncertainty due to the scarcity of data derived from prospective randomized studies.[5]

However, it is possible that this 'gap in evidence' is due to the low frequency, in the population referred to medical treatment, of elderly people *without* cardiovascular disease. In other words, in clinical practice when we decide whether to treat or not a patient aged >75 years with statins and with hypercholesterolaemia but without known cardiovascular disease very often we are faced with a subject who is also diabetic, or hypertensive, or with glomerular filtration rate <60 mL/min or with known sub-clinical atherosclerosis at the carotid and/or peripheral and/or coronary level. Therefore, this same patient becomes a very high-risk patient, equivalent to a patient with overt cardiovascular disease, to be treated with an LDL target <70 mg/dL.[1]

Furthermore, in the calculation of the SCORE, a male patient without cardiovascular disease but aged >75 years and with 'isolated' hypercholesterolaemia still has a risk of >10% at 10 years (high risk) and in any case must be treated in accordance with this risk profile. A further evaluation step with a search of subclinical cardiovascular disease can orient the treatment towards a more 'intensive' choice.[1]

Finally, in the cases not of asymptomatic 'over 75' subjects, with isolated hypercholesterolaemia, in which the calculation of the SCORE attributes an intermediate risk, it is logical to treat only correctable risk factor, however, evaluating the presence of sub-clinical vascular or coronary

disease with methods of images that allow to reclassify some patients in a higher risk class.

Conclusions

Since uncorrected hypercholesterolaemia in old age, even in the absence of known cardiovascular disease, still identifies subjects at high cardiovascular risk[3] there are no age limits for treatment with lipid-lowering drugs, whose efficacy and safety are independent of the age variable.[1–5]

The intensity of treatment in primary prevention of the elderly subject must be established on the basis of a correct and complete stratification of the risk of events with additional clinical indicators (diabetes, reduction of glomerular filtration rate) or instrumental (coronary CT scan/Calcium Score, Echo of carotids, and ankle-brachial index). The treatment targets are the same as for the younger subject.[1]

In the absence of 'frailty', which can make treatment futile, the presence of comorbidities does not in itself determine exclusion from treatment but greater attention in the choice of treatment modalities and in monitoring side effects.

Conflict of interest: none declared.

References

1. Mach F, Baigin C, Catapano A, et al. ESC/EAS Guidelines for the management of dyslipidemias. *Eur Heart J* 2019;**00**:1–78.
2. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019; **393**.
3. Mortensen MB, Nordestgaard BG, KyungAh I, et al. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. *Lancet* 2020;**396**: 1644–1652.
4. Gencer B, Marston NA, KyungAh I, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2020;**396**: 1637–1643.
5. Raal FJ, Mohamed F. Never too old to benefit from lipid-lowering treatment. *Lancet* 2020;**396**:1608–1609.