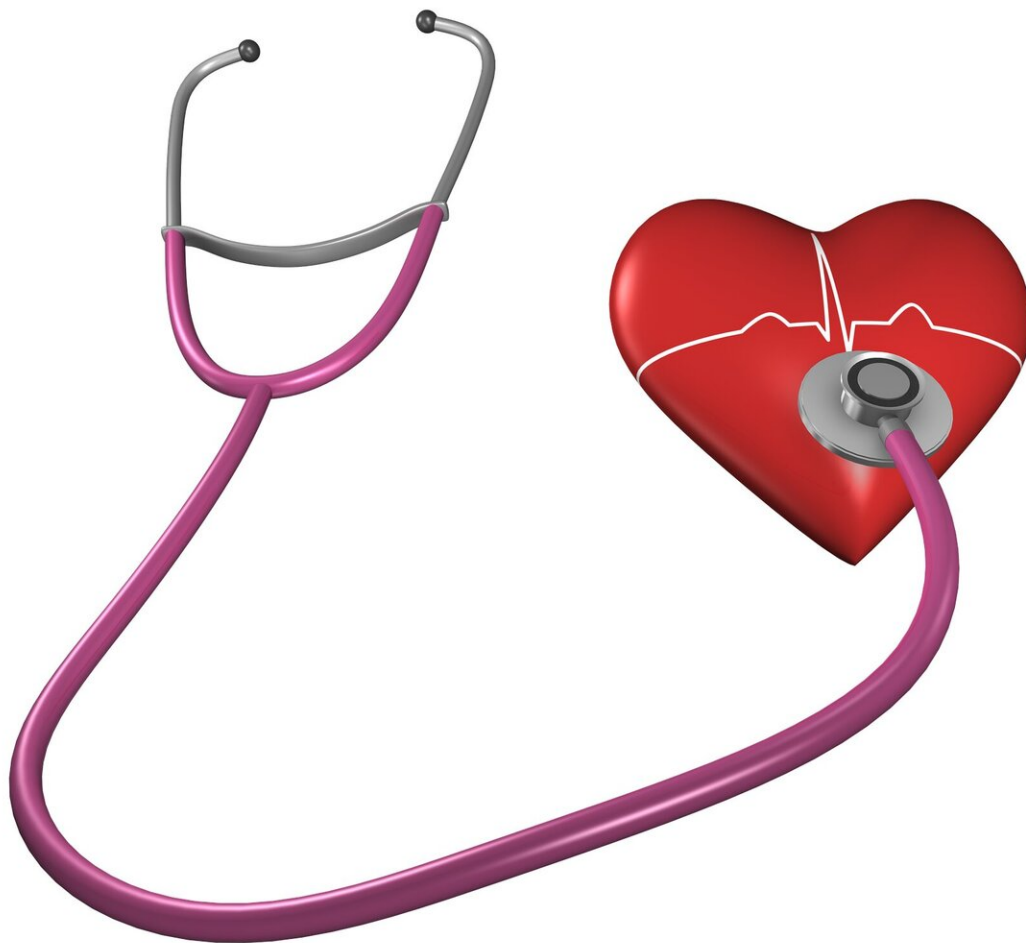


# Older adults at greater risk of cardiovascular events, benefit as much from cholesterol-lowering medications

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Two studies published today in *The Lancet* provide fresh evidence on the issue of whether LDL cholesterol-lowering therapies, including statins, can reduce the rate of major cardiovascular events in older people.

An observational study suggests that among people who have not had a previous cardiovascular event, those aged 70 to 100 years may gain the most benefit from taking medications that [lower cholesterol](#) compared to younger age groups, in terms of the number of [heart](#) attacks and cardiovascular events that could potentially be prevented per person treated. The study, involving more than 90,000 people living in Copenhagen, Denmark, including 13,779 people aged between 70 and 100 years, concluded that people aged over 70 years had the highest incidence of [heart attack](#) and cardiovascular disease of any age group (heart attacks per 1,000 people per year irrespective of LDL cholesterol levels: Age 80-100, 8.5; age 70-79, 5.2; age 60-69, 2.5; age 50-59, 1.8; age 20-49, 0.8—ie, in people aged 80-100 years, there were 8.5 heart attacks per 1,000 people each year). The study also estimates that the number of older people who need to receive a moderate-intensity statin therapy to prevent one heart attack in five years is fewer than for younger age groups. One heart attack will be prevented for every 80 people aged 80 to 100 years treated. In people aged 50 to 59 years, 439 need to be treated to prevent one incidence of heart attack, the researchers estimate.

In a separate systematic review and meta-analysis, researchers show that cholesterol-lowering therapies are as effective at reducing cardiovascular events in people aged 75 years or older as they are in younger people.

The study, which included data from more than 21,000 people aged 75 years or older from 29 randomised controlled trials, found that cholesterol-lowering medications reduced the relative risk of major vascular events in [older patients](#) by 26% per 1mmol/L reduction in LDL cholesterol, which is comparable to the risk reduction in patients younger than 75 years (15% per 1mmol/L reduction in LDL cholesterol).

Together, the findings strengthen evidence that cholesterol-lowering medications can benefit older adults, who have historically been underrepresented in clinical trials of these therapies, and could help reduce the burden of cardiovascular disease in an aging population.

Having high levels of LDL cholesterol can lead to narrowing of blood vessels, making it more likely that a person will have a heart attack or stroke. People aged over 70 years have been underrepresented in cardiovascular studies, so the evidence around cholesterol lowering therapies and the benefits of primary prevention in this age group have been less certain. These studies provide more up to date evidence.

## **Primary prevention study**

The first study is an [observational study](#) designed to assess primary prevention of cardiovascular events—meaning that participants did not already have clinical signs of heart disease when they joined the study. Researchers analysed data from 91,131 people aged 20 to 100 years who were not taking statins or other cholesterol-lowering medication, and were enrolled in the Copenhagen General Population Study between 2003 and 2015. Of those, 10,592 participants were aged 70 to 79 years, and 3,188 participants were aged 80 to 100 years.

Participants were followed for an average of 7.7 years, and the number of first-time heart attacks and cases of cardiovascular diseases, along with the LDL cholesterol levels, were recorded for each individual. To

evaluate the potential benefit of statins for each age group, the authors estimated the number of people who would need to be treated with a moderate-intensity statin therapy to prevent one incidence of heart attack in five years.

There was a total of 1,515 incidences of a first-time heart attack and 3,389 cases of cardiovascular disease in the study.

The risk of heart attack in the overall population was increased by 34% for every 1mmol/L rise in LDL cholesterol. The effect was amplified with increasing age, such that people aged 80 to 100 years with elevated LDL cholesterol levels had the highest absolute risk of heart attack (at the highest LDL cholesterol levels, >5mmol/L, the rates of heart attacks in 1,000 people per year for each age group were: age 80-100, 13.2, age 70-79, 6.6; age 60-69, 3.1; age 50 to 59, 3.1; age 20-49, 3.3—ie, in people aged 80-100 years with the highest levels of LDL cholesterol, there were 13.2 heart attacks per 1,000 people each year).

The incidence of cardiovascular disease also increased with age and rising LDL cholesterol levels and was highest in people aged 80 to 100 (at the highest LDL cholesterol levels, >5mmol/L, the rates of cardiovascular disease in 1,000 people per year for each age group were: age 80-100, 37.1, age 70-79, 14.6; age 60-69, 6.4; age 50 to 59, 5.4; age 20-49, 4.6—ie, in people aged 80-100 years with the highest levels of LDL cholesterol, there were 37.1 cases of cardiovascular disease per 1,000 people each year).

The researchers found that older people were likely to gain the greatest benefits from treatment of moderate-intensity statin therapy, compared to younger people. To prevent one cardiovascular disease event of any type, 42 people aged 80 to 100 would need to be treated with a moderate-intensity statin to prevent one cardiovascular disease event. The figures were 88 for those aged 70 to 79 years, 164 for those aged 60 to 69 years,

345 for those aged 50 to 59 years, and 769 for those aged 20 to 49 years.

To prevent one heart attack, 80 individuals aged 80 to 100 would need to be treated with a moderate-intensity statin for 5 years. The figures were 145 for people aged 70 to 79, 261 for those aged 60 to 69, 439 for those aged 50 to 59, and 1,107 for those aged 20 to 49.

The findings show that LDL cholesterol levels are an important risk factor for heart attack and cardiovascular disease in older people, contrary to historical reports. Previous evidence suggested there was no association, leading people to believe that those who had not had a heart attack before 70 years of age were healthier and at a lower risk. However, the lack of representation of this age group in trials, changing clinical practices, and increasing life expectancies for older populations means evidence was out of date. The two latest studies provide new evidence for this age group on both accounts.

Professor Børge Nordestgaard, joint author of the first study, of the Copenhagen University Hospital, Denmark, said: "Our study provides further evidence for the cumulative burden of LDL cholesterol over a person's lifetime and the progressive increase in risk for heart attack and cardiovascular disease with age. With the proportion of people living beyond 70 years of age worldwide rapidly increasing, these data point to the huge potential for primary prevention strategies aimed at lowering LDL cholesterol levels to reduce the population burden of heart disease. The findings should guide decision making about whether older individuals will benefit from statin therapy."

A strength of the first study is that the data originate from a large, present-day group of people. In addition, because all individuals in Denmark are assigned a personal identification number at birth or immigration with which they can be traced in national registries, not a single participant was lost during the follow up process.

However, a limitation of the first study is that it only included people of white European origin living in a high-income country, so it is not clear if the results would apply to other ethnic groups or people living in low-income settings. A second limitation is that the estimations for the number needed to treat in five years to prevent one incidence of heart attack and cardiovascular disease are based on modelling analyses with assumptions about the efficacy of LDL cholesterol-lowering drugs. However, the authors say that these estimates are reliable as the underlying event rates in different age groups and LDL cholesterol levels are based on actual data from the cohort study.

## **Meta-analysis on LDL lowering treatments**

A previous meta-analysis from the Cholesterol Treatment Trialists' Collaboration suggested that statin treatment reduced the number of major cardiovascular events in people aged 75 years and older, but ultimately concluded that the evidence of potential benefit was less strong than for younger people.

In the second study published today, researchers carried out a meta-analysis and systematic review of data from the Cholesterol Treatment Trialists' Collaboration meta-analysis of 24 trials and five individual randomised-controlled trials. The trials included in the analysis included both primary prevention studies, where participants did not have clinical signs of cardiovascular disease before joining the trial, and secondary prevention studies, where participants had already shown clinical signs of cardiovascular disease.

Data from a total of 244,090 participants were included in the analysis, including 21,492 people aged at least 75 years. Just over half of participants aged 75 years or older were from trials of statin therapies (54.7%, 11,750/21,482), 28.9% were from trials of the cholesterol-lowering drug ezetimibe (6,209/21,482) and the remaining 16.4% were

from trials of PCSK9 inhibitors (3,533/21,482), which are another class of drugs prescribed to lower cholesterol. The average time of study follow-up ranged from 2.2 to 6 years.

The analysis found that cholesterol-lowering therapies were associated with a reduction in the incidence of all cardiovascular events, including death, heart attack and stroke. The reduction in risk of major cardiovascular events for people aged over 75 years was statistically comparable to younger age groups—26% per 1mmol/L reduction in LDL cholesterol in people aged over 75 years, compared to a 15% risk reduction in patients younger than 75 years.

The authors warn that their findings do not mean that patients should wait to initiate treatment until they are older and stress the importance of keeping LDL cholesterol well controlled as early as possible in individuals to prevent the build-up of cholesterol in the arteries.

Deaths from all cardiovascular disease outcomes in people aged over 75 years were reduced by 15% per 1mmol/L reduction in LDL cholesterol (treatment group 723 deaths; control group 799 deaths). The incidence of heart attacks in this age group was reduced by 20% for every 1mmol/L reduction in cholesterol (treatment group 813 events, control group 971 events) and the occurrence of any type of stroke was reduced by 27% (treatment group 401 events; control group 486 events).

There was no difference in the magnitude of the risk reduction in major vascular events between statins and other cholesterol-lowering medications in the older age group.

Older individuals have higher rates of major cardiovascular events than younger people overall, and in this study, rates were almost 40% higher in those aged 75 years and older. The authors say this means it is expected that treating people aged over 75 years with cholesterol-

lowering therapies is likely to particularly prevent large numbers of cardiovascular events.

Professor Marc Sabatine, lead author of the study, from Brigham and Women's Hospital, Boston, Mass., U.S., said: "Cholesterol-lowering medications are affordable drugs that have reduced risk of heart disease for millions of people worldwide, but until now their benefits for older people have remained less certain. Our analysis indicates that these therapies are as effective in reducing cardiovascular events and deaths in people aged 75 years and over as they are in younger people. We found no offsetting safety concerns and together, these results should strengthen guideline recommendations for the use of [cholesterol](#)-lowering medications, including statin and non-statin therapy, in elderly people."

The authors acknowledge some limitations to their study. The definitions of cardiovascular events differed slightly between trials. However, the authors say these minor differences are unlikely to affect the clinical implications of their findings. Additionally, older patients who are included in clinical trials might not be representative of everyday practice, because people who already have multiple medical conditions or are unable to attend follow-up visits would not typically be enrolled in a clinical trial.

Writing in a linked Comment, Professor Frederick Raal, University of the Witwatersrand, South Africa, who was not involved in the study, said: "As the authors acknowledge, although lipid-lowering therapy was efficacious in older patients, we should not lose sight of the benefit of treating individuals when they are younger. The average age of patients in all the trials analysed was older than 60 years, an age when atherosclerotic cardiovascular disease is already well established. Lipid-lowering therapy should be initiated at a younger age, preferably before age 40 years, in those at risk to delay the onset of atherosclerosis rather



than try to manage the condition once fully established or advanced."

**More information:** Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort, [DOI: 10.1016/S0140-6736\(20\)32233-9](https://doi.org/10.1016/S0140-6736(20)32233-9) , [www.thelancet.com/journals/lan ... \(20\)32233-9/fulltext](http://www.thelancet.com/journals/lan... (20)32233-9/fulltext)

Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials , [DOI: 10.1016/S0140-6736\(20\)32332-1](https://doi.org/10.1016/S0140-6736(20)32332-1) , [www.thelancet.com/journals/lan ... \(20\)32332-1/fulltext](http://www.thelancet.com/journals/lan... (20)32332-1/fulltext)

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