The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 1, 2026 VOL. 395 NO. 13

Atorvastatin, Cardiovascular Events, and Disability-free Survival in Older Adults

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ABSTRACT

BACKGROUND

The effectiveness and safety of statins for the primary prevention of cardiovascular events and the extension of disability-free survival among older adults remain uncertain.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial at general medical practices across Australia. Community-dwelling adults at least 70 years of age with no history of cardiovascular disease, diabetes, or dementia were randomly assigned in a 1:1 ratio to receive atorvastatin at a dose of 40 mg once daily or identical placebo. The two primary end points were a composite of death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization (to assess effects on major cardiovascular events) and a composite of death from any cause, dementia, or persistent physical disability (to assess effects on disability-free survival). Analyses were performed according to a hierarchical testing plan.

RESULTS

A total of 9971 participants were enrolled: 4984 were assigned to receive atorvastatin and 4987 to receive placebo. The mean (±SD) age of the participants was 74.7±4.5 years, and 51.9% were women. After a median of 5.9 years, a primary cardiovascular event had occurred in 297 participants (10.9 events per 1000 person-years) in the atorvastatin group and in 412 participants (15.5 events per 1000 person-years) in the placebo group (hazard ratio, 0.70; 95% confidence interval [CI], 0.61 to 0.82; P<0.001). Death from any cause, dementia, or persistent physical disability occurred in 637 participants (21.6 events per 1000 person-years) in the atorvastatin group and in 676 participants (23.0 events per 1000 person-years) in the placebo group (hazard ratio, 0.94; 95% CI, 0.84 to 1.05; P=0.25). Serious adverse events occurred in 131 participants (2.7%) in the atorvastatin group and in 129 (2.7%) in the placebo group, with musculoskeletal, hepatobiliary, and diabetes-related adverse events occurring more commonly in the atorvastatin group.

CONCLUSIONS

Treatment with atorvastatin led to a lower risk of major cardiovascular events than placebo at a median of 5.9 years but did not result in longer disability-free survival among community-dwelling older adults without clinical cardiovascular disease. (Funded by the National Health and Medical Research Council and others; STAREE ClinicalTrials.gov number, NCT02099123.)

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This article was published on August 29, 2026, at NEJM.org.

N Engl J Med 2026;395:1259-72.
DOI: 10.1056/NEJMoa2607314
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A rapid demographic transition toward an older population is occurring throughout the world.[1] Increasing life span is a major contributor to this shift, with the percentage of older adults who survive into their 80s and 90s now almost twice what it was in the 1950s.[2] Over the same time period, healthy life span has not increased to the same extent; older adults still face major consequences from cardiovascular disease, as well as dementia and other disabling conditions.[3-6]

It is well established that statins reduce the risk of myocardial infarction and ischemic stroke in adults at high risk, including those with diabetes or established cardiovascular disease.[7,8] However, the effects of initiating treatment with statins in older patients remain uncertain and are intensely debated.[9,10] Clinical guidelines have not included strong recommendations to inform the prescription of statins for persons at least 70 years of age, with the evidence particularly sparse for those older than 75 years.[11] Recommendations have generally been based on pooled analyses of trials involving cardiovascular outcomes in which fewer than one in four participants were older than 70 years of age.[12] These pooled analyses have suggested that the use of statins for the primary prevention of cardiovascular events may be less effective in older adults without vascular disease than in younger persons: the reduction in the risk of cardiovascular events for every reduction of 38.7 mg per deciliter (1.0 mmol per liter) in the level of low-density lipoprotein (LDL) cholesterol was nonsignificant among older adults, at 16% among persons older than 70 years and 8% among persons older than 75 years.[8]

Few randomized trials have assessed the effects of statins on dementia and disability. The Heart Protection Study included participants with a wide range of ages (40 to 82 years) and used a single cognitive test that probably lacked the sensitivity to detect subtle cognitive decline, with the number of newly identified cases of dementia being too low for a definitive analysis.[13] Both the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) and HOPE-3 (Heart Outcomes Prevention Evaluation 3) trials included cognitive measures but did not formally assess newly diagnosed dementia as a clinical end point.[14,15] The JUPITER (Justification for the Use of Statins in Prevention) trial tracked dementia as an adverse event but did not use standardized, objective cognitive assessments and, despite enrolling 17,802 participants, identified very few cases of dementia (12 in the rosuvastatin group and 9 in the placebo group).[16] Data from large-scale, randomized trials evaluating disability-free survival (i.e., survival free of dementia or physical disability) as a prespecified primary end point are lacking.

Previous studies of statins have sparked concerns about muscle weakness or pain, impairment of liver function, cognitive impairment, new-onset diabetes, and hemorrhagic stroke.[17-19] Older adults are more likely to take a large number of medications than younger adults,[20] and older adults metabolize drugs differently[21]; therefore, older adults are at greater risk for statin–drug interactions and adverse events than younger persons. Fears of these adverse events may drive decisions about the prescription of statins and may lead to nonadherence to treatment.[22,23] Overall, the balance of benefits and harms from the use of statins in older adults remains uncertain.[12,24]

We conducted the Statins in Reducing Events in the Elderly (STAREE) trial to provide evidence to inform the prescription of statins for primary prevention in community-dwelling adults 70 years of age or older. The primary objective of the trial was to evaluate the effects of atorvastatin on major cardiovascular events and on disability-free survival (or survival free of dementia or physical disability) as a surrogate measure of independence.

METHODS

TRIAL ORGANIZATION AND OVERSIGHT

We conducted this investigator-initiated, double-blind, randomized, placebo-controlled, primary-prevention trial at general medical practices across Australia. The trial design has been described in detail previously,[12] and the trial protocol is available with the full text of this article at NEJM.org. Additional details about the trial methods, oversight, and author responsibilities are provided in the Supplementary Appendix, available at NEJM.org. The trial steering committee developed the protocol and operational plan after consultation with health care consumers and general practitioner co-investigators. The trial

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had no commercial or industry involvement. The protocol was approved by the Monash University Human Research Ethics Committee. An independent data monitoring committee reviewed the safety and efficacy data during the trial. The funders of the trial had no role in the trial design; in the collection, management, analysis, or interpretation of the data; in the writing of the manuscript; or in the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL POPULATION

Adults 70 years of age or older who were living independently and had no history of cardiovascular disease, diabetes, dementia, or other life-limiting conditions were identified from the clinical databases of 1013 general medical practices, among 1583 registered practices across metropolitan, regional, and rural areas of Australia. For trial eligibility, cardiovascular disease was defined as myocardial infarction, angina, heart failure, stroke, transient ischemic attack, carotid stenosis, abdominal aortic aneurysm, peripheral artery disease, or any coronary-artery blockage or narrowing leading to angioplasty, stent implantation, or bypass graft surgery. Eligible participants were invited to take part in two baseline screening visits 4 weeks apart. These baseline visits included the completion of cognitive tests to ascertain cognitive performance, assessment of physical independence with the use of a modified Katz Index of Independence in Activities of Daily Living, and laboratory assessments. During the period between visits, the participants were asked to take a once-daily placebo tablet to assess adherence to a daily medication regimen.[12] All the participants provided written informed consent.

RANDOMIZATION AND TRIAL REGIMEN

A Web-based system was used to randomly assign participants in a 1:1 ratio to the atorvastatin group or the placebo group according to a randomization schedule generated by an independent statistician. For both groups, the starting dose was one tablet daily for 4 weeks, with an increase to two tablets daily if the safety profile was acceptable. In the atorvastatin group, each tablet contained 20 mg of medication, for a total dose of 40 mg after the 4-week dose-adjustment period. Further adjustment (de-escalation and re-escalation of the dose) was permitted for management of side effects.

Participant follow-up occurred every 6 months. Open-label statins could be prescribed at the discretion of the usual treating clinician, with the assigned trial regimen discontinued. Fasting lipid levels were measured at baseline and at the end of the trial.

TRIAL END POINTS

The two primary end points were a composite of death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization and a composite of death from any cause, dementia, or persistent physical disability (a measure of disability-free survival). Reported events suspected of being primary end-point events were adjudicated by committees whose members were unaware of the trial-group assignments. The prespecified secondary end points included a composite of death from cardiovascular causes or nonfatal myocardial infarction or stroke, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, coronary revascularization, any arterial revascularization, death from any cause, dementia, persistent physical disability, and hospitalization for any cause.

Adverse events were coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 21.0,[25] and the seriousness of adverse events was categorized according to the 2007 National Statement on Ethical Conduct in Human Research of the National Health and Medical Research Council.[26] Adverse events of special interest included new diagnoses of myopathy, myositis, rhabdomyolysis, liver failure, and diabetes. Adverse events were considered to be related to the trial regimen if the trial physician, who was unaware of the trial-group assignments, judged that a causal relationship was possible, probable, or definite.

STATISTICAL ANALYSIS

Analyses were performed after the data were locked in February 2026 according to the prespecified statistical analysis plan, available with the protocol.[27] We calculated that 619 primary cardiovascular events and 1397 primary events

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related to disability-free survival would provide the trial with 80.0% power to detect a difference of 20.2% in the risk of major cardiovascular events and 14.5% in the risk of death, dementia, or persistent physical disability between the atorvastatin group and the placebo group. On the basis of expected event rates, we aimed to enroll 9631 participants to be followed for an average of 6 years.[12]

The primary end points were assessed in time-to-event analyses, as prespecified in the statistical analysis plan, and all comparisons of end points were performed according to an intention-to-treat approach.[27] Event rates were compared between the trial groups with the use of Cox proportional-hazards regression, with results expressed as cause-specific hazard ratios and 95% confidence intervals. A closed testing procedure was implemented to allow for multiple testing owing to the use of two primary end points.[28] This prespecified approach was based on the expectation that cardiovascular benefit would be the main contributor to improved disability-free survival and that a substantial effect of statins on disability-free survival would be unlikely in the absence of a cardiovascular benefit.[12,27] The cardiovascular end point was to be tested first at a two-sided alpha level of 0.05, and if the P value was less than 0.05, then the disability-free survival end point was to be tested at a two-sided alpha level of 0.05.[27]

Analyses of the secondary end points also used Cox proportional-hazards regression models that were based on the time to the first event that met the end-point definition. No statistical adjustment was made for the multiple secondary end points. Because the widths of the confidence intervals were not adjusted for multiplicity, they should not be used to infer treatment effects. The cumulative incidence was estimated for all end points, with death from causes other than those included in the end point accounted for as a competing risk. Prespecified subgroup analyses were undertaken as outlined in the statistical analytical plan. Safety analyses were conducted in the modified intention-to-treat population, which included all the participants who received at least one dose of atorvastatin or placebo. Additional information about the statistical analyses is provided in the Supplementary Appendix.

RESULTS

PARTICIPANT CHARACTERISTICS AND FOLLOW-UP

Between July 2015 and March 2023, a total of 9971 participants underwent randomization, with 4984 participants assigned to receive atorvastatin and 4987 to receive placebo (Fig. S1 in the Supplementary Appendix). The representativeness of the trial participants is summarized in Table S1. The characteristics of the participants at baseline were similar in the two trial groups (Table 1 and Table S2). The mean (±SD) age was 74.7±4.5 years, and 51.9% of the participants were women. Most participants reported current alcohol use and no history of smoking. The median number of medications at baseline was two (interquartile range, one to four), with 19.6% of the participants taking at least five medications, most commonly agents to lower blood pressure (46.3%), agents to manage acid-related gastrointestinal disorders (27.1%), and analgesic agents (20.6%). A total of 5.2% of the participants reported previous statin use.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Overall (N = 9971)	Atorvastatin (N = 4984)	Placebo (N = 4987)
Age group — no. (%)			
70–74 yr	5948 (59.7)	2959 (59.4)	2989 (59.9)
75–79 yr	2503 (25.1)	1274 (25.6)	1229 (24.6)
80–84 yr	1112 (11.2)	562 (11.3)	550 (11.0)
≥85 yr	408 (4.1)	189 (3.8)	219 (4.4)
Gender — no. (%)			
Man	4797 (48.1)	2411 (48.4)	2386 (47.8)
Woman	5174 (51.9)	2573 (51.6)	2601 (52.2)

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Table 1. (Continued.)

Characteristic	Overall (N=9971)	Atorvastatin (N=4984)	Placebo (N=4987)
Race or ethnic group — no. (%)†			
White	9803 (98.3)	4901 (98.3)	4902 (98.3)
Asian	84 (0.8)	40 (0.8)	44 (0.9)
Aboriginal or Torres Strait Islander	23 (0.2)	13 (0.3)	10 (0.2)
Other	61 (0.6)	30 (0.6)	31 (0.6)
First language — no./total no. (%)			
English	9535/9967 (95.7)	4768/4981 (95.7)	4767/4986 (95.6)
Other	432/9967 (4.3)	213/4981 (4.3)	219/4986 (4.4)
Smoking status — no./total no. (%)			
Current smoker	245/9967 (2.5)	130/4981 (2.6)	115/4986 (2.3)
Former smoker	4252/9967 (42.7)	2134/4981 (42.8)	2118/4986 (42.5)
Never smoker	5470/9967 (54.9)	2717/4981 (54.5)	2753/4986 (55.2)
BMI category — no./total no. (%)			
≥30.0	2483/9612 (25.8)	1248/4794 (26.0)	1235/4818 (25.6)
25.0–29.9	4078/9612 (42.4)	2043/4794 (42.6)	2035/4818 (42.2)
<25.0	3051/9612 (31.7)	1503/4794 (31.4)	1548/4818 (32.1)
Medication use — no. (%)			
Blood-pressure–lowering agents	4612 (46.3)	2306 (46.3)	2306 (46.2)
Agents for acid-related disorders	2700 (27.1)	1398 (28.0)	1302 (26.1)
Analgesic agents	2055 (20.6)	1060 (21.3)	995 (20.0)
Anticoagulant or antiplatelet agents	1486 (14.9)	728 (14.6)	758 (15.2)
Lipid levels — mg/dl			
Total cholesterol	211.2±32.0	210.8±31.6	211.6±32.5
LDL cholesterol	126.6±28.0	126.2±27.8	127.0±28.1
HDL cholesterol	61.6±17.5	61.6±17.7	61.7±17.3
Non-HDL cholesterol	149.6±30.7	149.2±30.4	149.9±31.0
Triglycerides	113.1±53.6	113.1±53.4	113.2±53.8
Blood pressure — mm Hg			
Systolic	135.8±16.1	135.8±16.0	135.7±16.2
Diastolic	80.1±9.4	80.1±9.3	80.2±9.6
Score on 3MS (IQR)‡			
In-person assessment	95.0 (91.0–97.0)	95.0 (91.8–97.0)	95.0 (91.0–97.0)
Telephone assessment	70.0 (67.0–71.0)	70.0 (67.0–71.0)	70.0 (67.0–71.0)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. BMI denotes body-mass index, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.

† Race and ethnic group were reported by the participant. Other includes Pacific Islander or Maori (8 participants), African (4 participants), more than one race (32 participants), and unknown or not reported (17 participants).

‡ Scores on the Modified Mini–Mental State (3MS) examination range from 0 to 100 for in-person assessment and from 0 to 73 for telephone assessment, with higher scores indicating better cognitive functioning. Scores were available for 8924 participants who were assessed in person and for 1047 participants who were assessed by telephone.

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The most common previous medical conditions were cancer and depression. Memory symptoms were uncommon (reported in 4.8% of the participants) at baseline, but muscle symptoms were common (in 46.1%). The median body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was 27.0 (interquartile range, 24.3 to 30.1), and the mean blood pressure was 136/80 mm Hg. The median cognitive score was 95 for those who completed the Modified Mini–Mental State (3MS) examination in person and 70 for those who completed the examination by telephone (scores range from 0 to 100 for in-person assessment and from 0 to 73 for telephone assessment, with higher scores indicating better cognitive functioning).[29] A total of 8849 participants (88.7%) reported having no difficulty with any of the six activities included on a modified Katz Index of Independence in Activities of Daily Living (bathing, dressing, toileting, transferring, walking across a small room, and feeding), with the remainder reporting minor difficulty, a little difficulty, or some difficulty with one or more of the activities.[30]

Participants were followed for a median of 5.9 years. Complete assessment for vital status was available through a median of 6.4 years by means of linkage to death record registers for 99.9% of the participants. Similar numbers of participants in the atorvastatin and placebo groups withdrew consent after randomization. Among those who began taking atorvastatin or placebo as assigned, fewer participants in the atorvastatin group than in the placebo group permanently discontinued the trial regimen (Table S3). In the atorvastatin group, 80.2% of the participants were still taking atorvastatin at 1 year, 66.1% at 3 years, and 55.6% at 5 years; the corresponding percentages in the placebo group were 79.5%, 61.3%, and 47.0% (Fig. S2). Open-label statin use was reported by an estimated 2.1% of the participants in the atorvastatin group by the end of year 1, 5.9% by the end of year 3, and 9.4% by the end of year 5; the corresponding estimated percentages in the placebo group were 3.5%, 12.1%, and 19.4%.

LIPID LEVELS

At baseline, the mean total cholesterol level was 211±32 mg per deciliter (5.46 ±0.83 mmol per liter), the mean LDL cholesterol level was 127±28 mg per deciliter (3.27±0.72 mmol per liter), the mean high-density lipoprotein cholesterol level was 62±17 mg per deciliter (1.59±0.45 mmol per liter), and the mean triglyceride level was 113±54 mg per deciliter (1.28±0.61 mmol per liter); the lipid levels were similar in the two groups (Table 1). At the end of follow-up, the mean reduction in the total cholesterol level was 53 mg per deciliter (1.37 mmol per liter) in the atorvastatin group and 18 mg per deciliter (0.47 mmol per liter) in the placebo group. The LDL cholesterol level was reduced by a mean of 48 mg per deciliter (1.23 mmol per liter) in the atorvastatin group and 16 mg per deciliter (0.42 mmol per liter) in the placebo group. The between-group difference in the mean reduction in cholesterol levels was 35 mg per deciliter (95% confidence interval [CI], 33 to 37 [0.90 mmol per liter; 95% CI, 0.84 to 0.95]) for total cholesterol and 31 mg per deciliter (95% CI, 30 to 33 [0.81 mmol per liter; 95% CI, 0.76 to 0.86]) for LDL cholesterol.

PRIMARY END POINTS

In the overall trial population, 709 participants (7.1%) had a primary cardiovascular event, and 1313 participants (13.2%) had a primary end-point event related to disability-free survival (Table 2). Among the primary cardiovascular events, death from cardiovascular causes was the first event in 83 of 709 participants (11.7%), nonfatal myocardial infarction in 208 participants (29.3%), nonfatal stroke in 247 participants (34.8%), and coronary revascularization in 171 participants (24.1%). Among the primary end-point events related to disability-free survival, death from any cause was the first event in 650 of 1313 participants (49.5%), dementia in 548 participants (41.7%), and persistent physical disability in 115 participants (8.8%).

Primary cardiovascular events occurred in 297 participants (10.9 events per 1000 person-years) in the atorvastatin group and in 412 participants (15.5 events per 1000 person-years) in the placebo group (hazard ratio for death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization, 0.70; 95% CI, 0.61 to 0.82; P<0.001) (Table 2 and Fig. 1A). The number needed to treat to prevent one major cardiovascular event at the median follow-up of 5.9 years was 37. The results of subgroup analyses are shown in Figure 2A.

A primary end-point event related to disability-

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Table 2. Primary and Secondary End Points.*

End Point	Overall (N=9971)	Atorvastatin (N=4984)	Placebo (N=4987)	Hazard Ratio (95% CI)†
	no. of events per 1000 person-yr (no. of participants with event)			
Death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization: primary end point	13.2 (709)	10.9 (297)	15.5 (412)	0.70 (0.61–0.82)‡
Death from cardiovascular causes or nonfatal myocardial infarction or stroke	10.1 (551)	8.6 (236)	11.7 (315)	0.73 (0.62–0.87)
Death from cardiovascular causes	2.4 (148)	2.4 (74)	2.4 (74)	1.00 (0.72–1.37)
Fatal or nonfatal myocardial infarction	3.9 (216)	2.9 (79)	5.0 (137)	0.57 (0.43–0.75)
Nonfatal myocardial infarction	3.8 (207)	2.8 (77)	4.8 (130)	0.58 (0.44–0.77)
Fatal or nonfatal stroke	4.7 (260)	4.4 (122)	5.1 (138)	0.87 (0.68–1.11)
Nonfatal stroke	4.2 (230)	3.7 (103)	4.7 (127)	0.80 (0.62–1.04)
Any arterial revascularization	6.4 (348)	4.6 (127)	8.2 (221)	0.56 (0.45–0.70)
Coronary revascularization	5.5 (300)	4.0 (110)	7.0 (190)	0.57 (0.45–0.72)
Death from any cause, dementia, or persistent physical disability: primary end point	22.3 (1313)	21.6 (637)	23.0 (676)	0.94 (0.84–1.05)§
Death from any cause	13.7 (828)	13.0 (395)	14.3 (433)	0.91 (0.79–1.04)
Dementia	10.5 (570)	10.6 (290)	10.3 (280)	1.03 (0.87–1.21)
Persistent physical disability	2.5 (140)	2.2 (60)	2.9 (80)	0.74 (0.53–1.04)
Hospitalization for any cause	149.9 (5515)	148.9 (2744)	150.9 (2771)	0.99 (0.94–1.04)

* Data are shown for the intention-to-treat population, which included all the participants who had undergone randomization.
† Hazard ratios and 95% confidence intervals were determined with Cox regression. The widths of the confidence intervals for secondary end points have not been adjusted for multiplicity and should not be used to infer treatment effects.
‡ P<0.001.
§ P=0.25.

free survival occurred in 637 participants (21.6 events per 1000 person-years) in the atorvastatin group and in 676 participants (23.0 events per 1000 person-years) in the placebo group (hazard ratio, 0.94; 95% CI, 0.84 to 1.05; P=0.25) (Table 2 and Fig. 1B). The results of subgroup analyses are shown in Figure 2B.

SECONDARY END POINTS

Death from cardiovascular causes, myocardial infarction, or stroke occurred in 236 participants (8.6 events per 1000 person-years) in the atorvastatin group and in 315 participants (11.7 events per 1000 person-years) in the placebo group (hazard ratio, 0.73; 95% CI, 0.62 to 0.87). Nonfatal or fatal myocardial infarction occurred in 79 participants (2.9 events per 1000 person-years) in the atorvastatin group and in 137 participants (5.0 events per 1000 person-years) in the placebo group (hazard ratio, 0.57; 95% CI, 0.43 to 0.75), and nonfatal or fatal stroke in 122 participants (4.4 events per 1000 person-years) and in 138 participants (5.1 events per 1000 person-years), respectively (hazard ratio, 0.87; 95% CI, 0.68 to 1.11). Coronary revascularization occurred in 110 participants (4.0 events per 1000 person-years) in the atorvastatin group and in 190 participants (7.0 events per 1000 person-years) in the placebo group (hazard ratio, 0.57; 95% CI, 0.45 to 0.72), and any arterial revascularization in 127 participants (4.6 events per 1000 person-years) and in 221 participants (8.2 events per 1000 person-years), respectively (hazard ratio, 0.56; 95% CI, 0.45 to 0.70). Dementia occurred in 290 participants (10.6 events per 1000 person-years) in the atorvastatin group and in 280 participants (10.3 events per 1000 person-years) in the placebo group (hazard ratio, 1.03; 95% CI, 0.87 to 1.21), and

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persistent physical disability in 60 participants (2.2 events per 1000 person-years) and in 80 participants (2.9 events per 1000 person-years), respectively (hazard ratio, 0.74; 95% CI, 0.53 to 1.04). Hospitalization for any cause occurred in 2744 participants (148.9 hospitalizations per 1000 person-years) in the atorvastatin group and in 2771 participants (150.9 hospitalizations per 1000 per-

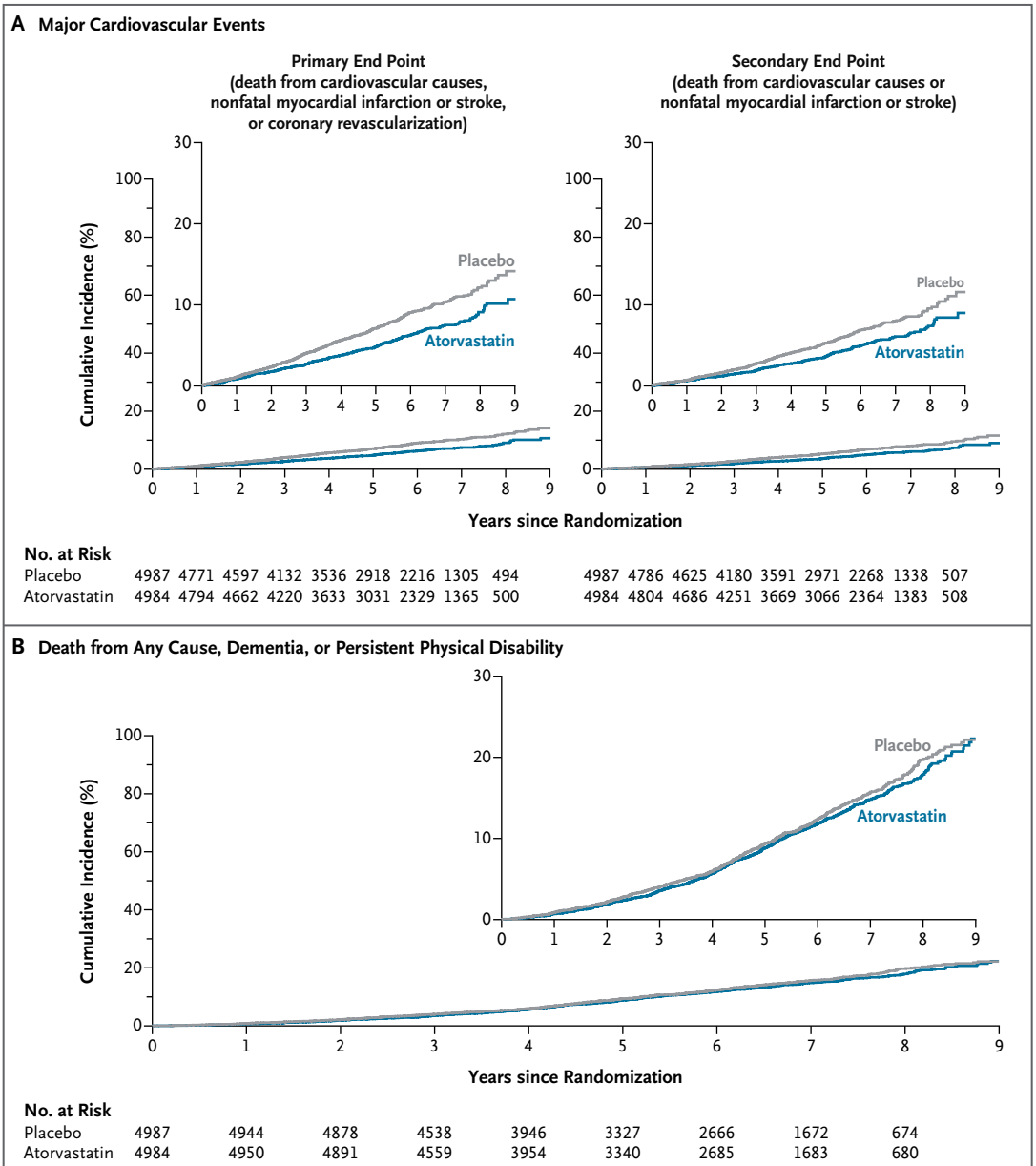


Figure 1. Major Cardiovascular Events and Disability-free Survival According to Trial Group.

Panel A shows the cumulative incidence of major cardiovascular events. The graphs on the left show the cumulative incidence of primary end-point events (death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization, whichever occurred first), and those on the right the cumulative incidence of composite secondary end-point events (death from cardiovascular causes, myocardial infarction, or stroke, whichever occurred first). Panel B shows the cumulative incidence of death from any cause, dementia, or persistent physical disability, whichever occurred first, as a measure of disability-free survival. Insets show the same data on an expanded y axis.

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son-years) in the placebo group (hazard ratio, 0.99; 95% CI, 0.94 to 1.04).

The incidence of death from any cause was 13.0 per 1000 person-years in the atorvastatin group and 14.3 per 1000 person-years in the placebo group (Table 2). The incidence of death from cardiovascular causes was 2.4 per 1000 person-years in both groups, and the incidence of death from noncardiovascular causes was 10.6 per 1000 person-years in the atorvastatin group and 11.9 per 1000 person-years in the placebo group. The incidence of death from any cause, death from cardiovascular causes, and death from noncardiovascular causes did not differ substantially between the two groups.

SAFETY

Adverse events in the modified intention-to-treat population that were considered by the trial physician to be related to the trial regimen are summarized in Table 3. Adverse events of any kind, medically important adverse events, and adverse events that led to discontinuation of the trial regimen were more commonly reported in the atorvastatin group than in the placebo group (Table 3). In cases of discontinuation of the assigned trial regimen, the most cited reason was "participant unwilling" (in 15.6% of the participants in the atorvastatin group and in 16.2% of those in the placebo group), with adverse events or an unacceptable side-effect profile leading to discontinuation in 7.2% and in 6.1%, respectively.

No substantial between-group difference in the percentage of participants with serious adverse events was observed. Serious adverse events that involved musculoskeletal or connective tissue were reported in 0.2% of the participants in each group, and medically important adverse events of this type were reported in 1.1% of the participants in the atorvastatin group and in 0.9% of those in the placebo group. Serious hepatobiliary events were reported in 0.2% of the participants in the atorvastatin group and in 0.1% of those in the placebo group, and medically important hepatobiliary events were reported in 1.4% and in 0.3%, respectively. Serious diabetes or diabetes-related adverse events were reported in less than 0.1% of the participants in each group, and medically important diabetes or diabetes-related adverse events were reported in 1.1% of the participants in the atorvastatin group and in 0.7% of those in the placebo group.

DISCUSSION

Among community-dwelling adults 70 years of age or older with no history of clinical cardiovascular disease, treatment with atorvastatin at a daily dose of 40 mg was associated with a lower risk of major cardiovascular events than placebo over an average follow-up of 6 years but did not result in longer disability-free survival. The reduction in the risk of major cardiovascular events appeared to be similar among participants 70 to 74 years of age and those 75 years of age or older. The difference in the risk of secondary cardiovascular end-point events was consistent with the overall treatment effect. The risk of death from any cause, dementia, persistent physical disability, or hospitalization for any cause did not differ substantially between the two trial groups. The incidence of serious adverse events was similar in the two groups, but medically important adverse events, especially those related to musculoskeletal or connective tissue, hepatobiliary events, and diabetes-related adverse events, were more common with atorvastatin than with placebo.

In contrast to previous primary-prevention trials involving statins,[7,8,14-16] our trial included only community-dwelling adults at least 70 years of age (>40% of the participants were older than 75 years). The groups were balanced with respect to gender, and the participants were equally distributed across metropolitan and regional or rural locations. Mean LDL cholesterol levels were in the normal range (upper limit, <135 mg per deciliter [<3.5 mmol per liter])[31] at baseline and, as anticipated, were reduced by a mean of 48 mg per deciliter in the atorvastatin group, as compared with 16 mg per deciliter in the placebo group. The overall cardiovascular benefits were consistent across subgroups defined by LDL cholesterol level, blood pressure, BMI, and kidney function at baseline.

The cardiovascular benefits from treatment with 40 mg of atorvastatin in this trial were greater than those observed in the PROSPER trial,[14] which involved pravastatin at a dose of 40 mg in an older population with a mean age of 75.4 years, but similar to those reported in the JUPITER trial,[16] with rosuvastatin at a dose of 20 mg in a population with a median age of 66.0 years, and in the HOPE-3 trial,[15] with rosuvastatin at a dose of 10 mg in a population with a mean age of 65.7 years. The benefits in the older population in our trial were

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A Major Cardiovascular Events

Subgroup	Atorvastatin	Placebo	Hazard Ratio (95% CI)
	no. of participants with event/total no. of participants (events per 1000 person-yr)		
Gender			
Woman	127/2573 (9.0)	149/2601 (10.5)	0.85 (0.67–1.08)
Man	170/2411 (13.0)	263/2386 (21.0)	0.62 (0.51–0.75)
Age			
70–74 yr	129/2959 (8.0)	193/2989 (12.0)	0.67 (0.53–0.83)
≥75 yr	168/2025 (15.2)	219/1998 (20.8)	0.73 (0.59–0.89)
Systolic blood pressure			
<128 mm Hg	71/1489 (8.5)	86/1548 (10.2)	0.84 (0.61–1.14)
128–141 mm Hg	107/1692 (11.4)	148/1640 (16.8)	0.67 (0.53–0.86)
≥142 mm Hg	116/1589 (13.2)	167/1595 (19.2)	0.69 (0.55–0.88)
Diastolic blood pressure			
<76 mm Hg	105/1566 (12.1)	125/1593 (14.7)	0.82 (0.63–1.06)
76–83 mm Hg	92/1576 (10.5)	136/1547 (16.2)	0.65 (0.50–0.85)
≥84 mm Hg	97/1628 (10.7)	140/1642 (15.5)	0.69 (0.53–0.90)
Body-mass index			
<25	92/1503 (11.2)	104/1548 (12.5)	0.89 (0.67–1.18)
25–29.9	123/2043 (10.8)	185/2035 (16.7)	0.65 (0.51–0.81)
≥30	78/1248 (11.3)	112/1235 (16.8)	0.67 (0.50–0.90)
Smoking status			
Current or former	151/2264 (12.2)	205/2233 (17.3)	0.70 (0.57–0.87)
Never	146/2717 (9.8)	207/2753 (14.0)	0.70 (0.57–0.87)
eGFR			
<60 ml/min/1.73 m^2	48/577 (15.4)	62/598 (19.4)	0.80 (0.55–1.16)
≥60 ml/min/1.73 m^2	249/4407 (10.3)	350/4389 (14.9)	0.69 (0.59–0.81)
LDL cholesterol			
<116.01 mg/dl	107/1614 (12.1)	129/1617 (15.0)	0.80 (0.62–1.03)
116.01–139.21 mg/dl	89/1677 (9.6)	117/1603 (13.5)	0.71 (0.54–0.94)
>139.21 mg/dl	101/1687 (11.1)	165/1756 (17.6)	0.63 (0.49–0.81)
HDL cholesterol			
<52.98 mg/dl	115/1686 (12.6)	185/1614 (21.9)	0.58 (0.46–0.73)
52.98–65.74 mg/dl	88/1398 (11.7)	109/1459 (14.1)	0.83 (0.63–1.10)
>65.74 mg/dl	94/1900 (8.9)	118/1914 (11.3)	0.78 (0.60–1.03)
3MS			
<Median z score	162/2384 (12.6)	207/2349 (17.0)	0.74 (0.60–0.91)
≥Median z score	135/2600 (9.4)	205/2638 (14.2)	0.66 (0.53–0.82)
Time of randomization			
Before pandemic	236/3292 (11.3)	320/3288 (15.8)	0.72 (0.61–0.85)
During or after pandemic	61/1692 (9.5)	92/1699 (14.5)	0.66 (0.48–0.91)

0.50 0.75 1.0 1.33

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B Disability-free Survival

Subgroup	Atorvastatin	Placebo	Hazard Ratio (95% CI)
	no. of participants with event/total no. of participants (events per 1000 person-yr)		
Gender			
Woman	288/2573 (18.8)	295/2601 (19.1)	0.99 (0.84–1.16)
Man	349/2411 (24.6)	381/2386 (27.4)	0.90 (0.78–1.04)
Age			
70–74 yr	241/2959 (13.8)	236/2989 (13.3)	1.04 (0.87–1.24)
≥75 yr	396/2025 (33.0)	440/1998 (37.7)	0.87 (0.76–1.00)
Systolic blood pressure			
<128 mm Hg	181/1489 (20.1)	215/1548 (23.5)	0.84 (0.69–1.03)
128–141 mm Hg	211/1692 (20.8)	217/1640 (22.1)	0.94 (0.78–1.14)
≥142 mm Hg	228/1589 (23.9)	232/1595 (24.0)	1.01 (0.84–1.21)
Diastolic blood pressure			
<76 mm Hg	236/1566 (25.0)	263/1593 (28.2)	0.88 (0.74–1.04)
76–83 mm Hg	178/1576 (18.8)	206/1547 (22.1)	0.85 (0.70–1.04)
≥84 mm Hg	206/1628 (21.0)	195/1642 (19.6)	1.08 (0.89–1.31)
Body-mass index			
<25	224/1503 (25.4)	223/1548 (24.4)	1.05 (0.88–1.27)
25–29.9	241/2043 (19.5)	285/2035 (23.5)	0.82 (0.69–0.97)
≥30	160/1248 (21.3)	156/1235 (21.0)	1.02 (0.82–1.27)
Smoking status			
Current or former	321/2264 (23.9)	342/2233 (25.8)	0.93 (0.79–1.08)
Never	316/2717 (19.7)	334/2753 (20.7)	0.95 (0.82–1.11)
eGFR			
<60 ml/min/1.73 m^2	122/577 (35.6)	115/598 (32.2)	1.12 (0.87–1.45)
≥60 ml/min/1.73 m^2	515/4407 (19.8)	561/4389 (21.7)	0.91 (0.81–1.02)
LDL cholesterol			
<116.01 mg/dl	252/1614 (26.3)	265/1617 (28.0)	0.93 (0.78–1.11)
116.01–139.21 mg/dl	202/1677 (20.3)	198/1603 (20.8)	0.97 (0.80–1.18)
>139.21 mg/dl	182/1687 (18.4)	212/1756 (20.5)	0.90 (0.74–1.10)
HDL cholesterol			
<52.98 mg/dl	214/1686 (21.6)	240/1614 (25.4)	0.85 (0.71–1.03)
52.98–65.74 mg/dl	184/1398 (22.5)	184/1459 (21.5)	1.05 (0.85–1.29)
>65.74 mg/dl	239/1900 (20.9)	252/1914 (22.1)	0.94 (0.79–1.13)
3MS			
<Median z score	418/2384 (30.2)	440/2349 (32.5)	0.93 (0.81–1.06)
≥Median z score	219/2600 (14.0)	236/2638 (14.9)	0.94 (0.79–1.13)
Time of randomization			
Before pandemic	542/3292 (24.0)	573/3288 (25.5)	0.94 (0.84–1.06)
During or after pandemic	95/1692 (13.8)	103/1699 (14.9)	0.92 (0.70–1.22)

0.50 0.75 1.0 1.33

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Figure 2 (facing page). Subgroup Analyses.
Shown are results from prespecified subgroup analyses of the effects of atorvastatin as compared with placebo. Panel A shows the incidence of primary major cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization), with associated hazard ratios. Panel B shows the incidence of death from any cause, dementia, or persistent physical disability, with associated hazard ratios, as a measure of disability-free survival. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Higher scores on the Modified Mini–Mental State (3MS) examination indicate better cognitive functioning. The pandemic refers to the coronavirus disease 2019 pandemic. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects. The term eGFR denotes estimated glomerular filtration rate, HDL high-density lipoprotein, and LDL low-density lipoprotein.

associated with substantial lowering of LDL cholesterol levels and were larger than those reported by the Cholesterol Treatment Trialists' Collaboration in meta-analyses of data from trial populations similar in age to the population in our trial.[7,8] The large treatment effects in this trial were due primarily to a lower incidence of nonfatal events, especially myocardial infarction and coronary revascularization, with atorvastatin than with placebo; numbers of deaths from cardiovascular causes were small overall. The effects were especially notable and are probably conservative given the substantial percentage of participants who discontinued the trial regimen, as well as the greater use of open-label statins in the placebo group than in the atorvastatin group. The lack of benefit with respect to death from cardiovascular causes might be explained by low case fatality rates with universal subsidized access to appropriate contemporary management of cardiovascular symptoms and by the competing risk of death from other causes in this older population.[32]

A notable finding is that the lower incidence of major, nonfatal cardiovascular events with atorvastatin than with placebo did not result in a corresponding improvement in disability-free survival. Explanations for this result might include the fact that 80% of the deaths in our trial were from noncardiovascular causes. Notwithstanding the purported pleiotropic biologic properties of statins and concerns about harm from low cholesterol levels,[33-36] no benefits or risks of atorvastatin with respect to death from any cause, dementia, or physical disability were observed in our trial. However, the number of new cases of physical disability was small, which limited our ability to draw conclusions about this component of the primary end point.

For many therapies, the incidence of adverse events increases substantially with age and with the use of multiple medications; in the case of statins, adverse events may include potentially disabling conditions, such as severe musculoskeletal and liver disorders.[19] Despite the advanced age of the trial population and our comprehensive monitoring, the frequency of serious adverse events was low and appeared to have little effect on the components of disability-free survival. Serious musculoskeletal and hepatobiliary adverse events of special interest were uncommon, with a total of 29 participants reporting such events. Our data are in accordance with the findings on adverse events from a meta-analysis of participant-level data from previous trials that evaluated the safety of statins.[37]

The present trial also provided the opportunity to monitor treatment adherence to therapy in the context of primary prevention. A higher incidence of discontinuation of the trial regimen was observed in this trial than in previous trials involving statins,[14-16,38,39] with the most commonly reported reason being "participant unwilling" (in 15.6% of the participants in the atorvastatin group and in 16.2% of those in the placebo group) rather than adverse events or an unacceptable side-effect profile (which led to discontinuation in 7.2% and in 6.1%, respectively). Combined with data from real-world studies showing 5-year adherence of only 25 to 50%,[40] our findings highlight the point that tackling persistence with statin use remains critical to future prescribing effectiveness for primary prevention in older adults.

The trial assessed the effects of statins on major cardiovascular events and disability-free survival in a large, community-dwelling population of older men and women through a primary care setting; the participants in our trial were representative of older adults who, largely based on age alone, would be considered to be at high risk for cardiovascular disease and eligible for therapies for primary prevention, including statins. The choice of high-dose atorvastatin[41] led to a reduction in the mean LDL cholesterol level of approximately 38%, in contrast to the 13% reduction in the placebo group. Ascertainment and adjudication of primary

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Table 3. Trial-Related Safety Events (Modified Intention-to-Treat Population).*

Event	Atorvastatin (N=4876)	Placebo (N=4847)
	no. of participants (%)	
Any adverse event	3073 (63.0)	2846 (58.7)
Serious adverse event	131 (2.7)	129 (2.7)
Medically important adverse event	430 (8.8)	324 (6.7)
Discontinuation of trial regimen due to adverse event	349 (7.2)	297 (6.1)
Adverse events of special interest		
Musculoskeletal and connective-tissue disorders		
Any adverse event	1562 (32.0)	1423 (29.4)
Serious adverse event	8 (0.2)	8 (0.2)
Medically important adverse event	54 (1.1)	43 (0.9)
Hepatobiliary disorders		
Any adverse event	163 (3.3)	44 (0.9)
Serious adverse event	9 (0.2)	4 (0.1)
Medically important adverse event	69 (1.4)	14 (0.3)
Diabetes and diabetes-related disorders		
Any adverse event	195 (4.0)	132 (2.7)
Serious adverse event	2 (<0.1)	1 (<0.1)
Medically important adverse event	56 (1.1)	33 (0.7)
Nervous system disorders		
Any adverse event	1148 (23.5)	1141 (23.5)
Serious adverse event	11 (0.2)	7 (0.1)
Medically important adverse event	20 (0.4)	29 (0.6)

* The modified intention-to-treat population included all the participants who received at least one dose of atorvastatin or placebo. Adverse events that were assessed by the trial physician as being related to the trial are included. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 21.0,[25] and the seriousness of adverse events was categorized according to the 2007 National Statement on Ethical Conduct in Human Research of the National Health and Medical Research Council.[26]

end-point events were rigorous, with long follow-up and complete ascertainment of vital status. Finally, the regular collection of detailed data regarding symptoms that had been associated with statin use (but with unclear causal links) addressed the broader risk–benefit balance associated with statin use in older adults.

Our trial has limitations. Despite a highly decentralized recruitment strategy through Australian general medical practices, participants were predominantly White, with English as their first language. The trial also recruited throughout the coronavirus disease 2019 pandemic, which required that many assessments be completed through remote rather than in-person visits and extended the recruitment period. Despite this challenge, rigorous ascertainment of end points was still possible, with no difference in effects observed between the participants who underwent randomization before the start of the pandemic and those who underwent randomization during or after the pandemic. Finally, the focus on primary prevention in the trial limits the ability to generalize our findings to older adults who are more frail and have more coexisting conditions.

In this trial, treatment with atorvastatin resulted in a lower risk of major cardiovascular events than placebo at a median of 5.9 years but did not lead to longer disability-free survival in older adults without clinical cardiovascular disease.

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Supported by grants (APP1068146, APP1161503, and APP2006611) from the National Health and Medical Research Council, by a Stroke Prevention grant from the Heart Foundation of Australia, and by Monash University.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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