

Discontinuation of statins for primary prevention of atherosclerotic cardiovascular disease in adults aged 75 years or older (SAGA/SITE): a multicentre, open-label, pragmatic, non-inferiority randomised trial

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Summary

Background Statins are among the most widely used drugs; however, their benefits for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in individuals aged 75 years or older without the disease remain uncertain. We aimed to assess the non-inferiority of statin cessation in terms of all-cause mortality under real-life conditions in individuals aged 75 years or older who were prescribed statins for the primary prevention of ASCVD.

Methods We performed a multicentre, open-label, parallel-group, phase 3 randomised controlled trial in 297 primary care offices. Individuals who were aged 75 years or older, were prescribed any statin for at least 1 year for the primary prevention of ASCVD, had no history of ASCVD, and could provide informed consent were randomly assigned (in an unbalanced 5:4 ratio) to continue or stop their statin treatment and were followed up for 36 months. Participants were excluded if they had a progressive disease with a life expectancy of 3 months or less, were diagnosed with dementia, had known homozygous or double heterozygous familial hypercholesterolaemia, or were unable to provide informed consent. Randomisation was computer-generated and implemented via a central electronic system; masking was not done. The primary endpoint was all-cause mortality at 3 years, analysed in participants according to the primary estimand (participants who met all key eligibility criteria and were randomly assigned to statin discontinuation or continuation less than 90 days after inclusion). Missing data were handled using multiple imputation. The non-inferiority margin was 5% for the absolute between-group difference in mortality. This trial is registered with ClinicalTrials.gov, NCT02547883 (completed).

Findings Between June 15, 2016, and Jan 7, 2020, 1180 participants were randomly assigned, and 1160 participants were included in the analysis of the primary estimand. 639 participants were randomly assigned to the statin continuation group, and 521 participants were assigned to the statin discontinuation group. The median age was 80 years (IQR: 78–84), and 775 (66.8%) of 1160 participants were women; 342 (29.5%) of 1160 participants had diabetes, and 896 (77.2%) of them had hypertension. At 36 months, 48 (7.9%) of 604 participants in the statin continuation group and 35 (7.2%) of 484 participants in the statin discontinuation group had died. The absolute difference in all-cause mortality between groups was -0.68% (95% CI -3.95 to 2.60). Statin discontinuation was non-inferior to continuation for 3-year all-cause mortality as the upper bound of the between group difference 95% CI did not exceed the prespecified non-inferiority margin. Adverse events occurred in 461 (73.1%) of 631 participants in the continuation group, and in 390 (74.0%) of 527 in the discontinuation group. Non-cardiovascular adverse events occurred in 456 (72.3%) of 631 participants in the continuation group and 383 (72.7%) of 527 in the discontinuation group.

Interpretation In persons aged 75 years or older receiving statins for primary prevention and with no previous history of ASCVD, discontinuation of statins was non-inferior to continuation in terms of all-cause mortality over 3 years. These findings support individualised decision-making regarding statin discontinuation in older adults.

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Introduction

Statins are cholesterol-lowering therapies that have been used for more than two decades for both primary and secondary prevention of atherosclerotic cardiovascular disease

(ASCVD). Statins are the cornerstone of cardiovascular prevention in individuals with elevated ASCVD risk, as defined by risk equations, or in those with established ASCVD, according to European and US guidelines.^{1,2}

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For the French translation of the abstract see [Online](#) for appendix 2

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Research in context

Evidence before this study

We searched PubMed for articles published from database inception to May 31, 2025, using the search terms “randomised”, “statin”, and “elderly”, without language restrictions, to identify randomised clinical trials assessing the effect of continuing statin therapy for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in people aged 75 years or older. No such trials were identified, and no evidence in the literature indicates the benefit of maintaining statin therapy in this age group for primary prevention. The only trial to date examining a deprescription strategy was conducted in individuals nearing the end of life and found no unfavourable effects on discontinuing therapy.

Added value of this study

This multicentre, randomised controlled trial enrolled 1160 individuals aged 75 years or older without established

ASCVD and directly compared statin discontinuation with continuation. Statin discontinuation was non-inferior to statin continuation in terms of all-cause mortality at 3 years. By providing robust randomised evidence in an understudied population, this trial addresses an important gap and informs clinical decisions about statin deprescribing in primary prevention.

Implications of all the available evidence

In persons aged 75 years or older with no previous history of ASCVD, discontinuation of statins should be driven by a patient-physician shared decision-making process. Given the shortage of large-scale trials, further studies are needed to assess long-term cardiovascular outcomes, subgroups at higher risk, and the effect of discontinuation on quality of life and functional status.

In primary prevention, statins have shown efficacy in large international randomised controlled trials (RCTs), with significant reductions in clinical outcomes such as myocardial infarction, CNS and peripheral vascular events, and revascularisation procedures, with a 20–30% reduction in the incidence of these events.³ The effect of statins on mortality was reported in the JUPITER trial⁴ using rosuvastatin and in a Cochrane meta-analysis of 18 RCTs, which reported a 14% reduction in all-cause mortality in a population with a median age of 57 years.³

However, most clinical trials have excluded individuals older than 70 or 80 years, and therefore, the benefit of statins for primary prevention in older populations remains unclear. Observational studies have reported conflicting results on the benefits of statins in reducing ASCVD and mortality events in individuals older than 70 years, and RCTs are scarce in this age group. In the PROSPER trial, which evaluated the effects of pravastatin (40 mg per day) versus placebo in 5804 participants aged 70–82 years over 3.2 years, no significant reductions in ASCVD or all-cause mortality were observed in the subgroup analysis of 3239 individuals at high risk of vascular disease (primary prevention).⁵ Similarly, a post-hoc secondary analysis of the ALLHAT-LLT study, which assessed the effects of pravastatin (40 mg per day), reported no benefit of pravastatin for primary cardiovascular prevention when analyses were restricted to individuals aged 65 years and older.⁶ These findings have led European and US guidelines to adopt a cautious stance, recommending lipid-lowering treatments for apparently healthy individuals aged 70 years and older only when the individuals are at very high risk of ASCVD (Class IIb).¹ Statins are also associated with numerous drug–drug interactions and adverse effects, particularly in ageing and multimorbid populations. Reported adverse events include myalgia, muscle weakness, rhabdomyolysis, diabetes, renal failure, cataracts and haemorrhagic stroke.⁷ In this context, the benefit–risk ratio of statins for primary

prevention in individuals aged 75 years or older remains unclear. Furthermore, it remains unclear whether individuals who are already receiving statins should continue treatment after the age of 75 years or whether discontinuation of treatment is safe in people older than 75 years who underwent earlier preventive measures, including lipid-lowering therapy.

Medication deprescription is essential for quality care in older adults with multiple comorbidities and polypharmacy, given the increased risk of adverse effects and drug interactions. The benefits of statin deprescription should be carefully weighed against the potential risks, such as increased ASCVD events that could lead to death or substantially affect quality of life. A 2024 systematic review of observational studies assessing statin discontinuation in older individuals suggested higher risks of all-cause mortality, cardiovascular mortality, and cardiovascular events, although the certainty of evidence was low.⁸ The only RCT on statin discontinuation, conducted in individuals nearing the end of life, found no significant difference in 60-day mortality or 1-year cardiovascular event risk between statin discontinuation and continuation.⁹ We therefore aimed to test formally the non-inferiority of statin discontinuation compared with continuation in terms of all-cause mortality among persons aged 75 years or older receiving statins for primary prevention.

Methods

Study design and participants

The Statins In The Elderly (SITE, also known as SAGA) study is a 3-year, open-label, multicentre, comparative, phase 3, non-inferiority randomised clinical trial with two parallel groups in outpatient primary care settings.¹⁰ The objective was to perform an RCT representative of usual care. The study was conducted in general practices across France, with eligibility criteria restricted, apart from regulatory requirements, to older individuals using statins for

primary prevention. We used the research network of French university general practice departments to support recruitment. Each department appointed a coordinating physician for a defined geographical area to recruit and support investigating physicians. These physicians then received specific training related to the clinical study and training in good clinical practice and were eligible to enrol participants in the study. The use of nationwide general practitioner recruitment enhanced representativeness and reduced the influence of local practice variations. Investigator representativeness was assessed based on socio-demographic characteristics, professional activity data, and training data.

Participant recruitment took place during consultations over 36 months. Participants were approached and screened by their general practitioners during routine medical visits or prescription renewals. General practitioners screened participants, who, after a reflection period of no predefined duration, provided written consent.

Eligible participants were individuals aged 75 years or older, with no documented history of ASCVD, who were prescribed a statin for at least 1 year for the primary prevention of ASCVD (as assessed by a specific questionnaire; appendix p 1), and who regularly visited their general practitioner in France and who were able to provide informed consent. Participants were excluded if they had a progressive disease with a life expectancy of 3 months or less, were diagnosed with dementia, had known homozygous or double heterozygous familial hypercholesterolaemia, or were unable to provide informed consent. Additionally, some investigators, with little experience in clinical research, included patients, continued or discontinued statins, and proceeded to randomisation afterward. In order to limit the effect of such practices, we excluded patients who were randomly assigned to statin discontinuation or statin continuation more than 90 days after inclusion.

Information on eligible individuals who were not included in the study was recorded, with reasons for non-inclusion.

Data on sex were collected from the participants' medical files. Data on race and ethnicity were not collected because of government restrictions.

The study protocol was approved by Comité de Protection des Personnes Sud-Ouest et Outre-mer III on April 29, 2015 (number 2015-A00600-49). All enrolled participants provided informed consent.

The study was registered with ClinicalTrials.gov (NCT02547883). The trial is closed to recruitment, and follow-up is complete.

Randomisation and masking

After the screening visit, site investigators performed randomisation centrally using a secure, web-based electronic case report form (Ennov-Clinsight, versions 7.5 and 8.1) on the day of inclusion, after participants provided consent. Participants were considered enrolled once randomly

assigned. The trial was open-label; participants, investigators, and outcome assessors were not masked to group assignment. The random assignment used an unbalanced, 5:4 ratio in favour of the statin continuation group to account for an anticipated 20% risk of statin discontinuation after randomisation for any reason (such as side-effects, participant choice, or physician decision). The allocation sequence was generated using computer-produced random numbers, and the randomisation lists were edited using SAS software (version 9.3) by a statistician in the clinical epidemiology unit before the trial. The allocation sequence was not stratified. Fixed blocks of size 9 were used. A document detailing the randomisation procedure was kept confidential within the clinical epidemiology unit. Continuing or discontinuing statins did not require any alteration to usual care pathways, including the use of other medications.

Intervention and procedures

This study adhered to the CONSORT guidelines. After enrolment, visits were scheduled at 3, 12, 24, and 36 months. During these visits, general practitioners collected data on vital status, outcome events, clinical parameters (including weight and blood pressure), symptoms, adverse events, ASCVD risk factors, quality of life (assessed using the 12-Item Short Form Health Survey [SF-12]), treatment adherence (Morisky questionnaire), concomitant medications, and physical activity. A Mini-Mental State Examination was performed at inclusion and at 36 months. General practitioners collected all data using a centrally administered electronic case report form.

The trial did not include collection or storage of biological specimens; however, participants' blood was sampled at a local laboratory at study inclusion and at 3, 12, and 24 months. Measurements included total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glycaemia, creatinaemia, HbA1c (in individuals with diabetes), blood electrolytes, albuminaemia, and proteinuria or creatininuria (in individuals with hypertension or diabetes at baseline). When participants were unable to attend the study clinic in person, follow-up was conducted by telephone to collect the same information.

In the statin discontinuation group, statins were stopped, and participants were instructed to end their treatment on the day of randomisation. In the comparison group, participants continued their statin therapy at the usual dosage. Participants in the statin discontinuation group who had an ASCVD event could restart statin therapy at the investigator's discretion and in accordance with good clinical practice. The intervention continued for 3 years or until death or participant withdrawal.

Outcomes

The primary clinical outcome was the between-group difference in all-cause mortality at 3 years. Secondary outcomes were the incidence of major ASCVD events (ie, myocardial infarction, angina, coronary or non-coronary revascularisation, and stroke), a composite outcome of mortality and

See Online for appendix 1

major ASCVD events, the incidence of non-cardiovascular events of special interest (myopathy, diabetes, cognitive disorders, severe bacterial infections, cataract, cerebral haemorrhage, and cancers), and quality of life assessed using the SF-12 health survey, which has been validated in older adults. All events were centrally assessed.

Statistical analysis

Based on data from the French National Institute for Statistics and Economic Studies (Institut National de la Statistique et des Études Économiques [INSEE]) on individuals aged 75 years or older,¹¹ we assumed the 3-year mortality rate to be 15% in both groups. The SITE study sample size was calculated to provide 90% power to show the non-inferiority of statin discontinuation compared with statin continuation, assuming a one-sided α of 2.5%, an anticipated between-group difference of 0, and a non-inferiority margin of 5% for the between-group difference in all-cause mortality at 3 years post-randomisation (nQuery Advisor software, version 7.0).

Although a 5% non-inferiority margin is commonly used, a 3-year follow-up period is less typical. This follow-up period corresponded to a low annual non-inferiority margin of 1.7%, which we considered acceptable.¹² To ensure 90% statistical power in the per-protocol analysis, we planned to include 20% more participants in the statin continuation group. In total, 2430 individuals, including 1080 in the statin discontinuation group and 1350 in the statin continuation group, were planned for enrolment in the SITE study. The sample size was not reassessed during the trial.

The scientific committee, which included clinical epidemiologists, statisticians, cardiologists, geriatricians, general practitioners, pharmacists, internists, and neurologists, defined and approved a statistical analysis plan before database freezing and analysis. In the non-inferiority analysis, we estimated the two-sided 95% CI for the between-group difference in 3-year mortality rates. We established non-inferiority if the upper bound of the 95% CI for the between-group difference was entirely below the non-inferiority margin (defined a priori). This approach directly evaluates whether the worst plausible treatment effect, given the observed data, remains within an acceptable loss of clinical efficacy.

The primary estimand was the between-group difference in 3-year all-cause mortality among participants aged 75 years or older who met all key eligibility criteria and who were randomly assigned to statin discontinuation or statin continuation less than 90 days after inclusion; the differences in the effects of treatment discontinuation, treatment switching, or any other intercurrent event between the two groups were measured. All intercurrent events were handled using a treatment policy strategy; that is, we analysed participant outcomes regardless of whether the participants were affected by an intercurrent event. Prespecified subgroup analyses were conducted in the same way for the following subgroups: history of diabetes, LDL cholesterol

level (<100 mg/dL vs ≥ 100 mg/dL), age (75–80, 81–85, and >85 years), sex, history of hypertension, eGFR (<60 mL/min or ≥ 60 mL/min per 1.73 m^2), antiaggregant (aspirin) use, anticoagulant use, Systematic Coronary Risk Evaluation 2-Older Persons (SCORE2-OP; $\geq 15\%$ or $<15\%$), and statin duration (≤ 10 years, >10 years).

As a secondary estimand, we used the same approach but with a principal stratum strategy in the subgroup of participants who adhered to their assigned treatment strategy, defined as receiving at least 50% of statin treatment in the statin continuation group and no more than 50% in the statin discontinuation group.

For participants with missing primary outcome data, a multiple imputation method stratified by randomisation group was used to replace missing data, by incorporating variables that were measured at pre-inclusion or inclusion and that could explain the missingness for the primary outcome (age, sex, cardiac history, history of cancer, history of diabetes, Mini-Mental State Examination score, smoking status, current alcohol consumption status, and occurrence of more than 30 minutes of walking per day). Twenty imputed datasets were created by replacing missing values with plausible values that preserved the characteristics of the observed data distribution. Analyses were performed on all 20 imputed datasets, and the results were combined using Rubin's rules¹³ to obtain overall estimates. We hypothesised that primary outcome data were missing at random, for instance, owing to general practitioners stopping their practice or to participant relocation.

A safety analysis, in which participants were analysed according to the treatment received during follow-up, was conducted in the as-treated population, regardless of the randomised allocation. The safety analysis and other secondary clinical analyses were conducted on available data. An independent statistical team, separate from the investigators, analysed all the data.

Analysis of biological data during follow-up was descriptive, and no statistical tests were done. Categorical data on demographic information, medication, and procedural characteristics were summarised as numbers and percentages. Continuous variables were expressed as mean (SD) or median (IQR), based on their distribution. Kaplan–Meier curves for time-to-event analyses were plotted based on the time from enrolment to the first event of interest during follow-up. The 95% CI for the 3-year survival difference between groups was estimated using bootstrapping (1000 iterations).

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participant recruitment took place from June 15, 2016, to Jan 7, 2020, with follow-up completed in December, 2022. The study scientific committee stopped recruitment in

January, 2020, as the initial enrolment target was not reached even after two extension periods.

1180 participants were randomly assigned to the statin continuation group or the statin discontinuation group between June 15, 2016, and Jan 7, 2020 (figure 1). 20 participants were deemed ineligible for randomisation (14 in the statin continuation group and six in the statin discontinuation arm group). 1160 participants were included in the analysis of the primary estimand (639 participants in the statin continuation group and 521 participants in the statin discontinuation group), with a median age of 80 years (IQR: 78–84). 385 (33.2%) of 1160 participants were men; a history of diabetes was reported in 342 (29.5%) participants, hypertension in 896 (77.2%) participants, and cancer in 242 (20.9%) participants. The mean BMI was 27.3 kg/m² (SD 4.6), and 716 (61.7%) participants had been prescribed statins for more than 10 years (table 1). The mean baseline total cholesterol concentration was 197.9 mg/dL (SD 41.7), and the mean LDL cholesterol concentration was 113.2 mg/dL (SD 35.8). According to the SCORE2-OP, 753 (65.8%) of 1146 participants (excluding those with missing data) had a theoretical 10-year cardiovascular event risk of 15% or more. Baseline characteristics were similar between the two groups (table 1).

By month 36, 48 (7.9%) of 604 participants in the statin continuation group and 35 (7.2%) of 484 participants in the statin discontinuation group had died. After multiple imputation for missing primary outcome data (n=35 in the continuation group and n=37 in the discontinuation group), the absolute difference in all-cause mortality between groups was –0.68% (95% CI –3.95 to 2.60) in the analysis of the primary estimand (table 2). Statin discontinuation was non-inferior to continuation for 3-year all-cause mortality as the upper margin is less than the prespecified non-inferiority margin. The Kaplan–Meier curve showed that the mortality rate remained stable over the 3 years of follow-up (figure 2). The between-group survival difference at 36 months was 0.0045 (–0.0261 to 0.0375, log-rank p-value 0.58).

Fifty-seven (4.9%) of 1160 participants crossed over between groups—25 (4.8%) of 521 participants in the statin discontinuation group resumed statins at some point during follow-up, whereas 32 (5.0%) of 639 participants in the continuation group discontinued statins during follow-up.

In the subgroup of participants who adhered to their assigned treatment strategy, the primary endpoint occurred in 44 (7.7%) of 571 participants in the statin continuation group and 35 (7.6%) of 460 participants in the statin discontinuation group (absolute difference 0.07% [–3.23 to 3.36]; table 2). The 3-year clinical endpoints of the subgroup of participants who adhered to their assigned treatment strategy are provided in the appendix (p 4).

Quality of life (SF-12), including both physical and mental component scores, did not differ between groups at 3 years (table 2). For secondary outcomes, a composite endpoint of all-cause mortality and major cardiovascular events occurred in 69 (11.4%) of 604 participants in the statin

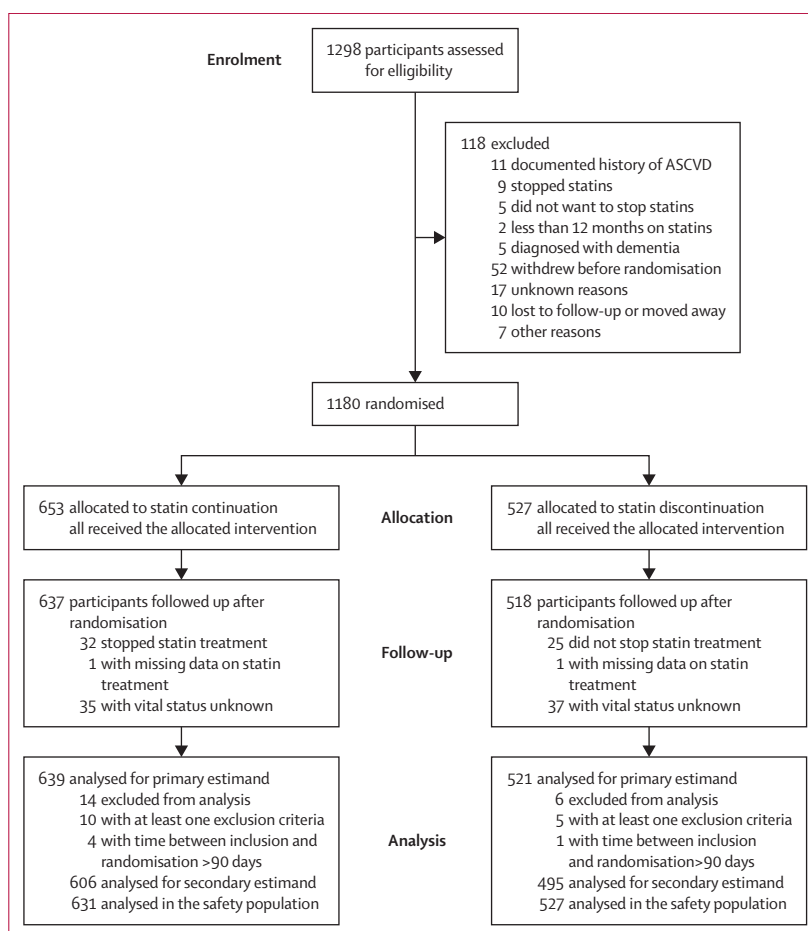


Figure 1: CONSORT flow diagram
ASCVD=atherosclerotic cardiovascular disease

continuation group and 58 (12.0%) of 484 participants in the statin discontinuation group (absolute difference 0.56% [–3.29 to 4.41]; table 2). Cardiovascular death occurred in four (0.6%) of 639 participants in the statin continuation group and four (0.8%) of 521 participants in the statin discontinuation group. Major ASCVD events were observed in 28 (4.4%) of 639 participants in the statin continuation group and 26 (5.0%) of 521 participants in the statin discontinuation group (absolute difference 0.61% [–1.84 to 3.06]; table 2), and the incidence of non-fatal stroke did not differ significantly between the two groups (absolute difference 0.81% [–0.93 to 2.55]; table 2). Non-cardiovascular adverse events were reported in 456 (72.3%) of 631 participants in the statin continuation group and in 383 (72.7%) of 527 participants in the statin discontinuation group, including 207 events (32.8%) of 631 participants of special interest (myopathy, diabetes, cognitive disorders, severe infections, cancer, cataract, and cerebral haemorrhage) in the statin continuation group and 154 (29.2%) of 527 participants in the statin discontinuation group (table 3). No difference was observed in the incidence of non-cardiovascular serious adverse events during the 3 years of follow-up.

	Total (n=1160)	Statin continuation group (n=639)	Statin discontinuation group (n=521)
Demographics			
Sex			
Female	775 (66·8%)	426 (66·7%)	349 (67·0%)
Male	385 (33·2%)	213 (33·3%)	172 (33·0%)
Age at enrolment, median (IQR) (years)	80 (78–84)	81 (78–84)	80 (77–84)
Distribution of age			
75–80 years	532 (45·9%)	287 (45·0%)	245 (47·0%)
>80–85 years	411 (35·4%)	224 (35·1%)	187 (35·9%)
>85 years	217 (18·7%)	128 (20·0%)	89 (17·1%)
Statin treatment			
Statin treatment			
Simvastatin	358 (30·9%)	205 (32·1%)	153 (29·4%)
Pravastatin	327 (28·2%)	188 (29·4%)	139 (26·7%)
Atorvastatin	272 (23·4%)	142 (22·2%)	130 (25·0%)
Rosuvastatin	151 (13·0%)	82 (12·8%)	69 (13·2%)
Fluvastatin	52 (4·5%)	22 (3·5%)	30 (5·8%)
Time from statin start			
1–2 years	51 (4·4%)	26 (4·1%)	25 (4·8%)
3–4 years	78 (6·7%)	39 (6·1%)	39 (7·5%)
5–10 years	315 (27·2%)	171 (26·8%)	144 (27·6%)
>10 years	716 (61·7%)	403 (63·1%)	313 (60·1%)
Cardiac history			
History of hypertension	896 (77·2%)	494 (77·3%)	402 (77·2%)
History of atrial fibrillation*	93/1159 (8·0%)	55/638 (8·6%)	38/521 (7·3%)
History of cardiac failure	45 (3·9%)	28 (4·4%)	17 (3·3%)
History of cancer			
History of cancer	242 (20·9%)	135 (21·1%)	107 (20·5%)
History of diabetes			
History of diabetes	342 (29·5%)	186 (29·1%)	156 (29·9%)
Cognitive testing			
Mini-Mental state at pre-inclusion	1157 (99·7%)	638 (99·8%)	519 (99·6%)
Mini-Mental state score, mean (SD)†	27·3 (3·1)	27·3 (3·1)	27·3 (3·2)
Mini-Mental state score <24†	132/1145 (11·5%)	71/631 (11·3%)	61/514 (11·9%)
Clinical examination			
Clinical data available at inclusion	1157 (99·7%)	637 (99·7%)	520 (99·8%)
BMI, mean (SD) (kg/m ²)‡	27·3 (4·6)	27·2 (4·6)	27·5 (4·7)
Distribution of BMI			
<25 kg/m ²	371/1135 (32·7%)	216/627 (34·4%)	155/508 (30·5%)
≥25 to <30 kg/m ²	490/1135 (43·2%)	262/627 (41·8%)	228/508 (44·9%)
≥30 to <35 kg/m ²	207/1135 (18·2%)	117/627 (18·7%)	90/508 (17·7%)
≥35 kg/m ²	67/1135 (5·9%)	32/627 (5·1%)	35/508 (6·9%)
Systolic blood pressure, mean (SD) (mm Hg)§	135·1 (13·5)	135·0 (14·0)	135·1 (12·8)
Distribution of systolic blood pressure			
<130 mm Hg	275/1146 (24·0%)	159/630 (25·2%)	116/516 (22·5%)
>130–140 mm Hg	600/1146 (52·4%)	322/630 (51·1%)	278/516 (53·9%)
>140–150 mm Hg	156/1146 (13·6%)	84/630 (13·3%)	72/516 (14·0%)
>150 mm Hg	115/1146 (10·0%)	65/630 (10·3%)	50/516 (9·7%)
Diastolic blood pressure, mean (SD) (mm Hg)§	75·4 (8·8)	75·9 (8·7)	74·7 (8·8)
Distribution of diastolic blood pressure			
<90 mm Hg	1071/1146 (93·5%)	590/630 (93·7%)	481/516 (93·2%)
90–100 mm Hg	71/1146 (6·2%)	38/630 (6·0%)	33/516 (6·4%)
>100 mm Hg	4/1146 (0·3%)	2/630 (0·3%)	2/516 (0·4%)

(Table 1 continues on next page)

	Total (n=1160)	Statin continuation group (n=639)	Statin discontinuation group (n=521)
(Continued from previous page)			
Lifestyle			
Participants with lifestyle data available at enrolment	1157 (99.7%)	637 (99.7%)	520 (99.8%)
Smoking status [¶]			
Current smoker	44/1154 (3.8%)	27/636 (4.2%)	17/518 (3.3%)
Former smoker	219/1154 (19.0%)	126/636 (19.8%)	93/518 (18.0%)
Never smoker	891/1154 (77.2%)	483/636 (75.9%)	408/518 (78.8%)
Alcohol consumption			
Participants who currently drink alcohol	397/1154 (34.4%)	219/635 (34.5%)	178/519 (34.3%)
Drinks per week, mean (SD)**	8.7 (15.1)	9.1 (18.7)	8.3 (8.9)
Number of ongoing treatments, median (IQR)	5 (3-7)	5 (3-7)	5 (3-7)
Biological variables			
Participants with biological tests performed at inclusion or pre-inclusion	1157 (99.7%)	636 (99.5%)	521 (100.0%)
Total cholesterol††			
Total cholesterol, mean (SD) (mg/100 mL)	197.9 (41.7)	196.9 (40.7)	199.0 (43.0)
Total cholesterol, median (Q1-Q3) (mg/100 mL)	195.0 (168.0-223.0)	194.0 (167.0-224.0)	196.0 (169.0-222.0)
HDL cholesterol‡‡			
HDL cholesterol, mean (SD) (mg/100 mL)	59.7 (16.4)	60.2 (16.7)	59.2 (16.0)
HDL cholesterol, median (Q1-Q3) (mg/100 mL)	57.0 (49.0-69.0)	58.0 (49.0-70.0)	57.0 (48.0-69.0)
LDL cholesterol§§			
LDL cholesterol, mean (SD) (mg/100 mL)	113.2 (35.8)	112.0 (35.2)	114.6 (36.4)
LDL cholesterol, median (Q1-Q3) (mg/100 mL)	108.5 (88.0-134.0)	108.0 (87.0-133.0)	110.0 (90.0-135.0)
eGFR, median (IQR) mL/min per 1.73 m ² ¶¶	76.0 (64.0-86.0)	75.5 (63.0-86.0)	76.0 (54.0-87.0)
Distribution of eGFR			
<30 mL/min per 1.73 m ²	23/1107 (2.0%)	15/609 (2.5%)	8/498 (1.6%)
≥30-60 mL/min per 1.73 m ²	195/1107 (17.6%)	106/609 (17.4%)	89/498 (17.9%)
>60 mL/min per 1.73 m ²	889/1107 (80.3%)	488/609 (80.1%)	401/498 (80.5%)
SF-12 questionnaire			
Participants for whom SF-12 questionnaire was assessed at enrolment	1142 (98.4%)	629 (98.4%)	513 (98.5%)
SF-12 results summary			
Physical component summary, median (Q1-Q3)	45.6 (39.3-51.6)	44.9 (38.0-51.2)	46.4 (40.3-51.7)
Mental component summary, median (Q1-Q3)	50.5 (45.8-54.9)	50.5 (45.5-54.9)	50.5 (46.2-54.9)
Treatment use			
Antiaggregant (aspirin)	349 (30.1%)	187 (29.3%)	162 (31.1%)
Anticoagulant	177 (15.3%)	111 (17.4%)	66 (12.7%)
SCORE-OP***			
7.5 to <15%	392/1146 (34.2%)	202/628 (32.2%)	190/518 (36.8%)
≥15%	753/1146 (65.7%)	426/628 (67.8%)	327/518 (63.1%)

CKD-EPI=Chronic Kidney Disease-Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. SCORE2-OP=Systematic Coronary Risk Evaluation 2-Older Persons. SF-12=12-Item Short Form Health Survey. Data are n (%) or n/N (%) unless otherwise indicated. *Calculated on 1159 participants, 638 in the statin continuation group and 521 in the statin discontinuation group, because of missing data on history of atrial fibrillation. †Calculated on 1145 participants, 631 in the statin continuation group and 514 in the statin discontinuation group, because of missing data on Mini-Mental State Score. ‡Calculated on 1135 participants, 627 in the statin continuation group and 508 in the statin discontinuation group, because of missing data on BMI. §Calculated on 1146 participants, 630 in the statin continuation group and 516 in the statin discontinuation group, because of missing data on systolic blood pressure or diastolic blood pressure. ¶Calculated on 1154 participants, 636 in the statin continuation group and 518 in the statin discontinuation group, because of missing data on smoking status. ||Calculated on 1154 participants, 635 in the statin continuation group and 519 in the statin discontinuation group, because of missing data on participants who currently drink alcohol. **Calculated on 394 of 397 participants, with 216 of 219 in the statin continuation group and 178 in the statin discontinuation group, because of missing data on number of units of alcohol consumed in the past 7 days among participants who currently drink alcohol. ††Calculated on 1109 participants, 603 in the statin continuation group and 506 in the statin discontinuation group, because of missing data on total cholesterol. ‡‡Calculated on 1107 participants, 601 in the statin continuation group and 506 in the statin discontinuation group, because of missing data on HDL cholesterol. §§Calculated on 1104 participants, 602 in the statin continuation group and 502 in the statin discontinuation group, because of missing data on LDL cholesterol. ¶¶CKD-EPI method, calculated on 1107 participants, 609 in the statin continuation group and 498 in the statin discontinuation group, because of missing data on eGFR. ||||Calculated on 1137 participants, 626 in the statin continuation group and 511 in the statin discontinuation group, because of missing data on SF-12 questionnaire. ***Calculated on 1146 participants, 628 in the statin continuation group and 518 in the statin discontinuation group, because of missing data on SCORE2-OP.

Table 1: Baseline characteristics of the groups defined by randomisation

	Statin continuation group (n=639)	Statin discontinuation group (n=521)	Absolute difference (95% CI)
Primary endpoint			
All-cause mortality: primary estimand	48/604 (7.9%)	35/484 (7.2%)	-0.68 (-3.95 to 2.60)*
All-cause mortality: secondary estimand	44/571 (7.7%)	35/460 (7.6%)	0.07 (-3.23 to 3.36)
Secondary efficacy endpoint			
Composite of all-cause mortality or major cardiovascular event (including non-fatal stroke)	69/604 (11.4%)	58/484 (12.0%)	0.56 (-3.29 to 4.41)
Major cardiovascular endpoints			
Cardiovascular death	4 (0.6%)	4 (0.8%)	0.14 (-0.95 to 1.43)†
Major cardiovascular events	28 (4.4%)	26 (5.0%)	0.61 (-1.84 to 3.06)
Myocardial infarction	9 (1.4%)	11 (2.1%)	0.70 (-0.83 to 2.24)
Peripheral artery disease	3 (0.5%)	1 (0.2%)	-0.28 (-1.23 to 0.67)†
Non-fatal stroke	12 (1.9%)	14 (2.7%)	0.81 (-0.93 to 2.55)
SF-12 at 36 months‡			
Physical component	42.3 (9.3)	42.5 (9.3)	0.28 (-0.96 to 1.53)
Mental component	48.5 (7.4)	49.0 (7.4)	0.50 (-0.49 to 1.49)

Data are n (n/N (%), or mean (SD). SF-12=12-Item Short Form Health Survey. *Value obtained after multiple imputation; other CI values were calculated using available data only when endpoint data were missing. †For binary variables with sample size less than five, 95% CIs were calculated using the exact method; for other binary variables, 95% CIs were calculated using the Wald method. The 95% CIs for quantitative variables were calculated using Student's method. ‡Calculated on 867 participants, with 467 in the statins continuation group and 400 in the statins discontinuation group, because of missing data on SF-12 questionnaire at 36 months.

Table 2: 3-year primary endpoint in the groups defined by randomisation

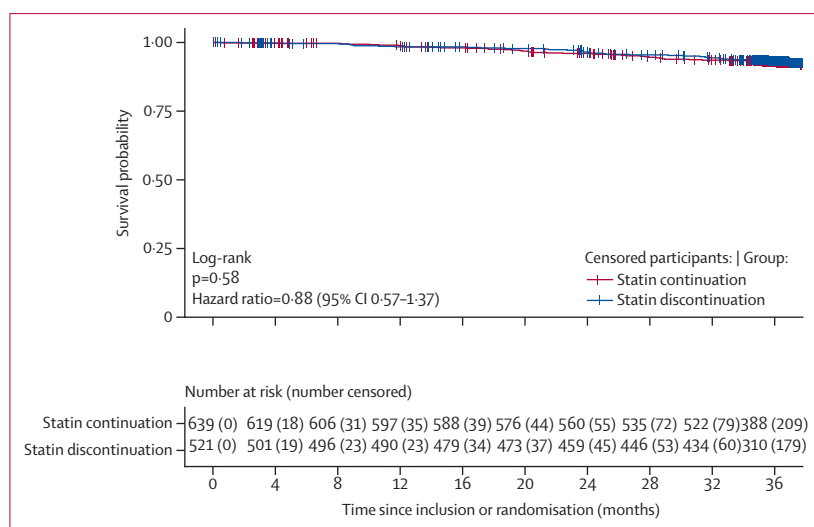


Figure 2: Kaplan-Meier curves of all-cause mortality for the primary estimand

Subgroup analyses showed that among participants with diabetes, 42 (13.0%) of 322 participants with available data died, compared with 41 (5.4%) of 766 among those without diabetes. At month 36, the mortality rate was 13.6% among participants with diabetes in the statin continuation group versus 12.4% in the statin discontinuation group (absolute difference between groups after multiple imputation 0.89% [-6.53 to 8.32]). Among participants without diabetes, the mortality rate was 5.6% in the statin continuation group versus 5.0% in the statin discontinuation group (absolute difference between groups after multiple imputation -0.68% [-3.95 to 2.60]). The results of prespecified subgroup analyses of the primary estimand are presented in figure 3. The effect of statin discontinuation versus

continuation on the primary endpoint was consistent across all subgroups but non-inferiority was not established in some subgroups owing to wide confidence intervals. These findings were also consistent in the analysis of the secondary estimand (appendix p 6).

At month 3, total cholesterol remained stable in the statin continuation group (from 196.9 mg/dL [SD 40.7] to 197.9 mg/dL [SD 43.0]), whereas it increased from 199.0 mg/dL (SD 43.0) to 257.3 mg/dL (SD 49.6) in the statin discontinuation group and then remained stable over time up to 3 years (appendix p 2). LDL cholesterol also remained stable in the statin continuation group (from 112.0 mg/dL [SD 35.2] to 111.6 mg/dL [SD 34.8]), whereas it increased from 114.6 mg/dL (SD 36.4) to 170.6 mg/dL (SD 43.6) in the statin discontinuation group.

Discussion

Among participants aged 75 years or older without previous ASCVD, statin discontinuation was non-inferior to continuation in terms of the primary clinical endpoint of all-cause mortality at 3 years. We did not observe an excess of cardiovascular events in the statin discontinuation group. We also did not observe significantly fewer adverse events in the statin discontinuation group than in the statin continuation group, possibly because participants had received statins for years, thus excluding people with early adverse events following statin administration. Surprisingly, quality of life, assessed using the SF-12 score, did not change significantly over time in either group and was not affected by statin discontinuation, which does not support the rationale for deprescribing. This contradictory observation might be related to the selection of participants who had previously been followed up in the outpatient setting and who were in good health for their age. Subgroup

	Statin continuation group (n=631)	Statin discontinuation group (n=527)	Absolute difference (95% CI)
All adverse events	461 (73.1%)	390 (74.0%)	0.95 (-4.15 to 6.04)
All serious adverse events	280 (44.4%)	232 (44.0%)	-0.35 (-6.09 to 5.39)
All non-cardiovascular adverse events	456 (72.3%)	383 (72.7%)	0.41 (-4.76 to 5.57)
Non-cardiovascular serious adverse events of special interest	207 (32.8%)	154 (29.2%)	..
Myopathy	36 (5.7%)	27 (5.1%)	-0.58 (-3.19 to 2.03)
Diabetes	7 (1.1%)	5 (0.9%)	-0.16 (-1.32 to 1.00)
Cognitive disorders	33 (5.2%)	27 (5.1%)	-0.11 (-2.67 to 2.45)
Severe infections	38 (6.0%)	29 (5.5%)	-0.52 (-3.21 to 2.17)
Cancer	60 (9.5%)	40 (7.6%)	-1.92 (-5.14 to 1.30)
Cataract	31 (4.9%)	23 (4.4%)	-0.55 (-2.97 to 1.88)
Cerebral haemorrhage	2 (0.3%)	3 (0.6%)	0.25 (-0.67 to 1.41)*
Other non-cardiovascular serious adverse events			
Non-ischaemic cardiovascular events	33 (5.2%)	26 (4.9%)	-0.30 (-2.83 to 2.24)
Kidney and urinary tract disorders	14 (2.2%)	12 (2.3%)	0.06 (-1.66 to 1.77)
Gastrointestinal events	19 (3.0%)	16 (3.0%)	0.02 (-1.96 to 2.01)
Haematological events	2 (0.3%)	10 (1.9%)	1.58 (0.37 to 3.18)*
Hepatological events	5 (0.8%)	3 (0.6%)	-0.22 (-1.37 to 0.96)*
Musculoskeletal events	24 (3.8%)	17 (3.2%)	-0.58 (-2.70 to 1.54)
Psychiatric events	12 (1.9%)	10 (1.9%)	0.00 (-1.58 to 1.57)
Respiratory events	28 (4.4%)	20 (3.8%)	-0.64 (-2.93 to 1.65)

Data are n (%). *For binary variables with sample size less than five, 95% CIs were calculated using the exact method; for other binary variables, 95% CIs were calculated using the Wald method.

Table 3: Adverse events in the safety population

analyses, particularly among participants with diabetes (or those with other cardiovascular risk factors), also showed no significant effect of statin discontinuation on mortality or ASCVD outcomes, despite mortality rates being nearly three times higher for persons with diabetes than for those without diabetes. However, non-inferiority was not established in some subgroups owing to wide confidence intervals, in which the upper bound exceeded the non-inferiority margin.

Our findings represent a major step forward in the management of older persons with respect to cardiovascular risk. Large trials and reviews on the efficacy of statins have shown that each mmol/L reduction in LDL cholesterol is associated with fewer major vascular events and lower mortality, both in primary and secondary prevention.^{14,15} However, the association between cholesterol and cardiovascular events weakens with age, and reviews of large observational cohort studies have reported higher all-cause mortality at low total cholesterol and LDL cholesterol concentrations—particularly when total cholesterol was less than 213 mg/dL (5.5 mmol/L) in individuals older than 80 years.^{16,17}

Many observational studies and systematic reviews have suggested that statins might reduce mortality and ASCVD in older adults. Three large observational cohort studies conducted within the past decade in individuals aged 75 years or older reported an approximately 30% higher risk of cardiovascular events among those who discontinued statins for primary prevention compared with those who continued treatment. These studies, conducted in Italy,

Denmark, and France, included between 29 047 and 120 173 participants and followed them up for 20 months to 5.5 years. However, the reasons for statin discontinuation were not reported.^{18–20} None of these studies could exclude the risk of bias—particularly confounding by indication—whereby decisions for initiating or discontinuing statins are guided by risk of poor outcomes, multimorbidity, high treatment burden, polypharmacy, or other complicating conditions. Such indication bias might explain the findings of these observational studies, which were not replicated in our controlled trial.

Although LDL cholesterol increased in the third month in the discontinuation group, statin discontinuation was not associated with an increase in ASCVD risk or mortality. This finding is consistent with the finding of the only previous trial on this intervention, conducted in individuals nearing the end of life.⁹ However, although benefits of statins accrue over time, whether the benefits of plaque stabilisation and remodelling might be lost and whether cardiovascular events occur after discontinuation of therapy at any age remains unclear.

Approximately 30% of Canadians aged 65 years or older,²¹ 33% of Americans aged 80 years or older,²² and 18% of Swedes aged 75–84 years²³ are given statins for primary prevention, with therapy often continued for many years, including near the end of life.²⁴ These figures represent millions of person-years of treatment, despite the insufficient evidence supporting statin use in these older age groups. In this context, our results suggest that lowering LDL cholesterol has less effect on ASCVD outcomes and

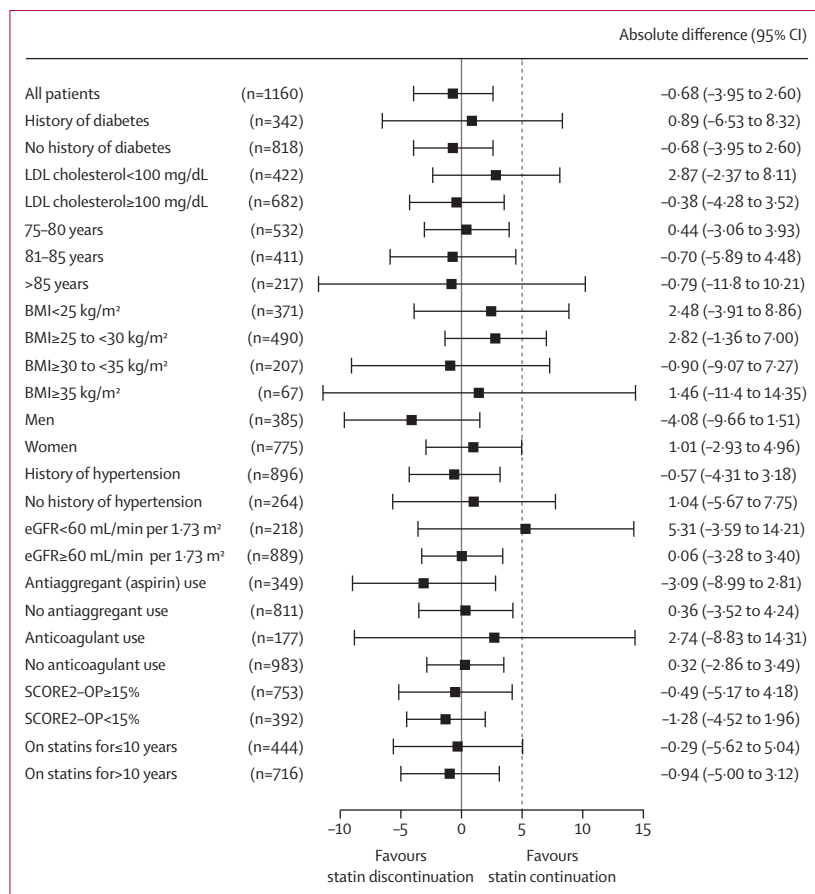


Figure 3: Subgroup analyses for the primary estimand

The vertical dashed line indicates the prespecified non-inferiority margin of 5.0% (absolute difference).

eGFR=estimated glomerular filtration rate. SCORE2-OP=Systematic Coronary Risk Evaluation 2-Older Persons.

mortality than other major risk factors such as diabetes, hypertension, smoking, cancer, and ageing. However, compared with statin continuation, discontinuation was not associated with changes in quality of life, symptom burden, or adverse event rates, suggesting that people who have tolerated statins over the long term might have no tangible benefit from stopping therapy. In this context, the rationale for deprescribing becomes less clear for individuals who are asymptomatic, adherent, and comfortable continuing treatment. All these factors should therefore be discussed between the patient and clinician as part of a shared decision-making process—an approach recently recommended (Grade II) by the National Lipid Association and the American Geriatrics Society.²⁵

A strength of this trial was that it was conducted in real-life settings—across 297 general practitioner offices in France—over a long duration of 3 years. The trial included individuals who were regularly followed up by their general practitioners, with many having comorbidities and at high risk of ASCVD according to the SCORE2-OP risk equation. However, our study has several limitations. First, the observed mortality in the trial (7.6%) was lower than

expected (15.0%), and we could not reach the planned sample size. This discrepancy arose because the calculation was based on all-cause mortality in the general French population, whereas the prognosis is better for individuals aged 75 years or older, recruited for primary prevention—despite having comorbidities. The better prognosis can be attributed to the absence of cardiovascular events, regular follow-up by a primary care physician, and the willingness of participants to take part in a clinical trial. Although the non-inferiority margin of 5% was achieved, this margin, based on reduced mortality rates, is not acceptable relative to the observed mortality. The observed 95% CIs for the between-group difference in 3-year mortality were -3.95 to 2.60 for the primary estimand and -3.23 to 3.36 for the secondary estimand. Thus, the CIs for both the primary estimand and secondary estimand exclude a difference of 3.5%, corresponding to an annual mortality difference of approximately 1%, which might be clinically acceptable. Despite two extension periods, the enrolment (1180 participants) was lower than planned (2430 participants), and recruitment was stopped owing to the slow enrolment rate and the exhaustion of available funding. The low enrolment was mainly related to the shortage of general practitioners available and willing to participate in this trial. This restricts the precision of the 95% CI for the between-group difference in mortality. Nevertheless, the observed mortality in the discontinuation group was slightly lower than that in the continuation group, counterbalancing this deficit in precision, as our sample size calculation was based on a hypothetical between-group difference of 0. The difference in the proportion of major cardiovascular events, another important endpoint, in the safety population can also be interpreted similarly. This between-group difference was 0.72% (-1.74 to 3.19), corresponding to an annual proportion difference of approximately 1%; thus, a worst plausible treatment effect also appears to be acceptable. However, as we did not adjust the α level to the multiplicity of calculated CIs, all our secondary analyses should be interpreted cautiously.

Second, we acknowledge the considerable heterogeneity in the types and doses of statins used among participants. Although unlikely, a potential effect of high-intensity statin therapy on cardiovascular risk or mortality cannot be completely ruled out.

Third, we performed an open-label trial; however, only 57 (4.9%) of 1160 participants crossed over between groups—25 (4.8%) of 521 participants in the statin discontinuation group resumed statins at some point during follow-up, mainly because of increases in total and LDL cholesterol, whereas 32 (5.0%) of 639 participants in the continuation group discontinued statins during follow-up. Concomitant cardiovascular treatments were not adjusted to compensate for statin discontinuation (appendix p 5). However, we cannot exclude the possibility that other unmeasured non-pharmacological interventions might have been modified to deal with statin treatment.

Fourth, we faced a non-negligible proportion of missing data (6.6%, 72 of 1088 patients) for the primary outcome when referring to the frequency of the primary endpoint overall (7.6%). However, most missing data were because of general practitioners stopping their practice or participants moving away. This mechanism of missingness can be considered at random, and the methods we chose for dealing with missing data (multiple imputation) are totally adapted.

Fifth, we cannot rule out recruitment bias among general practitioners, who might have been more likely to enrol individuals with healthier lifestyles or those who were more robust. That said, given that 29.5% of participants had diabetes, 77.2% had hypertension, and 65.7% had a SCORE-OP of 15% or more, we believe our population is fairly representative of older individuals in good health who are regularly monitored by their general practitioners.

Other potential limitations arise from the open-label design of our study. This may have introduced performance and reporting bias, particularly for subjective outcomes such as quality of life and symptom reporting, as participants and investigators were aware of their treatment allocation. However, our primary endpoint (mortality) is less likely to be affected. Second, follow-up assessments were conducted both in person and by telephone. Although standardized questionnaires and uniform assessment procedures were used irrespective of the mode of follow-up, and investigators were trained to administer the assessments consistently, some degree of measurement variability between assessment modalities may have occurred. These factors should be considered when interpreting the patient-reported outcomes. However, the same assessment procedures were used in both arms in our trial.

Finally, we did not collect ethnicity data in our trial as this type of data collection is not allowed in France. The absence of ethnicity data might be a limitation as the risk of cardiovascular events might vary according to ethnicity. However, given the number of individuals randomly assigned in our trial, such characteristics should be well balanced between groups.

Further trials are needed to assess the effect of statin deprescription in older adults. The STREAM study (NCT05178420 at ClinicalTrials.gov, recruitment and follow-up completed), built on the same design as that of the SITE study, includes 1870 participants aged 70 years or older given statins for primary prevention; participants were randomly assigned to either continue or stop statins, and death and ASCVD are the primary outcomes. The STAREE and PREVENTABLE studies are currently investigating whether treatment with statins, compared with placebo, can extend disability-free survival and reduce major cardiovascular events among healthy individuals aged 70 years or older in Australia and the USA.

Conclusion

Among patients aged 75 years and older receiving statins for primary prevention—including those on long-term

treatment courses—discontinuing statins was non-inferior to continuing statins and did not improve quality of life.

Contributors

FB: conceptualisation, funding acquisition, data interpretation, investigation, supervision, writing—original draft. PP: data curation, project administration, software, resources, writing—review and editing. NR: data collection, data interpretation, writing—review and editing. TC: data interpretation, supervision, writing—review and editing. GG: data interpretation, writing—review and editing. DB: data interpretation, writing—review and editing. M-AV: data interpretation, writing—review and editing. MR: pharmacovigilance survey, data interpretation, writing—review and editing. RC: data curation, formal statistical analysis, writing—review and editing. AB: conceptualisation, methodology, formal statistical analysis, data interpretation, writing—review and editing. J-PJ: conceptualisation, funding acquisition, data interpretation, supervision, writing—review and editing.

FB, PP, MR, RC, AB, and J-PJ have accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

FB reports non-financial support and personal fees Gilead, ViiV healthcare, and MSD, outside the submitted work. All other authors declare no competing interests.

Data sharing

Data sharing requests will be considered upon written request to the corresponding author. De-identified participant data, other prespecified data, trial protocol, and statistical analysis plan will be available subject to a written proposal and a signed data sharing agreement.

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