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ORIGINAL RESEARCH ARTICLE

Association of Statin Treatment and Dose With the Clinical Course of Small Abdominal Aortic Aneurysms in Men: A 5-Year Prospective Cohort Study From 2 Population-Based Screening Trials

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BACKGROUND: Abdominal aortic aneurysms (AAA) present with high morbidity and mortality when they occasionally rupture. No medical therapy has successfully been proven to reduce AAA growth, though both metformin and statins have been identified as potential treatments in multiple meta-analysis. This study aimed to investigate a potential relationship between statin use and AAA growth rates and risk of undergoing repair, rupture, or death.

METHODS: The study population included all men with screening-detected AAAs (30–55 mm) from the 2 large, population-based, randomized screening trials; the Viborg Vascular Screening trial (inclusion, 2008–2011) and the Danish Cardiovascular Screening trial (inclusion, 2014–2018). The clinical database was supplemented with data from the nationwide Danish Healthcare Registries, including prescription and outcome data. Statin exposure was quantified by defined daily doses (DDD). The primary outcome was AAA growth rate, whereas secondary outcomes included the need for repair and a composite of repair, rupture, and all-cause death. Growth rates were calculated using linear regression. To evaluate the risk of repair, patients were followed from inclusion until surgery, rupture, death, 5-year follow-up, or December 31, 2021.

RESULTS: A total of 998 aneurysmal men (median age, 69.5 [interquartile range (IQR), 67–72] years; median AAA diameter, 35.4 [IQR, 32–41.2] mm) were included. Statin use was significantly associated with reduced AAA growth rate; an increase of 1 DDD statin per day was associated with an adjusted change in growth rate of −0.22 mm/year [95% CI, −0.39 to −0.06]; *P*=0.009). The 5-year adjusted hazard ratio for undergoing repair per doubling of statin dose presented a significantly reduced adjusted hazard ratio (HR) of 0.82 ([95% CI, 0.70–0.97]; *P*=0.023), which was significant after 2.5 years. Statin use was associated with a significantly lower risk of the composite outcome (surgery, rupture, and death) in a dose-dependent manner, with an adjusted HR of 0.83 ([95% CI, 0.73–0.94]; *P*=0.003) per doubling of statin dose. Findings were robust in a variety of sensitivity analyses.

CONCLUSIONS: High-dose statin use was associated with decreased AAA growth rates and lowered risk of undergoing repair, rupture, and death. This nonrandomized study suggests that patients with AAA could benefit from high-dose statin use, beyond only targeting associated risk factors.

Key Words: aneurysm ■ aortic aneurysm, abdominal ■ cohort studies ■ drug repositioning ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ mass screening ■ registries

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Clinical Perspective

What Is New?

- High-dose statin use was associated with a dose-dependent reduction in abdominal aortic aneurysm (AAA) growth rates and a lower risk of undergoing repair, rupture, and death during a 5-year follow-up period using longitudinal registry data from 2 large, randomized screening trials.
- These findings suggest that high-dose statins may offer direct protection against AAA progression, beyond cardiovascular risk reduction alone.

What Are the Clinical Implications?

- Because of their proven cardiovascular benefits, safety profile, and cost-effectiveness, high-dose statins should be strongly considered for patients with small AAAs, particularly those without contraindications.
- Although randomized trials may be ethically challenging, further high-quality observational studies are needed to validate these findings and inform clinical guidelines.

Nonstandard Abbreviations and Acronyms

AAA	abdominal aortic aneurysm
DANCAVAS	Danish Cardiovascular Screening trial
DDD	defined daily doses
VIVA	Viborg Vascular trial

Abdominal aortic aneurysms (AAA) are associated with high risk for morbidity and mortality when they rupture.[1,2] AAA prevalence increases with age, particularly in older men, and remains largely asymptomatic until advanced stages, complicating early intervention.[1,3,4] Currently, no effective pharmacologic treatments exist to prevent or slow AAA progression. Standard management of AAAs involves regular imaging surveillance to monitor aneurysm size and elective surgery if the aneurysm reaches the threshold for prophylactic surgery, alongside modification of risk factors.[1,5]

Recent studies have suggested 2 promising pharmacological candidates (statins and metformin) that may reduce AAA growth and reduce risk of rupture.[6–8] While metformin is currently under investigation in 4 randomized controlled trials[9–12]; and therefore, expected to provide robust findings based on high-level evidence, statin associations to AAA progression have only been investigated in observational studies with no trials pending. The majority of the observational studies have been limited by simplistic binary measurement of statin exposure.[6]

We have recently reported that AAA growth rates were halved between the Viborg Vascular trial ([VIVA] 2008–2011)[13] and the Danish Cardiovascular Screening trial ([DANCAVAS] 2014–2018).[14,15] This observed association was difficult to explain even when considering changes in smoking, diabetes, or medications.[15] One possible explanation is the use of more intensive statin regimes between the 2bcohorts. In 2008, at the start of the VIVA study, statin use was 89.6 defined daily doses (DDD) per 1000 Danish citizens. By 2018, at the end of the DANCAVAS study, it had risen to 153.3 DDD.[16] By 2022, it had further increased to 202.9 DDD.[16]

Consequently, we hypothesize that high-dose statin therapy would slow the growth rate of AAA. To test this, the study aimed to evaluate the effect and dose-dependency of statin use across the combined screening cohorts. The primary outcome was the observed rate of AAA growth, whereas our secondary outcome was need for AAA repair and a composite of AAA-related events of repair, rupture, and all-cause death.

METHODS

Study Design

This cohort study is based upon data from 2 population-based, randomized controlled screening trials, supplemented with data from the Danish national registries. Reporting of the study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) cohort guidelines.[17] Data are not publicly available but may be shared upon reasonable request, in accordance with European GDPR regulations.

Study Population

Male participants identified with a screening-detected AAA between 30 mm and 55 mm from the VIVA trial[13] and the DANCAVAS trial[14] were included. Participants with AAAs ≥55 mm were routinely referred to elective surgery and were therefore not included in this study.

Materials

VIVA was a population-based, randomized controlled trial including 50 156 men 65 to 74 years of age in the Central Denmark Region, with no exclusion criteria during the enrollment period from 2008 to 2011.[13] DANCAVAS was a population-based, randomized controlled screening trial with 46611 Danish primarily men 65 to 74 years of age from the Region of Southern Denmark during 2014 to 2018, with no exclusion criteria.[14] Both VIVA and DANCAVAS provided baseline parameters through similar clinical interviews, objective measurements, blood tests, and measurements of the abdominal aorta. The clinical data were supplemented with data from the Danish health and administrative registries. In Denmark, each resident is assigned a unique personal identification number, enabling the linkage of registries on an individual level. Additionally, the accessibility of universal tax–supported health care facilitates population-based research on the entire Danish population and secures complete follow-up.[18] Data was available from the

relevant registries from time of AAA diagnosis (index date) until December 31, 2021.

For exposure to statins and other medications, data from the Danish National Prescription Registry were extracted.[19] This registry has been compiling data on all filled prescriptions at pharmacies in Denmark since 1995, providing details on the drug name, dispensed volume and strength, and dispensing date. The drug substances are categorized according to the Anatomical Therapeutic Chemical index.

To identify participants in the cohort experiencing AAA repair or AAA rupture, we utilized the Danish National Patient Register. This resource collects data on hospital diagnoses, employing the *International Classification of Diseases*, *10th edition*, along with the Danish medical classification system. The Danish National Patient Register includes all inpatient and outpatient, as well as emergency department, diagnoses in Denmark since 1995.[20] To identify mortalities during the study time, data from the Register of Causes of Death was extracted. This register contains information on causes of death along with the date of death and primary and secondary causes of death since 1970.[21]Finally, to be able to adjust for socioeconomic status we obtained the highest level of education using the Danish Education Registry.[22] All definitions used in this study are summarized in Table S1.

Imaging Protocols

The abdominal aortic measurement protocols differed between the VIVA and DANCAVAS trials.

In VIVA, a team of specially trained nurses operated mobile clinics in the trial area, using portable ultrasound scanners to measure aortic diameters. Abdominal aorta measurements were measured at peak systole using the anterior-posterior, inner-to-inner aortic diameter.[13] Annual follow-up scans were provided to monitor any expansion exceeding 55 mm.

In DANCAVAS, noncontrast electrocardiography-gated computed tomography scans were used to measure the maximal perpendicular outer to outer anterior-posterior diameter. Follow-up CT scan frequency was based on aortic diameter (50 to 54 mm: twice annually; 45 to 49 mm: annually; and 30 to 44 mm: every 2 years) to check for expansion >55 mm.[14,23]

Follow-Up

The date of screening was set as the index-date. A follow-up period of up to five years was applied, and participants were censored at time of death, AAA surgery, rupture, the completion of 5 years from the index date, or the final follow-up date of December 31, 2021, whichever came first.

Statistical Analysis

Baseline Characteristics

Each statin prescription redeemed during the follow-up period was accumulated into a combined cumulative dosage of statin usage measured in DDD, as defined by the World Health Organization Center for Drug Statistics Methodology.[24] The DDD is the assumed typical dose for a drug when used for its main indication in an adult,[24] thereby allowing us to use one consistent measure of quantity across statins with highly variable potency. In reporting of baseline characteristics and for the growth rate analyses, participants were divided into four sub-groups, determined by the daily average use of the accumulated statin exposure. The daily average use was defined as nonusers (0 DDD), low-intensity users (<1 DDD per day), middle-intensity users (1–2 DDD per day), and high-intensity users (≥2 DDD per day). Individuals who redeemed a single prescription were categorized as nonusers, as this was deemed indicative of a high risk of early discontinuation and therefore not representative of true exposure. Time of initial exposure was set to start at time of redemption of the second statin prescription. Low-intensity users were used as the reference group for all comparisons, as nonusers may be more likely to be noncompliant, increasing the risk of healthy user bias. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were presented as mean±SD, if normally distributed evaluated visually in probability plots and by histograms with an applied normal distribution curve; otherwise, they were reported as medians with interquartile ranges (IQR). The Wilcoxon rank-sum test and Pearson χ^2 test were employed to assess differences between groups for numerical and categorical variables, respectively.

Baseline medications were defined as prescriptions redeemed up to 1 year before the index date; just a single prescription was needed as some prescriptions are filled to outlast 1 year.

AAA Growth Rates

Growth rates were calculated for each participant using linear regression based on all available measurements, reducing the impact of variation between measurements. The resulting continuous variable was used in subsequent analyses. Linear regression was chosen as the observed growth rates followed a linear pattern.

The primary analysis with estimated AAA growth rates was based on the average daily statin use over the entire follow-up period. This approach was chosen based on the expectation of a constant, dose-dependent statin effect on growth rate and stable treatment over time. In the initial regression, unadjusted linear regression analysis was applied. Hereafter, a linear regression analysis adjusted for age, baseline abdominal aortic size, baseline diastolic blood pressure, baseline body mass index, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, smoking status at baseline, use of metformin at baseline, and highest achieved education was performed. These covariates were selected a priori based on their known association with risk of developing an AAA and AAA growth rate.[3,6,8,25,26] In a sensitivity analysis, residuals from the adjusted linear regression were derived to identify extreme outlies; hereafter, the adjusted analysis was repeated after excluding extreme outliers defined by a deviation from the regression model by 5 mm per year or more in either direction. This sensitivity analysis aimed to minimize the risk of bias arising from the presence of extreme outliers. Finally, a sensitivity analysis was performed including only previous nonusers in the adjusted linear regression model. The objective of this sensitivity analysis was to mitigate the impact of survivorship bias and healthy user bias, as previous initiation of preventive therapy could be related to socioeconomic factors, and the potential underreporting of early statin therapy events.

In a secondary analysis, statin exposure was included as a predefined categorical variable (low-use as reference, non-, medium-, and high-intensity use) instead of a continuous measure, to further assess a potential dose-response

association in the adjusted linear regression models. The linear regression was adjusted for the same covariates as mentioned above.

AAA Events

Incidence rates per 1000 person-years was calculated for AAA rupture, surgery, and all-cause death, respectively. To evaluate potential associations between statin use and undergoing repair, crude and adjusted Cox regression analyses were performed to obtain hazard ratios (HRs). The adjusted analyses included the same covariates used for the growth rate analyses, as well as a diagnosis of heart failure and unoperated lung cancer within 5 years of the index date, which were deemed critical for assessing the advisability of surgery for individual patients according to expert review by the senior author (J.S.L.) based on recommendations at the local institutions at the time. To avoid immortal time bias in the event-based analyses, a long-format data structure was used, with statin exposure included as a time-varying variable. Each redeemed prescription defined a unique exposure period for each participant, lasting from the date of redemption until the next prescription, an event, or the end of follow-up. Two models were considered: one based on increments of cumulative 1000 DDD and another using a log base 2 transformation of the cumulative dose. The logarithmic model was selected as the final, as the Schoenfeld Residuals test indicated that the 1000 DDD model violated the proportional hazards assumption. Moreover, this approach allows for the assessment of potential dose-effect correlation between statin exposure and the risk of undergoing repair, with each unit increase representing a doubling of cumulative dosage. To account for the competing risks of rupture and death, we repeated all analyses—first using a composite outcome of surgery and rupture, and then with a composite outcome of surgery, rupture, and death as sensitivity analyses. HRs were plotted over time, beginning at 1 year and adding successive 1-month intervals through the 5-year follow-up, to assess when the effect of statins became detectable and whether the treatment effect remained stable, in accordance with the proportional hazards assumption.

All-cause mortality was assessed over an adjusted follow-up period, concluding at the earliest occurrence of either death, 5 years follow-up, or December 31, 2021.

Missing data were not imputed, and a complete-subject analysis was used as we expect the missingness to be random.

As a sensitivity analysis, a falsification approach was applied to assess the potential for healthy user bias favoring statin users. The selected outcomes included acute kidney injury, pneumonia, nephrolithiasis, cataracts, podagra, femur fracture, and osteoporosis. These conditions were chosen as they are not expected to be influenced by statins, and a reduced hazard for these diagnoses could indicate the presence of bias. The same methods as for all-cause mortality was applied.

A *P* value <5% was considered significant in all analyses. All analyses were performed using Stata 18.5.[27]

Ad hoc analysis

A stratified sensitivity analysis was conducted to assess whether the known presence of atherosclerosis influenced the results. The dichotomous variable was defined as either the presence of established atherosclerosis, indicated by a previous atherosclerotic event, or the absence of any such history. In the absence of a documented event, individuals were considered to have asymptomatic cardiovascular disease because of the strong correlation between AAA and atherosclerosis. See Table S1 for definitions.

A stratified sensitivity analysis was performed to assess result consistency across studies, recognizing the limitation that statin dosage was largely determined by study participation, reducing dose variation and, along with a smaller sample size, lowering statistical power. For growth rates, exposure was categorized as high-intensity versus the rest of the cohort because of the limited number of high-intensity statin users in the VIVA trial. For the risk of undergoing repair, the original analytical method was used but stratified by study.

Ethics

The DANCAVAS trials were approved by the Southern Denmark Region Committee on Biomedical Research Ethics (journal No.: S-20140028) and the Danish Data Protection Agency.[14] VIVA was approved by the ethics committee of Central Denmark Region (journal No. M-20080028), and at the Danish Data Protection Agency (journal No. 1-16-02-1-08).[13] All participants from both screening studies provided informed consent. Data from Statistics Denmark were anonymous so individuals could not be identified. If any count number was <3 individuals, excluding 0, results were reported as "less than 3" to maintain privacy for the participants in accordance with Statistics Denmark's regulative.[28]

RESULTS

Patient Characteristics

The study population consisted of 998 men from the general Danish population with a screening-detected AAA between 30 mm and 55 mm. Of these, 550 (55.1%) participants were screened in the VIVA trial, and 448 (44.9%) participants were screened in the DANCAVAS trial. The median age at baseline was 70 (IQR, 67–72) years for VIVA and 69 (IQR, 66–71) years for DANCAVAS.

Amongst all 998 included participants, 110 (11%) were identified as *nonusers* of statin, 237 (23.8%) as low-intensity users, 484 (48.5%) as medium-intensity users, and 167 (16.7%) as high-intensity users. Fifty participants (29.9%) from the high-intensity group were from the VIVA cohort. The exposed cohort of 888 (89%) participants had an overall median statin exposure of 2041 (IQR, 1064–3000) DDD during the follow-up period. A total of 161 (29.1%) VIVA participants received a larger statin dose than the study protocol of 1.33 DDD per day, whereas 117 (26.1%) DANCAVAS participants received more than the recommended 2 DDD per day. Before being included in one of the 2 screening trials, 419 (42%) participants were nonusers, whereas just 31 (3.1%) and 28 (2.8%) qualified as medium- and high-intensity users, respectively.

In Table 1, baseline characterization of the study population can be seen stratified by averaged daily statin exposure. The overall baseline aortic diameter was 35.4 (IQR,

Table 1. Characterization of the 2 AAA Cohorts from the VIVA and DANCAVAS Trials According to Statin Dosage

Variables	Total	Low-intensity users (Ref)	Nonusers	Non-user *P* value	Middle-intensity users	Middle-intensity user *P* value	High-intensity users	High-intensity user *P* value
Cohort total (VIVA/DANCAVAS), N (n/n)	998 (550/448)	237 (165/72)	110 (63/47)		484 (272/212)		167 (50/117)	
Age, y, median (IQR)	69.5 (67–72)	70 (67–72)	70 (67–72)	0.582	69 (67–72)	0.020	69 (67–72)	0.042
Smoking status, n (%)				0.534		0.282		0.391
Never	82 (8.22)	23 (9.7)	10 (9.09)		35 (7.23)		14 (8.38)	
Former	524 (52.5)	117 (49.4)	48 (43.6)		265 (54.8)		94 (56.3)	
Current	390 (39.1)	97 (40.9)	52 (47.3)		182 (37.6)		59 (35.3)	
Size of AAA at baseline, mm, median (IQR)	35.4 (32–41.2)	34.7 (32.1–39.7)	37.7 (32.5–43.6)	0.015	35.1 (31.7–41.1)	0.612	37.1 (32.4–41.6)	0.033
Systolic blood pressure, mm Hg, mean±SD	152±20.6	154±22.5	152±18.8	0.815	152±20.2	0.636	150±20	0.126
Diastolic blood pressure, mm Hg, mean±SD	85.1±11.4	86.5±11.6	86.3±11	0.747	85.2±11.7	0.262	81.9±10	0.000
BMI, kg/m^2, mean±SD	28.2±4.31	27.7±4.04	27.7±5.58	0.427	28.2±3.94	0.081	29±4.63	0.010
BSA (DuBois), m^2, mean±SD	2.05±0.172	2.03±0.156	2.05±0.192	0.454	2.05±0.172	0.155	2.07±0.178	0.053
Statin before index date, DDD/day, median (IQR)	0.544 (0–1.23)	0.358 (0–0.726)	0 (0–0)	0.000	0.723 (0–1.3)	0.000	1.46 (0.411–2.99)	0.000
Other medication, n (%)								
Anticoagulant	89 (8.92)	18 (7.59)	10 (9.09)	0.634	38 (7.85)	0.904	23 (13.8)	0.043
Platelet inhibitor	459 (46)	104 (43.9)	39 (35.5)	0.138	214 (44.2)	0.933	102 (61.1)	0.001
NSAID	249 (24.9)	55 (23.2)	26 (23.6)	0.930	127 (26.2)	0.379	41 (24.6)	0.755
Beta-blocker	304 (30.5)	69 (29.1)	25 (22.7)	0.213	137 (28.3)	0.821	73 (43.7)	0.002
Thiazide	141 (14.1)	38 (16)	18 (16.4)	0.938	67 (13.8)	0.433	18 (10.8)	0.132
ACE inhibitor	302 (30.3)	65 (27.4)	24 (21.8)	0.266	150 (31)	0.326	63 (37.7)	0.028
AT2 antagonist	195 (19.5)	41 (17.3)	21 (19.1)	0.685	97 (20)	0.379	36 (21.6)	0.283
Calcium channel blocker	305 (30.6)	71 (30)	24 (21.8)	0.114	150 (31)	0.777	60 (35.9)	0.207
Metformin	88 (8.82)	22 (9.28)	5 (4.55)	0.125	41 (8.47)	0.717	20 (12)	0.382
Oral antidiabetica	61 (6.11)	14 (5.91)	4 (3.64)	0.375	24 (4.96)	0.592	19 (11.4)	0.048
Bronchodilator	223 (22.3)	55 (23.2)	19 (17.3)	0.209	105 (21.7)	0.646	44 (26.3)	0.470
Comorbidities, n (%)								
Hypertension	666 (66.7)	156 (65.8)	61 (55.5)	0.063	317 (65.5)	0.931	132 (79)	0.004
Diabetes	122 (12.2)	27 (11.4)	10 (9.09)	0.518	55 (11.4)	0.991	30 (18)	0.062
Chronic obstructive lung disease	223 (22.3)	55 (23.2)	19 (17.3)	0.209	105 (21.7)	0.646	44 (26.3)	0.470
Chronic kidney disease	29 (2.91)	7 (2.95)	6 (5.45)	0.254	12 (2.48)	0.709	4 (2.4)	0.734
Heart failure	78 (7.82)	17 (7.17)	8 (7.27)	0.973	35 (7.23)	0.977	18 (10.8)	0.205
Peripheral arterial disease	220 (22)	49 (20.7)	22 (20)	0.885	115 (23.8	0.353	34 (20.4)	0.938
Former myocardial infarction	182 (18.2)	34 (14.3)	13 (11.8)	0.522	91 (18.8)	0.138	44 (26.3)	0.003
Former stroke	101 (10.1)	25 (10.5)	8 (7.27)	0.333	50 (10.3)	0.928	18 (10.8)	0.941
Atherosclerosis								0.136
Established atherosclerosis	435 (43.6)	100 (42.2)	37 (33.6)	0.129	215 (44.4)	0.571	83 (49.7)	
Asymptomatic cardiovascular disease	563 (56.4)	137 (57.8)	73 (66.4)	0.129	269 (55.6)	0.571	84 (50.3)	

Groups were defined as an average daily statin usage during the observation period: nonusers, 0 DDD; low-intensity users, <1 DDD; middle-intensity users, <2 DDD; and high-intensity users, ≥2 DDD. Categorical variables are expressed as frequencies (n) and percentages (%). Continuous variables are presented as mean±SD if normally distributed, otherwise, they are reported as median (IQR). The Wilcoxon rank-sum test and Pearson χ^2 test for numerical and categorical variables, respectively, were used to calculate differences between groups compared with the reference group of low-intensity group. All medicine dates are for prescriptions 1 year before inclusion.

AAA indicates abdominal aortic aneurysm; ACE inhibitor, angiotensin-converting enzyme inhibitor; AT2 antagonist, angiotensin II–receptor antagonist; BMI, body mass index; BSA, body surface area; DANCAVAS, Danish Cardiovascular Screening trial; DDD, defined daily dose; IQR, interquartile range; MACE, major adverse cardiovascular event; NSAID, nonsteroidal anti-inflammatory drug; and VIVA, Viborg Vascular trial.

32.0–41.2) mm, with the largest diameters observed in the nonuser and high-intensity groups. The high-intensity group had a higher body mass index and were more likely to use medications such as anticoagulants, platelet inhibitors, beta-blockers, angiotensin-converting enzyme inhibitors, and oral antidiabetics. Moreover, the participants in the high-intensity group also presented higher prevalence of comorbidities, including hypertension, previous myocardial infarctions, and previous major adverse cardiovascular events compared to the low-intensity statin group. Missing data was minimal; please refer to Supplemental Results for details.

AAA Growth Rates

Consecutive imaging of the abdominal aorta was performed in 823 (82.5%) participants (ie, these were eligible to be included in the analyses estimating growth rates). It should be noted that among the statins nonuser group, only 52 (47.3%) had consecutive imaging performed, whereas more than 85% of participants in the exposed groups had sequential measurements.

The overall growth rate was 2.2±2.4 mm/year. Rates were 2.1±2.2 mm/year in the unexposed group, 2.4±2.3 mm/year in the low-intensity group, 2.3±2.5 mm in the medium-intensity group, and 1.5±2.1 mm/year in the high-intensity group. Growth rates stratified by exposure groups are shown in Figure 1. In crude linear regression analyses, a significant difference in growth rates was observed between the high-intensity and low-intensity groups (2.4±2.3 mm/year versus 1.5±2.1 mm/year; *P*=0.001), whereas no significant differences were observed between the other groups. The overall unadjusted effect of increasing statin usage by 1 DDD per day was a change in AAA growth rate of −0.3 (95% CI, −0.48 to −0.13] mm per year; *P*=0.001). After adjustment, the association was reduced, but still statistically significant at 0.22 ([95% CI, −0.39 to −0.06] mm per year; *P*=0.009) per 1-DDD increase per day average (Figure 2). Notably, metformin performed well with a result of −1.07 (95% CI, −1.99 to −0.16) mm per year. The histogram plot of the residuals from the adjusted linear regression analysis displayed a tail towards higher growth rates (ie, which could indicate possible extreme outliers; Figure S1). In the sensitivity analysis excluding outliers (22 [2.2%]), the result was unchanged at −0.22 ([95% CI, −0.34 to −0.09] mm/year; *P*=0.001; Figure S2), and the resulting histogram of the residuals was symmetrical (Figure S3). The sensitivity analysis, restricted to the 419 participants with no history of statin use for ≥1 year before inclusion, showed a similar estimated effect on growth rate (−0.16 [95% CI, −0.50 to 0.17] mm per year per 1 daily average DDD increase), although the association was not statistically significant

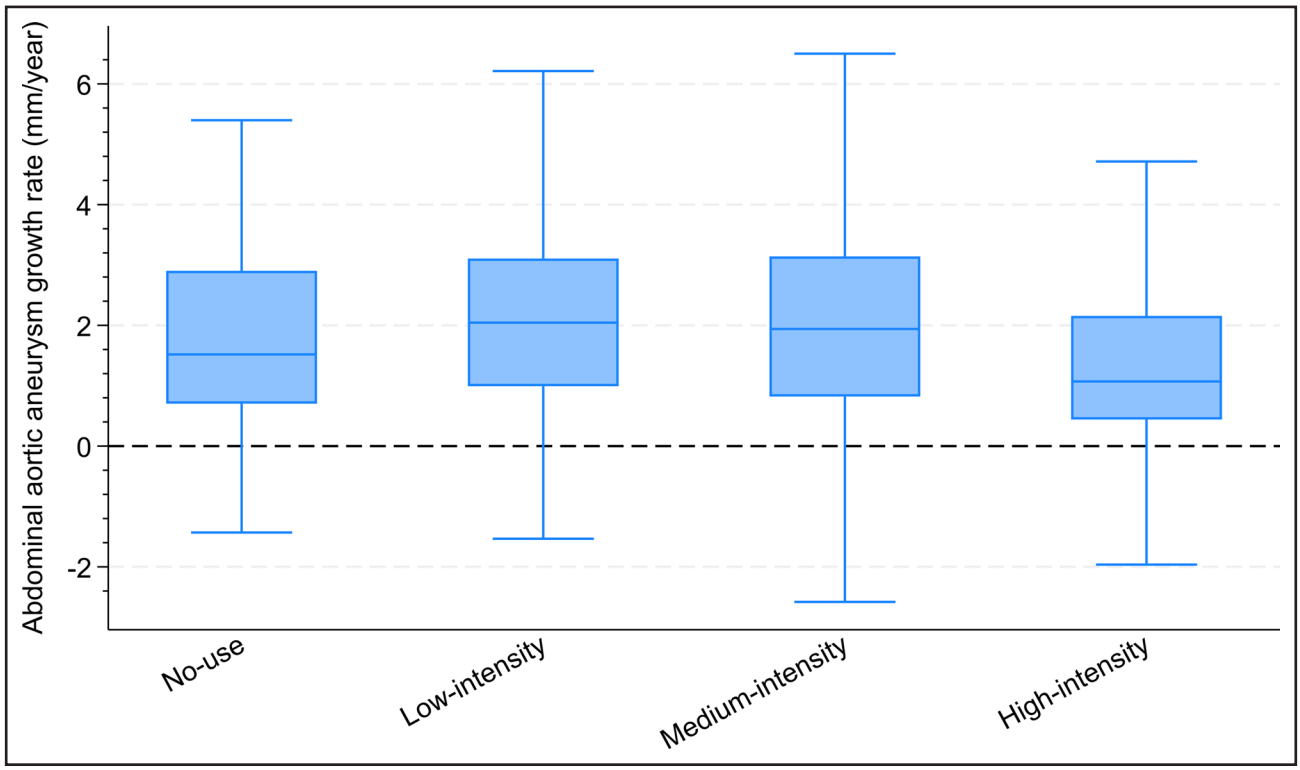

Figure 1. Box plots of the estimated growth rates stratified by the statin exposure groups.
Groups were defined as an average daily statin usage during the observation period: nonusers, 0 DDD, low-intensity users <1 DDD, middle-intensity users <2 DDD, and high-intensity users ≥2 DDD. Growth rate was calculated using linear regression. Because of data safety concerns and in accordance with Statistics Denmark guidelines, individual outliers have been concealed.

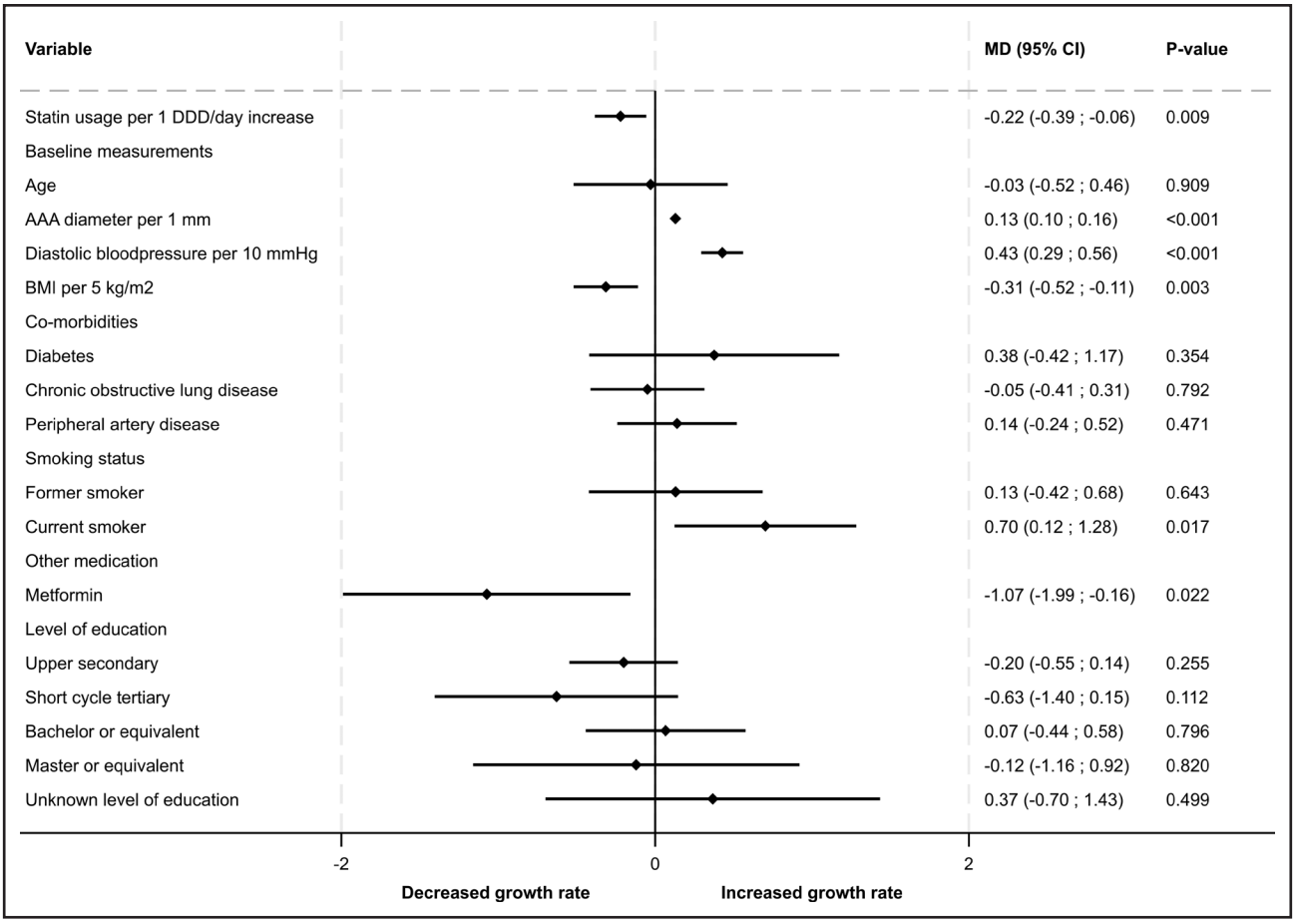

Figure 2. Adjusted linear regression analysis of the average statin dose and its effect on AAA growth rate.
Mean difference in growth rate estimates generated from adjusted linear regression analyses in mm/y. The adjusted analyses were adjusted for age, baseline aortic size, baseline diastolic blood pressure, baseline BMI, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, baseline smoking status, use of metformin at baseline, and highest achieved education. AAA indicates abdominal aortic aneurysm; BMI, body mass index; DDD, defined daily dose; and MD, mean difference.

(*P*=0.33). In comparison, the 579 participants with previous statin use exhibited a significant change in growth rate of −0.21 (95% CI, −0.40 to −0.02) mm per year per daily average DDD increase. No difference in growth rate was observed between previously unexposed and exposed participants when included as a variable in the adjusted analysis (*P*=0.47). Categorizing statin exposure showed a significantly lower AAA growth rate in the high-intensity group, with an adjusted mean difference of −0.67 (95% CI, −1.15 to −0.19] mm per year; *P*=0.006) compared with the low-intensity group (Figure S4).

AAA Events

The cohort had complete follow-up with a median follow-up time of 4.97 (IQR, 3.2–5) years and a total observation time of 3995 person-years. A median of 2.97 (IQR, 0.65–5) years and 311 person-years of follow-up was observed for the group unexposed to statins during follow-up.

A total of 212 aortic surgeries, 15 cases of rupture, and 132 deaths during the follow-up were observed (Table 2). Fewer than 3 individuals died within 30 days after elective repair; 4 (1.9%) died within 90 days. Additionally, 8 of 15 individuals (53.3%) died at the 30- and 90-day marks after rupture. All 8 rupture cases died within 5 days of diagnosis. The 5-year HR for undergoing repair per doubling of dose of cumulative statin exposure was significant in both the unadjusted and adjusted analyses. The adjusted analysis displayed a HR of 0.82 ([95% CI, 0.70–0.97]; *P*=0.023) per doubling of dose (Figure 3). Metformin showed a strong association with a HR of 0.24 (95% CI, 0.08–0.74). Evaluation of the Cox regression model of undergoing repair using the Schoenfeld residuals test yielded a global *P* value of 0.16, with a *P* value of 0.23, specifically for the exposure of interest.

The secondary analysis for outcomes including surgery or rupture, and surgery, rupture, or death, showed significant results with similar HRs (Table 3).

When analyzing the HR over time, a statistically significant protective effect against undergoing repair alone was observed, starting after 2.5 years from baseline per doubling of cumulative statin use (Figure 4).

Table 2. Statin Dose-Dependent Outcomes in AAA Cohorts from the VIVA and DANCAVAS Screening Trials

Variable	Total	Nonusers	Low-intensity users	Middle-intensity users	High-intensity users
Cohort total (VIVA/DANCAVAS), N (n/n)	998 (550/448)	110 (63/47)	237 (165/72)	484 (272/212)	167 (50/117)
Statin exposure, DDD/day, mean±SD	1.32±0.951	0±0	0.586±0.26	1.44±0.293	2.88±0.813
Statin cumulative, DDD	1849 (760–2800)	0 (0–0)	900 (520–1300)	2251 (1719–2648)	4000 (3333–6000)
Multiple AAA scans	823 (82.5)	52 (47.3)	205 (86.5)	424 (87.6)	142 (85)
Follow-up time, y	4.97 (3.2–5)	2.97 (0.646–5)	5 (4–5)	4.97 (3.35–5)	4.95 (3.71–5)
Growth rate, mm/y	2.16 (2.38)	2.06 (2.24)	2.35 (2.33)	2.3 (2.48)	1.5 (2.08)
Surgery	212 (21.2)	35 (31.8)	39 (16.5)	109 (22.5)	29 (17.4)
Incidence rate	53 (46–61)	113 (81–157)	38 (28–52)	55 (46–67)	42 (29–60)
rAAA	15 (1.5)	3 (2.73)	3 (1.27)	9 (1.86)	0 (0)
Incidence rate	3.8 (2.3–6.2)	9.7 (3.1–30)	2.9 (0.95–9.1)	4.6 (2.4–8.8)	0 (0–0)
Deaths	132 (13.2)	25 (22.7)	37 (15.6)	52 (10.7)	18 (10.8)
Incidence rate	33 (28–39)	81 (54–119)	36 (26–50)	26 (20–35)	26 (16–41)
All-cause mortality*	152 (15.2)	29 (26.4)	41 (17.3)	62 (12.8)	20 (12)
Incidence rate*	33 (28–38)	63 (44–91)	37 (27–50)	27 (21–35)	25 (16–39)

Groups were defined as an average daily statin usage during the observation period: nonusers, 0 DDD; low-intensity users, <1 DDD; middle-intensity users, 1–2 DDD; and high-intensity users, ≥2 DDD. Categorical variables are expressed as frequencies (n) and percentages (%). Continuous variables are presented as mean±SD if normally distributed or otherwise specified, or they are reported as median (IQR).

AAA indicates abdominal aortic aneurysm; DANCAVAS, Danish Cardiovascular Screening trial; IR, incidence rate per 1000 person-years; rAAA, ruptured abdominal aortic aneurysm; and VIVA, Viborg Vascular trial.

*Follow-up extending to the earliest occurrence of death, 5 years, or December 31, 2021.

No associations were observed between statin exposure and the investigated falsification end points (Table S2).

Ad Hoc Results

The influence of asymptomatic cardiovascular disease remained consistent in both growth rate and event-based analyses. Among the 563 participants with asymptomatic cardiovascular disease, each unit increase in average daily DDD was associated with a change in growth rate of −0.31 (95% CI, −0.54 to −0.08) mm/year, and each doubling of dosage was linked to a lower risk of undergoing repair (adjusted HR, 0.75 [95% CI, 0.61–0.94]). A similar trend was observed among the 435 participants with established atherosclerosis for both growth rate and risk of undergoing repair, though the effect was attenuated and not statistically significant. Notably, the majority of individuals without a documented history of atherosclerosis at baseline were also previous nonusers of statins (58%).

In the sensitivity analyses comparing high-intensity statin users to the rest of the cohort stratified by screening trial, the change in growth rate was −0.18 (95% CI, −1.10 to 0.69) mm/year in the VIVA trial and −0.13 (95% CI, −0.47 to 0.21) mm/year in the DANCAVAS trial. For the risk of undergoing repair per doubling of cumulative dose, the results were not statistically significant, with an HR of 1.1 (95% CI, 0.87–1.4) in the VIVA trial and 0.83 (95% CI, 0.55–1.25) in the DANCAVAS trial (Figures S5 and S6).

DISCUSSION

In this 5-year prospective follow-up study relaying on longitudinal cohort data from 2 large, population-based, randomized screening trials undergoing standardized surveillance, a dose-dependent effect from use of statin on AAA growth rates and AAA-related events were observed. The findings strongly suggest a significant association between high-dose statin use and reduced AAA growth rates; an increase of 1 DDD in the average daily statin dosage was associated with an adjusted change in AAA growth rate of −0.22 mm per year. With a maximal dosage of 4 DDD per day, equivalent to 80 mg of atorvastatin or 40 mg of rosuvastatin (assuming equal effects), this would be associated with a 0.88-mm/year reduction in growth rate, corresponding to approximately half the overall growth rate. In addition to the association with lower AAA growth rates, statin use was strongly and independently associated with a reduced risk for undergoing repair, beginning after 2.5 years from initiation of statin treatment. Supporting this, a doubling of cumulative statin exposure was associated with a reduced risk of undergoing repair within 5 years, with an HR of 0.82. However, there is also a risk that the growth rate finding is attributable to chance, as only the high-dose group showed a significant association with lower growth rates. These combined observations suggest 2 possible interpretations: either a sufficiently high statin dose is necessary to limit AAA growth, or the association may be incidental or confounded by time trends not available for adjustment. Nevertheless, the results remained robust

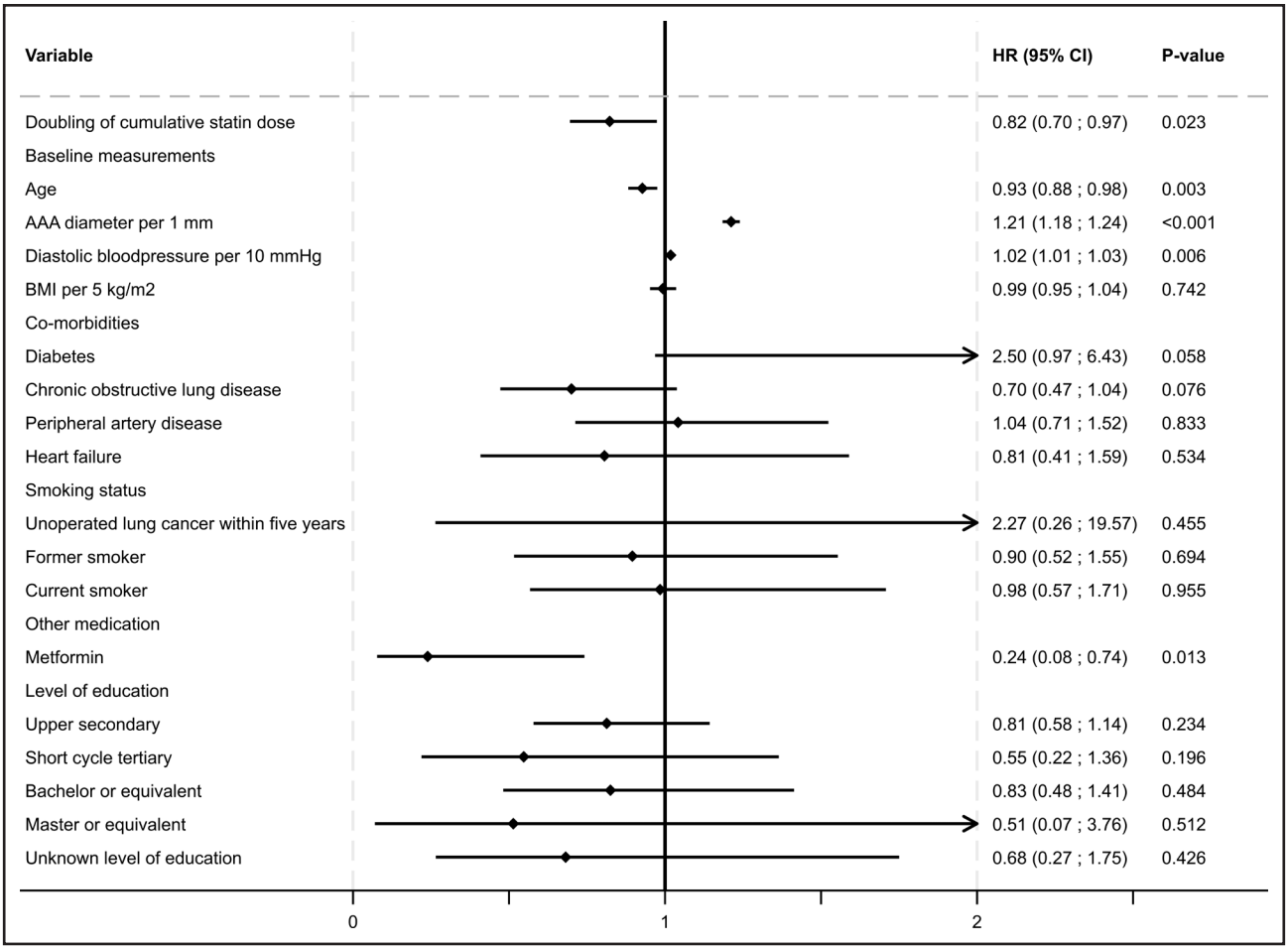

Figure 3. Adjusted Cox regression analysis of doubling of statin dose and the risk of undergoing repair.
Hazard ratio estimates were generated from adjusted Cox regression analyses. The adjusted analyses were adjusted for age, baseline aortic size, baseline diastolic blood pressure, baseline BMI, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, baseline smoking status, use of metformin at baseline, highest achieved education, heart failure, and unoperated lung cancer within 5 years of the index date. AAA indicates abdominal aortic aneurysm; BMI, body mass index; and DDD, defined daily dose.

and consistent across sensitivity analyses. Overall, these findings suggest a direct protective effect of statins on both AAA growth rates and AAA-related events.

The consistent association between higher statin dosage and reduced AAA growth and repair risk in individuals with asymptomatic cardiovascular disease suggests undiagnosed atherosclerosis rather than its absence. These findings further support statin use in AAA patients without previous cardiovascular events.

Our findings align with previous research suggesting that statins may slow the progression of AAA and reduce the risk of undergoing repair, rupture, and death.[6–8,29] The observed dose-dependent effect of statins on AAA growth rates corroborates the results of earlier meta-analysis, underscoring the potential direct therapeutic role of statins in AAA management.[6] In the aforementioned meta-analysis,[6] the overall mean difference was found to be a reduction of growth rate of 0.84 (95% CI, 0.04–1.63); however, this was using a simple binary exposed/unexposed of statins and was recognized as very low GRADE certainty of evidence related to unexplained heterogeneity. Some of the heterogeneity observed in the meta-analysis could be speculated to arise from differences in statin dosage. Metformin, previously identified as a potential treatment for AAA,[6] showed favorable results in both growth rate and event-based analyses, providing further support for its potential efficacy.

The significant association between high intensity statin use and reduced AAA growth rates indicates that maximal dose statins could be a valuable adjunctive therapy in directly managing AAA and preventing progression. Additionally, this approach would be expected to provide better cardiovascular protection for this patient group as recognized by the European Society for Vascular Surgery guidelines.[5] In the 2024 update of the European Society for Vascular Surgery guidelines, statins are recommended in general terms without a specific dose recommendation in the European Society for Vascular Surgery guidelines.[5] With

Table 3. Unadjusted and Adjusted Cox Regression for Secondary Outcomes in the VIVA and DANCAVAS Cohorts

	Unadjusted				Adjusted			
	N	Events, n	HR (95% CI)	*P* value	N	Events, n	HR (95% CI)	*P* value
Surgery								
Per doubling of statin dose	888	177	0.87 (0.74–1)	0.081	867	174	0.82 (0.7–0.97)	0.023
Surgery or rupture								
Per doubling of statin dose	888	189	0.87 (0.74–1)	0.070	867	186	0.83 (0.71–0.98)	0.026
Surgery, rupture, or death								
Per doubling of statin dose	888	296	0.85 (0.75–0.95)	0.006	867	291	0.83 (0.73–0.94)	0.003
Rupture								
Per doubling of statin dose	888	12	0.86 (0.48–1.6)	0.627	867	12	0.96 (0.46–2)	0.921
All-cause mortality*								
Per doubling of statin dose	921	125	0.78 (0.66–0.93)	0.007	900	123	0.81 (0.68–0.98)	0.027

HR estimates were generated from Cox regression analyses. The adjusted analyses were adjusted for age, baseline aortic size, baseline diastolic blood pressure, baseline body mass index, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, baseline smoking status, highest achieved education, heart failure, and unoperated lung cancer within 5 years of the index date. N indicates number of individuals included in the Cox regression. Doubling of dose was calculated using the log base 2 transformed cumulative dosage.

DANCAVAS indicates Danish Cardiovascular Screening trial; DDD, defined daily dose; HR, hazard ratio; and VIVA, Viborg Vascular trial.

*Follow-up extending to the earliest occurrence of death, 5 years, or December 31, 2021.

the increasing certainty of the overall evidence, we argue that guidelines should advocate for high-dose statins to achieve maximal effect on both the AAA growth rate and risk of cardiovascular events. Supporting this, statin therapy is widely used, demonstrating a well-established safety profile with minimal adverse effects. Additionally, statin therapy is cost-effective at reducing major cardiac adverse events, noncoronary

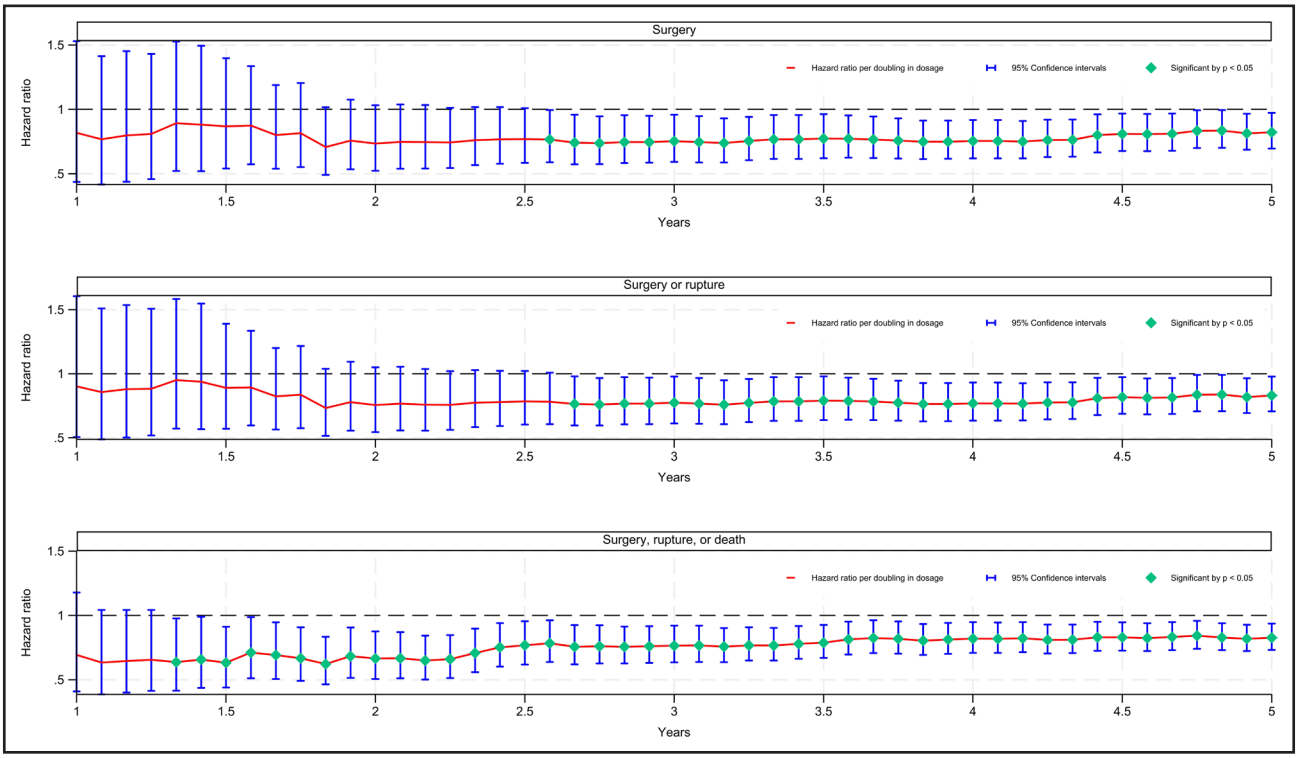

Figure 4. Risk of abdominal aortic surgery, rupture, and death from doubling of statin dosages.
Hazard ratio estimates were generated from Cox regression analyses, adjusted for age, baseline aortic size, baseline diastolic blood pressure, baseline body mass index, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, baseline smoking status, use of metformin at baseline, highest achieved education, heart failure, and unoperated lung cancer within 5 years of the index date. Results were calculated in increments of months from year 1 to year 5 from the index date. Results were considered statistically significant if *P* value <5; indicated by green diamonds in the plots.

revascularization, AAA repair, and major amputation, making them an attractive option for long-term treatment across diverse patient populations.[30] These attributes, combined with the likely effect on growth and AAA-related outcomes presented in this study, make high-dose statins an obvious candidate for potential use in managing AAA progression, because of their widespread acceptance and proven safety in other vascular conditions.

Although the precise mechanism by which statins may impact AAA is not fully clarified, prevalent theories suggest involvement of various pathways associated with vascular inflammation, matrix metalloproteinases inhibition, increased synthesis of the extra cellular matrix with collagen and elastin, and reduction of reactive oxygen species.[31] Understanding the observed role of statins in slowing AAA progression could provide valuable insights into the natural history of AAA.

A major strength of this study is the utilization of clinical prospective cohort data from population-based, large, randomized screening studies from the general Danish population. Combining the clinical data with prescription and outcome data from the high-quality Danish national registries allowed for unique precise individual-level exposure data, complete follow-up regarding events, and accurate event timing. The universal healthcare system in Denmark ensures comprehensive data coverage, enhancing the internal validity of the findings.

Because of the risk of collinearity and mediation effects, adjustments could not be made for the different imaging modalities used in the 2 screening trials. VIVA employed ultrasound, and DANCAVAS used noncontrast, ECG-gated CT scans. Additionally, the statin regimens varied between the 2 studies as VIVA used 40 mg of Simvastatin (1.33 DDD), whereas DANCAVAS used 40 mg of Atorvastatin (2 DDD). Thus, correcting for imaging modality would also inadvertently account for differences in statin recommendations. Somewhat mitigating the risk of bias regarding image modality, Liisberg et al has shown agreement on mean of abdominal aortic diameters between the 2 imaging modalities explained by ultrasound-based measurement in the peak of the systole, and ECG-gated CT scan measurements in the end-diastole, a cyclic difference known to be 2 mm.[32] Because of this limitation, adjusting for time-related factors such as smoking trends or improvements in secondary prevention is not possible. Partially mitigating the impact of smoking trends over time is the absence of any observed differences in smoking patterns at baseline. If the observed negative association between statins and risk of undergoing repair was merely a reflection of time trends, rather than a protective effect of statins, changes in surgical practice would be expected to weaken rather than support this relationship. The adoption of endovascular aortic repair has allowed surgical intervention in patients previously considered to be too high risk, making it more likely that individuals in the more recent study period, who also tend to have higher statin exposure, would undergo repair.[33] This shift would bias the results towards a higher rate of surgical intervention in the statin-exposed group, working against the observed protective association. This study included only male participants because of limitations in the source material, which reduces the generalizability of the results to the female population. Future studies should aim to validate these findings in female or mixed-sex populations. Additionally, as our cohort primarily consists of White individuals from a Western society between 60 and 74 years of age, caution is warranted when extrapolating these findings to other racial and ethnic groups, age groups, or different societal contexts. Nonusers differed from the other groups in terms of follow-up time and the percentage of sequential abdominal aorta measurements. Although the exact reason for this discrepancy is unknown, it could be attributed to inherent differences in compliance between the nonusers and the exposed groups as all were recommended the same statin dose. Another possible explanation for the discrepancies is that it is customary to discontinue statin treatment in patients with short life expectancy. This practice could potentially bias the results, as those who continue treatment might be healthier overall, inflating the observed effectiveness of statins. We addressed this potential bias using the low-intensity user group as reference. Furthermore, the risk of residual confounding is as always present in an observational design.

Future research should focus on explaining the precise mechanisms by which statins influence AAA and determining optimal dosing strategies to maximize patient outcomes. Although randomized controlled trials are typically the gold standard, it would seem unethical to randomize patients to placebo treatment given the current knowledge of cardiovascular risk mitigation with active and well tolerated statin treatment. A randomized controlled trial comparing various statin dosages is theoretically feasible. However, such a study would require a large sample size and be constrained by current guidelines recommending high-intensity statin therapy for AAA patients because of their elevated cardiovascular risk.[1] Accordingly, we advocate for observational studies with a similar design, emphasizing precise exposure measurement and detailed dose-response outcomes, to replicate and further validate our findings especially in women and other ethnic groups.

Conclusions

In conclusion, this study suggests that higher statin dosage may be associated with slower AAA growth rates and a lower hazard for undergoing repair, rupture, and death. Although these findings indicate a potential benefit of

high-dose statins in AAA management, further research is needed to confirm these effects, clarify underlying mechanisms, and determine optimal treatment strategies.

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Disclosures

None.

Supplemental Material

STROBE Checklist
Supplemental Results
Figures S1–S6
Tables S1 and S2

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