

Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study

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Aim

We tested the hypothesis that statin-related news stories, cardiovascular disease, diabetes, statin dose, calendar year, and socio-demographic status are associated with early statin discontinuation. We also examined frequency and consequences of early statin discontinuation.

Methods and results

From the entire Danish population, we studied 674 900 individuals aged 40 or older who were initiated on statin therapy in 1995–2010, and followed them until 31 December 2011. Individuals on statins increased from <1% in 1995 to 11% in 2010, while early statin discontinuation increased from 6% in 1995 to 18% in 2010. The odds ratios for early statin discontinuation vs. continued use were 1.09 (95% confidence interval, 1.06–1.12) for negative statin-related news stories, 1.04 (1.02–1.07) per increasing calendar year, 1.04 (1.02–1.06) per increasing defined daily dose of statin, 1.05 (1.03–1.06) for male sex, 1.13 (1.11–1.15) for living in cities, 1.67 (1.63–1.71) for other ethnicity than Danish, 0.92 (0.90–0.94) for positive statin-related news stories, 0.73 (0.72–0.74) for baseline cardiovascular disease, and 0.91 (0.90–0.93) for baseline diabetes. During follow-up, the hazard ratios for individuals with vs. without early statin discontinuation were 1.26 (1.21–1.30) for myocardial infarction and 1.18 (1.14–1.23) for death from cardiovascular disease.

Conclusion

Early statin discontinuation increased with negative statin-related news stories, calendar year, statin dose, male sex, living in cities, and with other ethnicity than Danish, while the opposite was true for positive statin-related news stories and for baseline cardiovascular disease and diabetes. Early statin discontinuation was also associated with increased risk of myocardial infarction and death from cardiovascular disease.

Keywords

Statin compliance • Myocardial infarction • Death from cardiovascular disease • Statin-related news stories

Introduction

Although statins are considered among the safest drugs,^{1–3} initiation on statin therapy may lead to side effects ranging from very rare rhabdomyolysis to less rare and milder symptoms of muscle aches and other forms of discomfort^{4–9} leading potentially to early discontinuation of statin therapy.¹⁰ More than 90% of the milder symptoms occur during the first 6 months from initiation of statin therapy or from up-titration of the statin dose.¹¹ Exposure to negative and

positive statin-related news stories during this early phase may play a role for the patient in the decision to continue or discontinue statin therapy beyond the first dispense. This may especially be true for the patient without a history of cardiovascular disease or diabetes, and who previously considered him- or herself to be in good cardiovascular health. Additionally, as statin use reaches widespread population level use, statins are being prescribed to individuals of diverse health and socio-demographic status, individuals who may differ from the participants recruited into major statin trials.^{12–19}

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Importantly, the frequency, predictors, and consequences of early statin discontinuation on a population level are largely unknown.

We tested the hypothesis that statin-related news stories, cardiovascular disease, diabetes, statin dose, calendar year, and socio-demographic status are associated with early statin discontinuation. For this purpose, we studied all individuals initiated on statin therapy from 1995 through 2010 in the entire Danish population, and also followed them until 31 December 2011 for myocardial infarction and for death from cardiovascular disease.

Methods

Study population and early statin discontinuation

The national Danish Civil Registration System records all births, immigrations, emigrations, and deaths in Denmark through the civil registration number, which uniquely identifies all inhabitants in Denmark and includes information on age and sex. This registry is 100% complete; that is, for practical purposes, no persons are lost to follow-up.²⁰

Individuals using statins from 1 January 1995 through 31 December 2010 were identified using record linkage with the national Danish Registry of Medicinal Products Statistics by searching for records of statin dispensations classified according to the Anatomical Therapeutic Chemical Classification of Drugs code C10AA, while other cholesterol-lowering medications were C10AB–C10AX and C10BA. The national Danish Registry of Medicinal Products Statistics records information on all prescribed drugs dispensed at Danish pharmacies from 1995 onwards. Available data for each prescribed drug dispense for each individual are the drug name, date of dispensing, the recommended defined daily dose per pill, and the total amount of pills dispensed.

To ascertain individuals with early statin discontinuation vs. continued use not influenced by early mortality, we only looked at individuals still alive at 6 months following the first dispense of a statin (Supplementary material online, *Figure S1*). Individuals with early statin discontinuation were those without a second dispense of statin during that period of 6 months, while continued users were those that collected a second or more dispenses during the 6 months (Supplementary material online, *Figure S2*); to avoid bias due to individuals with a first statin dispense covering 6 months or more, we only included those with < 120 pills in the first statin dispensation (Supplementary material online, *Figure S3*), corresponding to a maximum of 4 months of regular use.

Statin-related news stories

Statin-related news stories from 1 January 1995 and onwards were identified by searching in the Danish Infomedia database using the Danish search terms 'statin', or the combination of terms 'kolesterol' and 'medicin'. The Infomedia database records all news stories from Danish newspaper and magazine articles, Danish radio and television stations, and Danish websites and news bureau feeds from 1990 and onwards. Available data for each news story include date of publication, name of the publishing media, and a textual transcription of the story. All 1931 transcripts were read by S.F.N., and of these 110 were graded as negative, 1090 as neutral, and 731 as positive statin-related news stories, blinded to individual patient data; questionable stories were discussed with B.G.N. before final grading.

Myocardial infarction, diabetes, and death from cardiovascular disease

Individuals with myocardial infarction diagnosed from 1 January 1977 through 31 December 2011 were identified using the national Danish

Patient Registry,²¹ which records information on all inpatient hospital visits in Denmark in this period, including outpatient and emergency ward visits from 1 January 1995. Diagnoses of myocardial infarction were classified according to the International Classification of Diseases 8th edition²² codes 410 until 1994 and thereafter 10th edition codes I21–I22, as described previously.²³

Individuals with diabetes mellitus were identified either from inpatient and outpatient hospital records from the national Danish Patient Registry or from dispense records from the national Danish Registry of Medicinal Products Statistics of the first dispense of oral glucose-lowering medication or insulin prescribed by the family doctor, whichever came first.²⁴ Diagnoses of diabetes were codes 249–250 (ICD-8) and E10–E14 (ICD-10). Oral glucose-lowering medication was classified according to the Anatomical Therapeutic Chemical Classification of Drugs codes A10BA–A10BX, while insulin was codes A10A–A10AF.

Death from cardiovascular disease was identified by searching in the national Danish Patient Registry for any hospital records with diagnoses of ischaemic heart disease during up to 30 days prior to the date of death. Diagnoses of ischaemic heart disease were codes I00–I25 (ICD-10).

Other covariates

Antihypertensive medication was diuretics (classified according to the Anatomical Therapeutic Chemical Classification of Drugs code C08DA, C08CA, C08DB, and C08DB), calcium antagonists (C03AA, C03AB, C03BA, C03CA, C093CB, C03DA, and C03EA), angiotensin-converting enzyme inhibitors (C09AB, C09BA, C09BB, and C09DA51), angiotensin II receptor blockers (C09CA, C09DA, and C09DB01), and vascular dilators for cardiovascular diseases β_1 antagonists (C07AA, C07AB, C07BB, C07CB, C07AG01, and C07AB02).

Additionally, Statistics Denmark has gathered information concerning ethnic descent, highest obtained level of education, and geographical residence for persons living in Denmark since 1980.

Statistical analyses

We used STATA13.0MP. We excluded individuals initiated on a statin below age 40 years as these individuals are more likely to suffer from familial disposition to elevated cholesterol levels, and thus different from the typical statin user. For similar reasons, we excluded individuals treated with other types of cholesterol-lowering medication before start of statin therapy. *P*-values for comparison of baseline characteristics between individuals with early statin discontinuation vs. continued use were estimated using method by Kruskal–Wallis, not taking into account possible correlations between the predictors.

For estimation of statin-related nationwide media exposure, the total negative, neutral, and positive media exposure were each estimated separately (Supplementary material online, *Figure S4*). For each individual, the negative statin-related nationwide media exposure was estimated as the weighted sum of all the negative news stories, published during the 6 months period following the first statin dispense, for which the individual could be exposed to; that is, statin-related news stories that were published in media with nationwide distribution together with news stories published in media with non-nationwide distribution but published in the same geographical region were the specific individuals lived. Each negative statin-related news story was weighted by the official readership, number of listeners, or number of viewers for the media publishing the story, divided by the total number of individuals in Denmark. Multiple publications or later republication of the same story in different media within the 6-month period from the first statin dispense was considered as independent stories. The estimation of corresponding individual-specific neutral and positive statin-related media

exposures was calculated identically (Supplementary material online, Figure S4).

For predictors of early statin discontinuation including all 674 900 statin users, logistic regression models including negative, neutral, and positive statin-related news stories, cardiovascular disease before the first statin dispense, diabetes before the first statin dispense, calendar year (=year of initiation of statin therapy), percentage of the population on a statin, statin dose per pill of the first statin dispense, sex, age at start of statin therapy, geographical residency, highest obtained level of education, and ethnic descent (95% Danish vs. 5% other) calculated odds ratios with 95% confidence intervals; the missing indicator method was used to account for 4% missing information on education.²⁵ Additionally, models were adjusted for statin drug name of the first statin dispense.

Population attributable risk was estimated as $f \times RR / (1 + f \times RR)$, where f is the frequency of the predictor (for continuous variables calculated as average exposure) and RR is the odds ratio for early statin discontinuation vs. continued use associated with the predictor relative to the reference.

Predictors of early discontinuation of antihypertensive medication and of early discontinuation of insulin use were also estimated among the 674 900 statin users, where 332 974 (84%) continued antihypertensive medication after the first antihypertensive prescription and 63 538 (16%) discontinued antihypertensive medication early; 37 344 (94%) continued insulin use after the first prescription for insulin and

2550 (6%) discontinued insulin use early. Odds ratios on logistic regression were from a model including negative, neutral, and positive statin-related news stories calculated during the first 6 months following initiation on the pharmaceutical drug in question, estimated equivalently as for initiation on a statin; odds ratios were adjusted for cardiovascular disease before the first dispense of the drug in question, diabetes before the first dispense of the drug in question, calendar year, percentage of the population on the drug in question, dose per pill of the first dispense of the drug in question, sex, age at start of therapy of the drug in question, geographical residency, highest obtained level of education, ethnic descent, and drug name of the first dispense of the drug in question.

For consequences of early statin discontinuation, we conducted a nested 5 : 1 matched study by selecting exactly five statin users with continued use at random for each statin user with early discontinuation evaluated at 6 months from start of statin therapy, matching on sex, age at initiation of statin therapy, ethnicity, calendar year, prior cardiovascular disease, prior diabetes, statin drug name, and statin dose per pill of the first statin dispense. Cumulative incidence curves were estimated by the method of Fine and Gray,²⁶ and compared with log-rank tests. Cox regression models using time after 6 months following start of statin therapy as time scale (Supplementary material online, Figure S1) calculated hazard ratios with 95% confidence intervals, adjusted for geographical residency and highest obtained level of education. All 508 800 statin users in the nested 5 : 1 matched study were followed

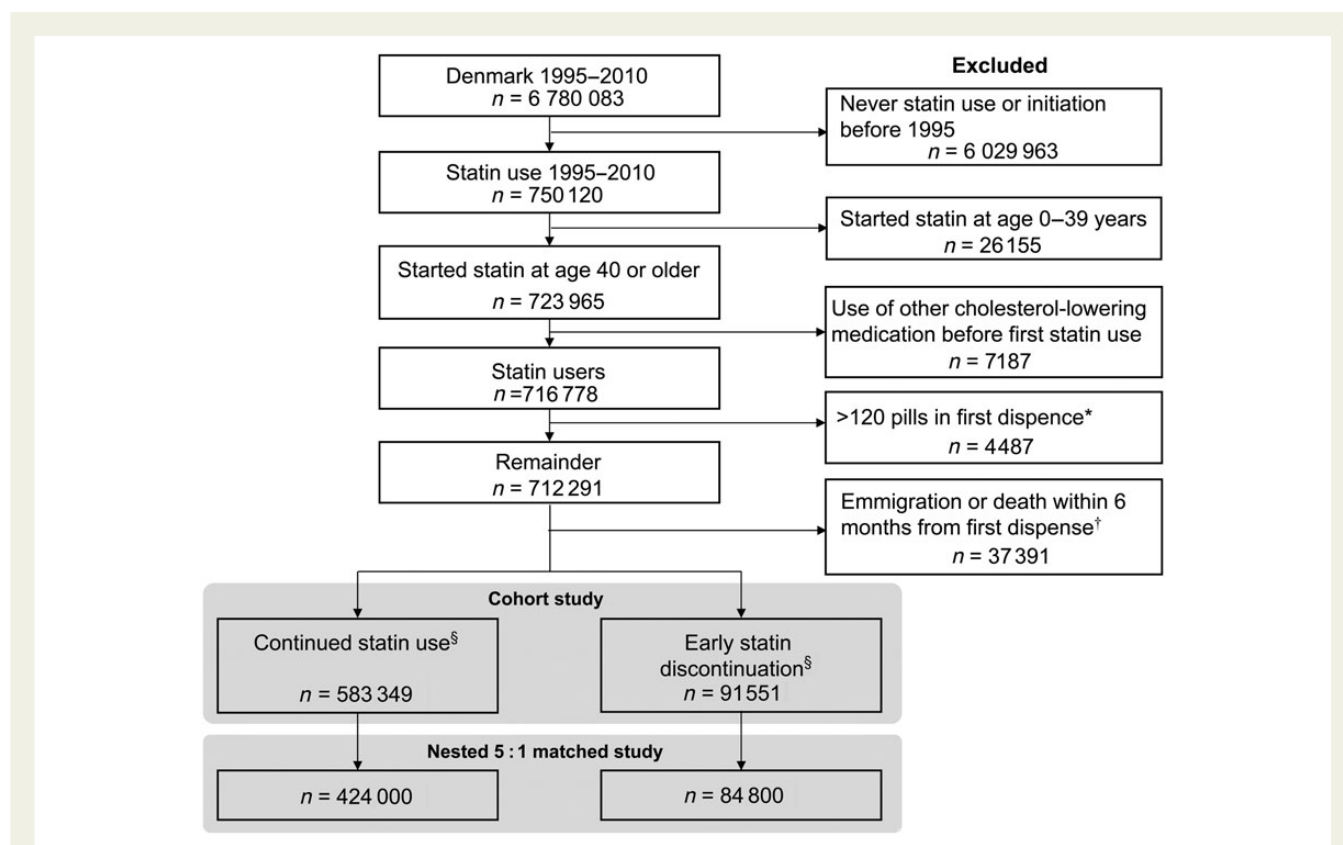


Figure 1 Selection of individuals on statin therapy aged 40 years or older in the entire Danish population entering into the study. *Individuals using > 120 pills in the first dispense of statin were excluded. †Early statin discontinuation was evaluated at 6 months after initiation of statin therapy, and individuals dying or emigrating during these 6 months were excluded. §Early statin discontinuation was evaluated at 6 months after initiation of statin therapy, and continued use was for individuals with at least one additional dispense of statin following the first dispense, where early statin discontinuation was for individuals with no new dispense of statin during those 6 months from initiation of statin therapy.

from 6 months after the start of statin therapy and forwards, censored at relevant endpoint, date of death ($n = 53\,937$), emigration ($n = 1684$), or 31 December 2011, whichever came first. Thus, competing risk of death and emigration was accounted for in the analysis by censoring at the date of death or emigration, information that are 100% complete in the Danish registries. Competing risk of death and emigration was also allowed for by calculating subhazard ratios using the method of Fine and Gray, using date of any cause of death as competing event for risk of myocardial infarction, or using date of any non-cardiovascular cause of death as competing event for risk of death from cardiovascular disease, while in both instances censoring at the date of emigration or 31 December 2011, whichever came first. For Cox proportional hazards regression analyses, we detected no major violations of the proportional hazards assumption.

Mediation analyses were conducted using a single-mediator model with negative statin-related news stories as the independent variable, early statin discontinuation as the mediator, and the relative risk of myocardial infarction as outcome. In this model, the mediated effect is the product of the β coefficient corresponding to the odds ratio for early discontinuation of statin per negative nationwide statin-related news and the β coefficient corresponding to the hazard ratio for risk of myocardial infarction per early discontinuation of statin.²⁷ The

corresponding confidence limits were estimated from the asymptotic standard error using the multivariate delta method.²⁸ The estimation of corresponding mediated effect of negative nationwide statin-related news stories on death from cardiovascular cause was calculated identically.

Results

We included all individuals aged 40 or older who started statin therapy during 1995–2010 in the entire Danish population, except those who used other cholesterol-lowering medication prior to statin use, those who received >120 pills in the first dispense, and those who died or emigrated during the 6 months following the first dispense of a statin (Figure 1, Supplementary material online, Figure S1). Of the 674 900 statin users included, 583 349 (86%) continued statin use, while 91 551 (14%) discontinued statin use early (Table 1).

Frequency of early statin discontinuation

The percentage of individuals in the entire Danish population aged 40 or older on statins increased from <1% in 1995 to 11% in 2010

Table 1 Characteristics of statin users with or without early statin discontinuation among individuals aged 40 years or older from the entire Danish population in 1995–2010

	Early statin discontinuation		P-value
	No	Yes	
Number of individuals	583 349	91 551	
Age at start of statin therapy, years (SD)	63 (10)	61 (11)	9×10^{-230}
Sex, n (%)			
Woman	300 302 (51%)	47 322 (52%)	0.29
Men	283 047 (49%)	44 229 (48%)	
Statin dose in first dispense, DDD (SD)	0.92 (0.43)	0.96 (0.44)	1×10^{-187}
Cardiovascular disease before first statin dispense, n (%)			
No	394 358 (68%)	69 595 (76%)	$<1 \times 10^{-300}$
Yes	188 991 (32%)	21 956 (24%)	
Diabetes mellitus before first statin dispense, n (%)			
No	481 829 (83%)	76 043 (83%)	0.03
Yes	101 520 (17%)	15 508 (17%)	
Size of residential area, n (%)			
<12 000 residents or rural	241 754 (41%)	36 135 (39%)	2×10^{-61}
12 000–100 000 residents	161 619 (28%)	24 002 (26%)	
>100 000 residents	179 969 (31%)	31 403 (34%)	
Highest level of education, n (%)			
Primary and high school	251 568 (43%)	37 267 (41%)	6×10^{-66}
Vocational training	208 783 (36%)	32 546 (36%)	
College degree	100 000 (17%)	17 243 (19%)	
Missing data	22 998 (4%)	4495 (5%)	
Ethnicity, n (%)			
Danish descent	552 622 (95%)	82 809 (90%)	1×10^{-96}
Other	30 727 (5%)	8742 (10%)	

DDD, defined daily dose; SD, standard deviation.

(Figure 2, top panel). In the same period, the percentage of early statin discontinuation among individuals initiated on statin therapy that year increased from 6% in 1995 to 18% in 2010 (Figure 2, middle panel). Finally, in Denmark, the number of negative, neutral, and positive statin-related news stories combined increased from 30 stories per year in 1995 to 400 in 2009 (Figure 2, bottom panel).

Predictors of early statin discontinuation

The multivariable adjusted odds ratio for early statin discontinuation vs. continued use were 1.09 (95% confidence interval, 1.06–1.12) for negative statin-related news stories, 1.04 (1.02–1.07) per increasing calendar year, 1.04 (1.02–1.06) per increasing defined daily dose of statin, 1.05 (1.03–1.06) for male sex, 1.13 (1.11–1.15) for living in cities, 1.67 (1.63–1.71) for other ethnicity than Danish, 0.92 (0.90–0.94) for positive statin-related news stories, 0.73 (0.72–0.74) for baseline cardiovascular disease, and 0.91 (0.90–0.93) for baseline diabetes (Figure 3). Early statin discontinuation was in the multivariable adjusted model not associated with neutral statin-related nationwide news stories, the percentage of the population on a statin, with age at the start of statin therapy, or with education.

Among significant predictors of early statin discontinuation, the population attributable risk for early statin discontinuation was 1.3% for negative statin-related news stories, 3.6% per increasing defined daily dose of statin, 2.5% for male sex, 4.2% for living in large cities with >100 000 residents, 3.7% for other ethnicity than

Danish, –5.3% for positive statin-related news stories, –9.3% for baseline cardiovascular disease, and –1.5% for baseline diabetes.

Consequences of early statin discontinuation

During 2 176 361 person-years (median follow-up 4.3 years, range 0–14) in the nested 5 : 1 matched study, 19 429 individuals developed myocardial infarction and 19 173 died from cardiovascular disease.

For myocardial infarction, the cumulative incidence as a function of years from 6 months after initiation on statin therapy was higher for individuals with early statin discontinuation compared with individuals with continued use (log-rank: $P = 2 \times 10^{-27}$; Figure 4, top panel). After 10 years of follow-up, 9.9 and 8.0% of those with early statin discontinuation and continued statin use had developed myocardial infarction. During follow-up, the multivariable adjusted hazard ratio for myocardial infarction was 1.26 (95% confidence interval, 1.21–1.30) for individuals with early statin discontinuation vs. individuals with continued use. The mediated effect from negative nationwide statin-related news stories through early statin discontinuation to risk of myocardial infarction was 1.02 (1.01–1.03).

For death from cardiovascular disease, the cumulative incidence as a function of years from 6 months after initiation on statin therapy was higher for individuals with early statin discontinuation compared with individuals with continued use (log-rank: $P = 3 \times 10^{-15}$; Figure 4, bottom panel). After 10 years of follow-up, 10.6 and 9.5% of those with early statin discontinuation and continued

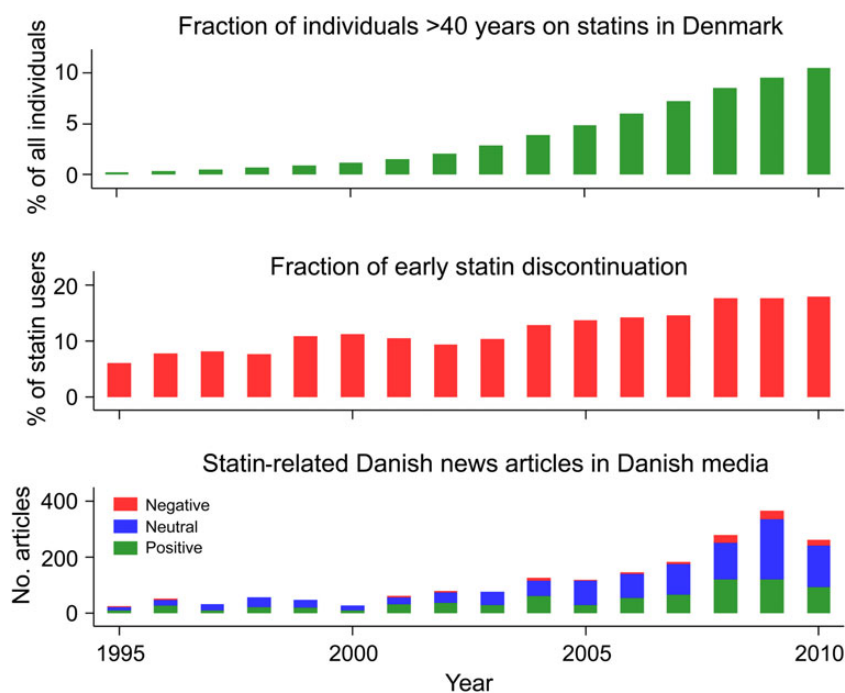


Figure 2 The percentage of individuals in the entire Danish population aged 40 or older on statins (top panel), the percentage discontinuing statin use within 6 months following start of statin therapy (middle panel), and the number of negative, neutral, and positive statin-related news stories published during 1995–2010 in Denmark. We studied all individuals on statins during 1995–2010 in the entire Danish population, comprising 583 349 (86%) who continued statin use and 91 551 (14%) who discontinued early.

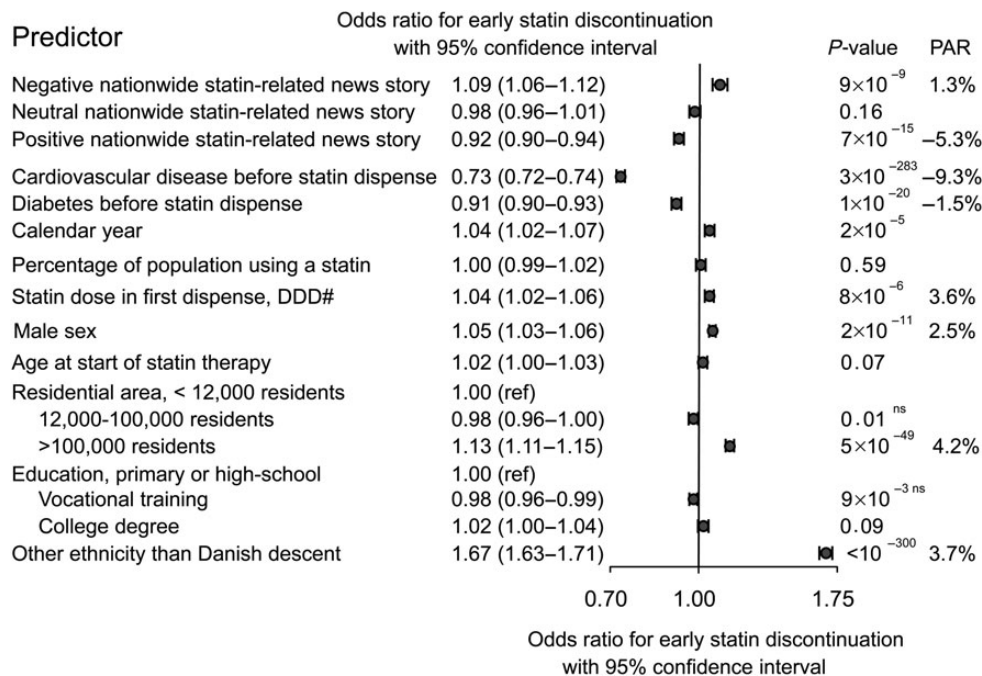


Figure 3 Predictors of early statin discontinuation. We studied all individuals initiated on statin therapy from 1995–2010 in the entire Danish population, comprising 583 349 (86%) who continued statin use and 91 551 (14%) who discontinued early. Odds ratios with 95% confidence intervals on logistic regression were from a model including negative, neutral, and positive statin-related news stories, cardiovascular disease before the first statin dispense, diabetes before the first statin dispense, calendar year, percentage of the population on a statin, statin dose per pill of the first statin dispense, sex, age at start of statin therapy, geographical residency, highest obtained level of education, and ethnic descent (95% Danish vs. 5% other); the missing indicator method was used to account for 4% missing information on education. Additionally, models were adjusted for statin drug name of the first statin dispense. ns = non-significant after correction for 15 multiple comparisons using the Bonferroni method (required P -value: $0.05/15 = 0.003$). PAR, population attributable risk for selected risk factors.

statin use had died from cardiovascular disease. During follow-up, the multivariable adjusted hazard ratio for death from cardiovascular disease was 1.18 (95% confidence interval, 1.14–1.23) for individuals with early statin discontinuation vs. individuals with continued use. The mediated effect from negative nationwide statin-related news stories through early statin discontinuation to risk of death from cardiovascular disease was 1.01 (1.01–1.02).

Sensitivity analyses

Negative statin-related news stories were associated with a multivariable adjusted odds ratio of 1.15 (95% confidence interval, 1.09–1.21) for early discontinuation of antihypertensive medication, while neutral and positive statin-related news stories were not associated with early discontinuation of antihypertensive medication among statin users (Figure 5). Neither negative, neutral, nor positive statin-related news stories were associated with early discontinuation of insulin use among statin users.

During follow-up in the nested 5 : 1 matched study, 216 individuals died from traffic-related causes with a trend towards higher risk for individuals with early statin discontinuation vs. individuals with continued use (log-rank: $P = 0.21$; Supplementary material online, Figure S5). Removing the statin-related news stories from the model, results for predictors of early statin discontinuation

were similar (compare Figure 3 with Supplementary material online, Figure S6).

Discussion

In this Danish nationwide study of all statin users aged 40 or older, early statin discontinuation increased with negative statin-related news stories, calendar year, statin dose, male sex, living in cities, and other ethnicity than Danish, while the opposite was true for positive statin-related news stories and baseline cardiovascular disease and diabetes. Early statin discontinuation was also associated with increased risk of myocardial infarction and death from cardiovascular disease.

Previous studies suggest that the decision to discontinue statin therapy after a first dispense can be attributed to the patients' experience of symptoms of statin intolerance or discomfort,^{2,5,7,10,29–31} medical history and current clinical presentation,^{10,19,32} socio-demographic status,^{12,13} and attitude towards statin therapy or pharmaceutical therapy in general.³³ Also, the decision to discontinue therapy may have been taken with or without the consultation of a medical doctor.¹⁰ Based on the available data in our study, it is not possible to account for all of these suggested predictors, or to infer any causality; nonetheless, our data suggest

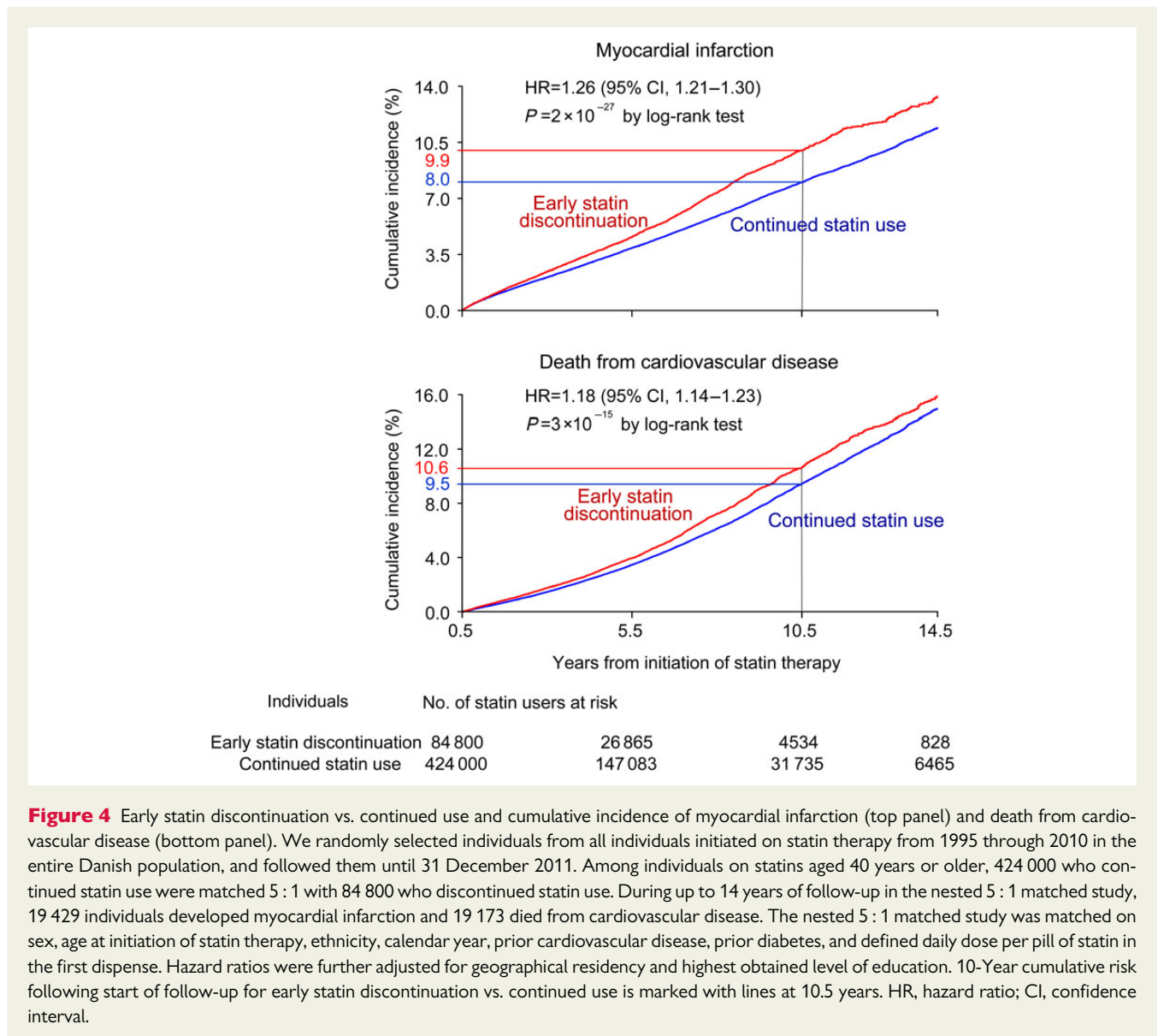


Figure 4 Early statin discontinuation vs. continued use and cumulative incidence of myocardial infarction (top panel) and death from cardiovascular disease (bottom panel). We randomly selected individuals from all individuals initiated on statin therapy from 1995 through 2010 in the entire Danish population, and followed them until 31 December 2011. Among individuals on statins aged 40 years or older, 424 000 who continued statin use were matched 5 : 1 with 84 800 who discontinued statin use. During up to 14 years of follow-up in the nested 5 : 1 matched study, 19 429 individuals developed myocardial infarction and 19 173 died from cardiovascular disease. The nested 5 : 1 matched study was matched on sex, age at initiation of statin therapy, ethnicity, calendar year, prior cardiovascular disease, prior diabetes, and defined daily dose per pill of statin in the first dispense. Hazard ratios were further adjusted for geographical residency and highest obtained level of education. 10-Year cumulative risk following start of follow-up for early statin discontinuation vs. continued use is marked with lines at 10.5 years. HR, hazard ratio; CI, confidence interval.

that media exposure during the early period following initiation on statin therapy may play a role in the patients' attitude towards statin therapy and thus the decision to discontinue or continue statin therapy.

Development of symptoms of statin intolerance or discomfort, in particular muscle-related side effects,⁹ has been reported to range from 10 to 29% among current statin users^{10,19,30,31} and is reported as the main reason for discontinuing statin therapy in up to 65% of former statin users.¹⁰ Mechanistically, statins down regulate the mevalonate pathway effectively lowering cholesterol, but also lowering other downstream products, such as isoprenoid intermediates and ubiquinone.^{5,34–36} Depletion of these metabolites leads to mitochondrial respiratory impairment and mitochondrial apoptosis, which is thought to be responsible for the development of muscle-related side effects,^{5,37} and which is consistent with our findings of a dose–response relationship between early statin discontinuation and statin dose.

Strengths of the present study include the large size of the study, including all individuals using statins in Denmark from 1995 through 2010, entering at the first dispense of a statin prescription. In Denmark, all dispenses of prescription-based medications are subsidized by the Danish government, monopolized by Danish pharmacies, and all such dispenses are recorded in the national Danish Registry of Medicinal Products Statistics. Furthermore, all Danish pharmacies are required by law to offer the least expensive product on the market, including generic variants with the same therapeutic effect. There is a copayment fee; however, there is a yearly ceiling on the total amount each individual can spend on all pharmaceuticals combined; thus, the individual copayment fee is down-regulated the more medication the individual purchases until it eventually disappears. As both the copayment is low, and likewise the payment ceiling, the economic incentive to either supply or buy statins elsewhere, e.g. online, is near non-existent. Thus, for all practical purposes, the records of the Danish Registry of Medicinal Products

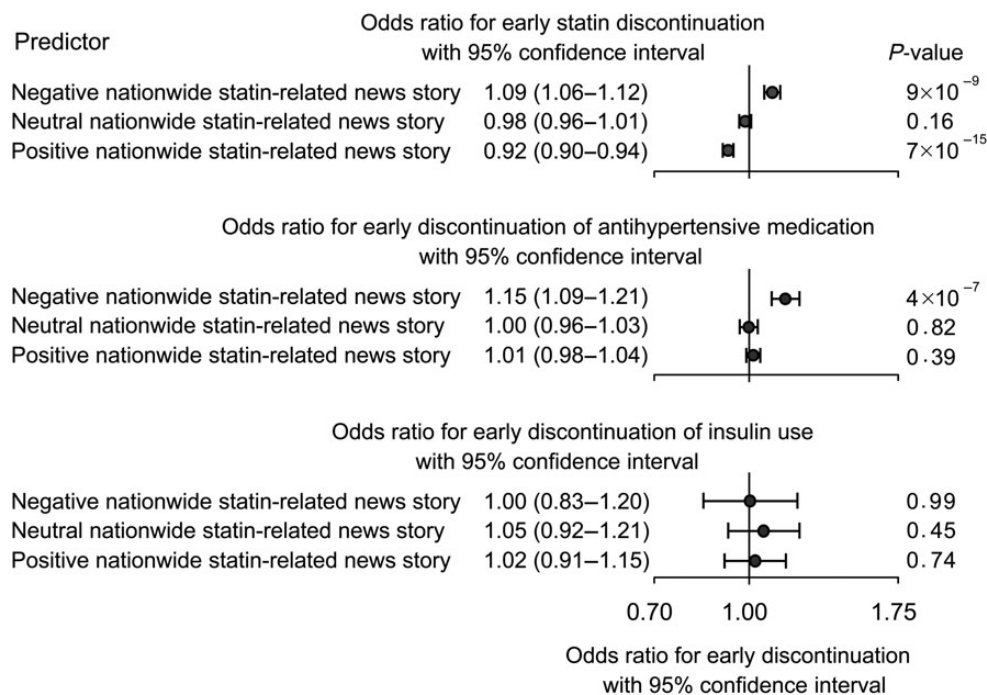


Figure 5 Statin-related news stories and early discontinuation of statin, antihypertensive medication, and use of insulin among statin users. We studied all individuals initiated on statin therapy from 1995 through 2010 in the entire Danish population comprising 674 900 individuals; of these, 583 349 (86%) continued statin after the first statin prescription, and 91 551 (14%) discontinued statin use early; 332 974 (84%) continued antihypertensive medication after the first antihypertensive prescription, and 63 538 (16%) discontinued antihypertensive medication early; 37 344 (94%) continued insulin use after the first prescription for insulin, and 2550 (6%) discontinued insulin use early. Odds ratios on logistic regression were from a model including negative, neutral, and positive statin-related news stories (calculated during the first 6 months following initiation on the pharmaceutical drug in question); cardiovascular disease before the first dispense of the drug in question; diabetes before the first dispense of the drug in question; calendar year; percentage of the population on the drug in question; dose per pill of the first dispense of the drug in question; sex; age at start of therapy of the drug in question; geographical residency; highest obtained level of education; and ethnic descent (95% Danish vs. 5% other); the missing indicator method was used to account for 4% missing information on education. Additionally, models were adjusted for drug name of the first dispense of the drug in question.

Statistics mirrors 100% the prescription-based medications dispensed over the counter in Denmark during the period of observation in this study. However, this also means that private economy usually do not play a major role in the decision to continue or discontinue treatment; thus, our findings for socio-demographic status may not necessarily be generalizable to other countries, unless such countries have health-care systems similar to the Danish. Theoretical possible limitations of our data include selection bias; however, as we included all individuals aged 40 or older ever taking statins in the entire Danish population, this is not an issue. Another potential limitation concerns the availability and completeness of the registry information; however, the national Danish Patient Registry captures 100% of all hospital visits in Denmark, and the national Danish Civil Registration System captures 100% of all deaths and emigrations. Additionally, as 95% of individuals were whites of Danish descent, our results for other ethnicity may simply reflect poorer integration of people of other ethnic descent in Denmark. Indeed, we are not aware of data to suggest that our main results should not be applicable to most races and countries, but they clearly illustrate excessive early statin discontinuation among immigrants in a European country. Another limitation is that early statin discontinuation may be a

marker of a 'healthy adherer effect'; a confounding behavioural characteristic of the individual impacting both statin adherence, but also on risk of myocardial infarction and death by cardiovascular disease beyond the effect of early statin discontinuation alone, as illustrated by a tendency towards increased risk of death by traffic-related causes.³⁸ Finally, bias by indication and residual confounding can never fully be excluded in this type of study, and therefore, great care should be taken in the interpretation of the present results.

In conclusion, early statin discontinuation increased with negative statin-related news stories, calendar year, statin dose, male sex, living in cities, and with other ethnicity than Danish, while the opposite was true for positive statin-related news stories and for baseline cardiovascular disease and diabetes. Early statin discontinuation was also associated with increased risk of myocardial infarction and death from cardiovascular disease. These findings suggest a need for protocols aimed at increasing early adherence to statin therapy.

Authors' contributions

S.F.N. performed statistical analysis. S.F.N. and B.G.N. handled funding and supervision ; S.F.N. acquired the data. S.F.N. and B.G.N.

conceived and designed the research. S.F.N. obtained permissions to access data records and gathered and analysed the data. B.G.N. oversaw all analyses and contributed to the interpretation of data. S.F.N. wrote the first draft of the paper. B.G.N. edited the paper and both authors approved this paper in its final form.

Supplementary material

Supplementary Material is available at *European Heart Journal* online.

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