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Association Between Statin Use and Cardiovascular Mortality at the Population Level

An Ecologic Study

Maarten J. Bijlsma,^a Fanny Janssen,^{b,c} Jens Bos,^a Pieter W. Kamphuisen,^d Stijn Vansteelandt,^e and Eelko Hak^a

Background: We assessed the contribution of statin use to the decline in cardiovascular mortality for The Netherlands over the period 1994–2010.

Methods: We combined aggregated mortality data from Statistics Netherlands with dispensing data from a representative drug dispensing database. We estimated mortality as if prevalence of statin use had remained at its observed 1994 levels throughout the period 1994–2010 for acute myocardial infarction, other ischemic heart disease, and cerebrovascular disease using Poisson models adjusted for various confounders.

Results: We estimated that keeping prevalence of statin use at observed 1994 levels would have resulted in 6.3 (95% confidence interval [CI] = 4.9, 7.8), 1.6 (95% CI = 0.8, 2.6), and 3.4 (95% CI = 2.2, 4.6) more acute myocardial infarction, ischemic heart disease, and cerebrovascular deaths per 10,000 person-years, respectively.

Conclusion: The findings indicate that statin therapy was associated with decreasing national cardiovascular mortality rates in the period 1994 to 2010.

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Cardiovascular disease is a major cause of death in both industrialized and developing countries and a threat to

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healthy aging.^{1–3} In much of the Western world, nationwide age-specific cardiovascular mortality has been declining steadily since 1970.⁴ There is ongoing debate about the role of several determinants of this decline. Lifestyle changes at the population level, such as changes in diet and smoking behavior, are important contributors.⁵ Also, improvements in, and wider application of, procedures such as coronary bypass artery grafting and percutaneous coronary intervention may be important.^{2,6,7} Finally, improved cardiovascular care with a wide arsenal of medicines aimed at preventing or treating cardiovascular disease such as thrombolysis, statins, ace-inhibitors, beta-blockers, and angiotensin receptor blockers may also have a major impact.^{8–10}

The effectiveness of statins in reducing the risk of cardiovascular disease in high-risk individuals was demonstrated in various clinical trials (e.g., 11–13). Because end-users potentially differ demographically and behaviorally from trial participants, observational studies that combine population level drug utilization data with (cause specific) mortality data can provide additional insights into the impact of pharmaceutical measures for society as a whole.

We investigate the association between statin use and cardiovascular mortality at the population level in The Netherlands from 1994 to 2010.

METHODS

Study Population

In this ecologic study, we used aggregate data based on individuals in The Netherlands ages 50–83 years during the study period 1994 to 2010. A large number of patients above age 84 years are dispensed drugs from institutional pharmacies and hence their drug utilization histories are not fully recorded in the dispensing database used for this study. This makes estimation of prevalence of drug use less valid above age 84 years.¹⁴ Approval from an institutional review board was not required to perform this study.

Primary Exposure

Statin use is our primary exposure. Information on person-years at risk of prescription was obtained from Statistics Netherlands. In the study period and age range, Statistics

Netherlands covers on average 5 million individuals annually. Data on statin use were received from the Dutch drug dispensing data base IADB.nl, which contains information from 55 community pharmacies in The Netherlands, covering on average 500,000 persons annually.¹⁴ The database is representative for The Netherlands and has been used in previous studies on statin use.^{15,16} In The Netherlands, statin therapy first started around 1994 and cannot be received over the counter. Individuals were considered users of statins in a half-year period if they received at least one prescription for statins (anatomic-therapeutic-chemical [ATC]-code C10AA) in that period. We calculated prevalence of statin use by dividing the number of users of statins by the person-years at risk of prescription.

Outcome Measure

The primary outcome measure of this study is the count of mortality due to acute myocardial infarction (AMI; ICD9 code 410; ICD10 code I21).^{17,18} We also studied mortality due to other ischemic heart diseases (other IHD; ICD9 codes 411–414; ICD10 codes I20, I22–I25) and cerebrovascular disease (ICD9 codes 430–438; ICD10 codes I60–I69).^{17,18} We refer to these three outcomes together as cardiovascular disease mortality. These data were obtained from Statistics Netherlands by 5-year age and half-year period and by 2-year age and 1-year period.¹⁹ We tabulated this into 2-year age by half-year period using linear interpolation. Cause-specific mortality rates were obtained by dividing these numbers of deaths by person-years at risk.

Covariates

We predefined potential confounders for the association between prevalence of statin use and cardiovascular mortality. These were prevalence of other cardiovascular drug use, diabetes, birth cohort, age, and sex. Other cardiovascular drugs we included were prevalence of antithrombotic agents (ATC code B01), ACE inhibitors (ATC codes C09AA, C09BA, and C09BB), angiotensin receptor blockers (ATC codes C09C and C09D), calcium channel blockers (ATC code C08), beta blockers (ATC code C07), diuretics (ATC code C03; this category includes important antihypertensives), fibrates (ATC code C10AB), nitrates (ATC code C01AD), and cardiac glycosides (ATC code C01A). Individuals were considered users of a drug in a half-year period if they received at least one prescription for that drug in that period. Patients who received at least one prescription for blood glucose lowering drugs (ATC codes A10A or A10B) were considered diabetic patients. As also nondiabetic patients may receive insulins (ATC code A10A), patients who were only prescribed insulins were not considered diabetic patients. We calculated the prevalence of users of each drug in a half-year period by dividing the number of users by the person-years at risk in that respective half-year period.

Analysis

To assess the association between cause-specific mortality and statin prevalence, we fitted a Poisson regression model with the number of deaths due to a given cause (AMI, other

IHD, or cerebrovascular disease) in a half-year period as the outcome variable and the natural log of person-years at risk as an offset variable. Covariates in this model were prevalence of statin use, 2-year age category (50–51, 52–53, ..., 82–83), 4-year birth cohort (1916–1919, 1920–1924, ..., 1956–1959), sex, prevalence of diabetes, and other cardiovascular drug use. As a sensitivity analysis, we also evaluated a model with a 2-year lag between mortality and statin use, and a model with an additional linear time trend to adjust for other (unmeasured) factors that may have changed linearly over time (see eAppendix section 3 and eTables 9–14; <http://links.lww.com/EDE/A962>).

To determine the association of statin use with decline in cardiovascular mortality in The Netherlands in the period 1994–2010, we calculated excess mortality.²⁰ That is, while letting other covariates change as empirically observed, we predicted mortality as if prevalence of statin use had remained at its 1994 level, and subtracted this from predicted mortality in the model where also prevalence of statin use was allowed to change as observed (eAppendix section 2; <http://links.lww.com/EDE/A962>). Excess mortality was divided by observed person-years at risk so as to make the results more readily interpretable.

RESULTS

Association Between Statin Use and Cardiovascular Mortality Decline

Adjusting for age, sex, birth cohort, other drug use, and diabetes, an increase in statin use which amounts to 100 per 10,000 person-years in a half-year period was associated with a 1.6% decrease in the number of individuals that would die of AMI in that half-year period (95% confidence interval [CI]: 1.3%, 1.8%). There was a corresponding 1.1% (95% CI = 0.7%, 1.6%) decrease in mortality due to other IHD and a 1.2% (95% CI = 0.9%, 1.5%) decrease in cerebrovascular mortality. These effect estimates became somewhat stronger if we allowed for a 2-year lag between statin use and cardiovascular mortality, and if we took into account linear decline in cardiovascular mortality over time (eAppendix section 3; <http://links.lww.com/EDE/A962>). The results of our analysis did not substantially change when the definition of diabetes also included insulin-only users.

Statin Use and Mortality Decline

In the study population, prevalence of statin use increased from 439.8 users per 10,000 person-years in 1994 to 2,653.9 users per 10,000 person-years in 2010, with simvastatin (ATC code C10AA01) as the most often prescribed statin. The cardiovascular mortality rate changed from 54.2 deaths per 10,000 person-years in 1994 to 20.0 deaths per 10,000 person-years in 2010. Keeping prevalence of statin use at the observed 1994 levels, the AMI mortality rate over the study period was predicted to have been on average 6.3 deaths per 10,000 person-years higher (95% CI = 4.9, 7.8; Figure).

FIGURE. Observed AMI mortality and predicted AMI mortality if prevalence of statin use had remained constant in The Netherlands in the period 1994–2010, ages 50 to 83 years.

For other IHD and cerebrovascular mortality, this was 1.6 (95% CI = 0.8, 2.6) and 3.4 (95% CI = 2.2, 4.6) per 10,000 person-years higher, respectively.

The eAppendix (Sections 4 and 5; <http://links.lww.com/EDE/A962>) includes more information on demographic composition of the Dutch population, changes in statin utilization, and (excess) cardiovascular mortality during the study period.

DISCUSSION

Many factors are believed to contribute to cardiovascular mortality decline. Nevertheless, it is noteworthy that our model predicts that keeping prevalence of statin use at its observed 1994 levels resulted in 6.3 more AMI deaths per 10,000 person-years during the study period. This is quite considerable, given that the observed AMI mortality rate in the study period was between 7.8 and 27.9 deaths per 10,000 person-years. The excess mortality of other IHD and cerebrovascular mortality is similarly considerable.

It should be noted that we did not adjust for changes in dosage or duration of use, because most of the patients using statins are chronic users and, on the population level, dosage did not change over time. In addition to the cardiovascular drugs, which we controlled for, another important factor that affects cardiovascular mortality and has changed over time during the study period is smoking. However, research indicates that smoking behavior is strongly tied to birth cohort,^{21–23} which was included in the study. Furthermore, many other factors may still contribute to changes in cardiovascular mortality, such as changes in dietary factors, physical activity, or changes in patient comorbidity profiles. From external sources, we found that alcohol consumption increased somewhat in early years but then remained stable (eAppendix section 8; <http://links.lww.com/EDE/A962>). Overweight increased over time, but this development would be expected to increase cardiovascular mortality and thereby weaken the parameter estimates of cardiovascular drugs (eAppendix section 7; <http://links.lww.com/EDE/A962>). In a

sensitivity analysis, we added a linear term for time to correct for the influence of such potential unmeasured confounders, but some residual bias may remain from unmeasured confounders that changed in a nonlinear manner. Our estimates may be subject to bias resulting from the use of aggregated data because of the ecologic fallacy and, for the analysis with 2-year lagged mortality, the fact that the population composition may have changed gradually in the 2-year time period. Therefore, while we seek to approximate the causal effect of statin prevalence on cardiovascular mortality, the estimates should be seen as associations. It is unlikely that our findings are distorted by competing risks because there is currently no evidence that statins strongly increase mortality due to non-cardiovascular causes.

A Cochrane review of trial evidence indicated that statins are protective against fatal cardiovascular events (risk ratio: 0.83, 95% CI = 0.72, 0.96), although not against fatal stroke (risk ratio: 0.61, 95% CI = 0.18, 2.23).¹³ However, in our study, the percentage reduction in mortality that we found associated with an increase in statin prevalence cannot be directly compared with results from clinical trials. This is because of the nature of the data and the consequent difference in explanatory variables. Where clinical trials and some observational studies compare the hazard of mortality between users and nonusers of statins, we investigated the relationship between prevalence of statin use in a group of patients and the cardiovascular mortality rate in that group. This was done to find evidence of the impact of statins on cardiovascular mortality at the population level, because end-users potentially differ demographically and behaviorally from trial participants. The findings from our study indicate that statin therapy was strongly associated with decreased national cardiovascular mortality rates in the period 1994 to 2010.

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