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Impact of Incident Diabetes on Atherosclerotic Cardiovascular Disease According to Statin Use History among Postmenopausal Women

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Abstract

Objective—To compare impact of incident diabetes on atherosclerotic cardiovascular disease (ASCVD) risk among postmenopausal women according to statin use.

Research Design and Methods—Prospective data from 120,499 postmenopausal women without prevalent diabetes or cardiovascular disease at baseline from the Women's Health Initiative (WHI) were used. Incident diabetes was self-reported annually and defined as treatment with pills or injectable medication for diabetes. Current statin use was determined at enrollment and years 1, 3, 6, 9 and 13.5 in the three clinical trial arms, and at baseline, year 3, and 13.5 for the observational study. The primary outcome was incident ASCVD events, self-reported annually and adjudicated by blinded local and central physicians. Incident diabetes and statin use status were fitted as time-varying covariates in Cox regression models to assess ASCVD risk during an average follow-up of 13.6 years.

Results—For those not on statins at the time of diabetes diagnosis, there was a 42% increased risk of ASCVD [hazard ratio (HR)=1.42, 95% CI, 1.28–1.58] among women with incident diabetes vs. those without diabetes. Among women on statins, there was a 39% increased risk of ASCVD (HR=1.39, 95% CI, 1.12–1.74) in women with incident diabetes vs. those without diabetes. The increased ASCVD risk due to diabetes was similar between women before or after initiating statins (p=0.89).

Conclusions—Whether diabetes was diagnosed before or after statin use did not alter the increased risk of ASCVD associated with diabetes. Mitigating the increased incidence of diabetes in statin users could increase the ASCVD benefit-to-risk ratio of statins.

Keywords
epidemiology; diabetes; drug-related problem; cardiovascular disease

Presence of diabetes is a strong predictor of primary atherosclerotic cardiovascular disease (ASCVD) events (1–3). The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines (4) and the 2015 American Diabetes Association guidelines reflect ample evidence that statin therapy decreases ASCVD events in individuals with and without diabetes(5). However, statin use also has been shown to increase risk for new-onset diabetes by 9–13%(6–9), correlating with dose intensity(10) and with pre-existing risk status(7,8,11,12).

Though adequate information exists concerning ASCVD risk in women with existing diabetes(1), less is known about ASCVD risk among women who newly develop diabetes before or after initiation of statins. It is possible that clinical diabetes after statin initiation may be milder due to a shorter duration and earlier diagnosis or that the adverse effect of diabetes on ASCVD may be blunted by concurrent statin use. In attempt to clarify this issue,
we estimated diabetes-associated risk of ASCVD events relative to statin use in an established prospective cohort of postmenopausal women.

RESEARCH DESIGN AND METHODS

Participants

The Women’s Health Initiative (WHI) recruited community dwelling postmenopausal women (N=161,808) aged 50–79 at 40 clinical centers across the U.S. from 1993 to 1998 with ongoing follow-up. Of these, 68,132 participants were enrolled in up to three randomized controlled clinical trials (CT) of hormones, diet, or calcium/vitamin D supplements, and 93,676 women were enrolled in the observational study (OS)(13). The original period of follow-up ended in 2005. The analysis herein used WHI data obtained during the original follow-up as well as during an extension through September 30, 2010. Of women followed through 2005, 77% re-enrolled in the extension and were followed through 2010. After exclusion for prevalent diabetes, baseline self-report for CVD, and anytime use of cerivastatin, 120,499 women were included in the present analysis (Flow Chart Figure 1).

Identification of diabetes

Prevalent diabetes at baseline was defined as a self-report of ever having received a physician’s diagnosis of diabetes when not pregnant. Incident diabetes status was ascertained by self-report annually; women were identified as diabetic if they reported being newly treated with medication for diabetes since their last health assessment. Self-reported diabetes has been shown to be a valid indicator for diabetes diagnosis in the WHI (14,15).

Assessment of statin medication use

The medication regimens of all CT participants were inventoried at baseline, year 1, 3, 6, and 9 visits, and during the extension [years 10–15 (median 13.5)]. The product name of the medication was entered into the database and matched to the corresponding item in the Master Drug Data Base (MDDB: Medi-Span, Indianapolis, IN). In the OS, medication data were collected at baseline, year 3, and during the extension. For some analyses, statin use was categorized by potency into low (fluvastatin, pravastatin, lovastatin) or high (simvastatin, atorvastatin, rosuvastatin).

Identification of ASCVD, MI, stroke, and CVD death

Primary total ASCVD was the main study endpoint in this analysis. Myocardial infarction (MI), stroke, and coronary heart disease (CHD) deaths were secondary endpoints in the present analysis. Each of these endpoints are also WHI primary outcomes, determined by the collection of medical records, and adjudicated by blinded local and central physician review. Total ASCVD was derived from the 2013 ACC/AHA definition as nonfatal MI or CHD death, or fatal or non-fatal stroke(4). The MI and stroke variables were both defined as fatal or non-fatal, and CVD death was classified as death from CHD or stroke. Time to first event was modeled; repeated events were not used.
Covariates

Demographic and medical health history data were self-reported at baseline. All participants completed a standardized Food Frequency Questionnaire developed for the WHI to estimate average daily nutrient intake over the three-month period prior to enrollment (16). The Healthy Eating Index was calculated to measure overall diet quality (17–21) and was included in the analyses.

Total recreational physical activity energy expenditure was summarized in metabolic equivalent hours per week (MET-hr/wk) computed as the summed product of frequency, duration, and intensity for activities reported on a self-administered questionnaire. WHI-certified staff measured resting blood pressure by auscultation methods, and body weight, height, and waist circumference according to standardized clinical anthropometric procedures. Body mass index (BMI, kg/m\(^2\)) was computed from measured height and weight. Fasting concentrations for lipids, glucose, and insulin were available at baseline for a subset of approximately 20% of the women. These measures are reported descriptively but were not used in the main analyses because of inadequate statistical power.

Statistical analysis

Statin use was summarized at each observation time (baseline, 1 year, 3 years, 6 years, 9 years, and during extension). For descriptive purposes, participant characteristics were summarized (means and standard deviations or counts and percentages) overall, by statin use (never, ever), and by diabetes status during the study (no, yes).

For modeling purposes, five diabetes and statin states were defined (Figure 2): (a) No Diabetes and No Statin Use, (b) Diabetes but No Statin Use, (c) No Diabetes but Statin Use, (d) Statin Use followed by Diabetes, and (e) Diabetes followed by Statin Use. State membership was time-dependent, potentially changing at each visit as statin use and diabetes status were updated. Arrows in the directed graph (Figure 2) indicate the possible transitions: (a) to (b); (a) to (c); (b) to (e); and (c) to (d). Note that women can return neither from Statin Use to No Statin Use, nor from Diabetes to No Diabetes.

Four outcome variables were investigated: total ASCVD as main study endpoint, MI, stroke, and CVD death as separate secondary endpoints. Proportional hazard regression models (22,23) with time-dependent covariates were used to estimate the association of diabetes with total ASCVD (and associated 95% confidence intervals) as a function of statin use at time of diagnosis. The associations were estimated by including in a single model terms for statin use, diabetes diagnosis before statin use, and diabetes diagnosis after statin use:

\[
\log(h(t|Z(t))) = \log(h_0(t)) + \beta_S S(t) + \beta_{DBS} DBS(t) + \beta_{DAS} DAS(t)
\]

where \(h_0(t)\) was an unspecified baseline hazard function, \(S(t)\) indicated whether a statin was initiated prior to time \(t\), \(DBS(t)\) indicated whether diabetes was diagnosed prior to time \(t\) and before statin initiation (if any), and \(DAS(t)\) indicated whether diabetes was diagnosed prior to time \(t\) and after statin initiation. The parameter \(\beta_{DBS}\) was the log hazard ratio primarily comparing the event rates from states (b) to (a). The parameter \(\beta_{DAS}\) was the log hazard
ratio primarily comparing the event rates from states (d) to (c). Group (e) provided additional information for estimating $\beta_{DBS}$ and $\beta_S$. The primary comparison of the two diabetes effects, $\beta_{DBS}$ and $\beta_{DAS}$, i.e., diabetes diagnosis before statin initiation and diabetes diagnosis after statin initiation, were compared using a likelihood ratio test. Multivariable-adjusted analyses were conducted including the following covariates: age, race/ethnicity, education, region, cigarette smoking, BMI, physical activity, alcohol intake, healthy eating index, medical history of hypertension, systolic blood pressure, family history of cardiovascular disease, hormone therapy use, and study arms in the models. Similar analyses were conducted separately for the other three outcomes. Because abdominal obesity (waist circumference >88 cm) can influence ASCVD risk prior to diagnosis of clinical diabetes or statin initiation(24, 25), analyses were also stratified by waist circumference.

Models were used to estimate 10-year rates of the four outcomes for typical covariate values (median values for continuous covariates and modal values for categorical covariates) for five hypothetical women representing the five states (a–e).

Sensitivity analyses were conducted to probe the robustness of the results, as follows: 1) each woman was censored 3 years after last available medication data collection, 2) each woman with diabetes onset before statin use was censored at the time of any later statin use, i.e., upon entry to state (e), 3) each woman reporting no statin use subsequent to reporting statin use was censored for non-adherence, and 4) women taking a statin at baseline were excluded. The adjusted proportional hazard regression models were also refit with weights determined by propensity scores for baseline statin use. Variables included in the propensity score model were age, race/ethnicity, education, region, cigarette smoking, BMI, physical activity, alcohol intake, healthy eating index, medical history of hypertension, systolic blood pressure, family history of cardiovascular disease, hormone therapy use, and study arms. To further understand the influence of statin use on diabetes-associated ASCVD risk, we also conducted an analysis using duration-adjusted statin data and an analysis by statin potency defined according to statin agents as low (fluvastatin, pravastatin, lovastatin) or high (simvastatin, atorvastatin, rosuvastatin). Finally we repeated the analysis using only the CT data. Analyses were performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC) and/or R software (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participant Characteristics

Use of statin medication demonstrated a substantial upward trend from baseline (1993–1998) through extension 1 (2010) of the OS and CT arms, following similar national trends (Appendix Table 1). Table 1 lists the baseline participants' characteristics for the overall sample and according to statin use at any time and post-baseline incident diabetes status during follow-up through 2010. At baseline, women who used a statin at some point were similar in age to those who did not use statins [62.4 years (n=39,432) versus 62.7 years (n=81,067)]. However, those who used statins had a higher mean BMI [28.2 versus 27.3 kg/m²] and waist circumference (87.0 vs. 84.5 cm), and higher prevalence of treated hypertension (26.3% vs. 18.4%) and family history of CVD (69% vs. 62%) as compared to
those who did not use statins. Based on the subset of women with information on biomarkers at baseline, a more adverse lipid profile was seen in women who used statins compared to those who did not (e.g., mean LDL 160.8 mg/dl vs. 139.0 mg/dl).

Regardless of statin use, women who developed post-baseline diabetes had significantly more adverse risk profiles for ASCVD than women who did not develop diabetes, such as a higher mean BMI (31.1 vs. 27.2 kg/m²) and waist circumference (94.4 vs. 84.4 cm). Compared to women who did not develop diabetes, those with incidence diabetes had a higher percentage of hypertension treatment (33.9% vs. 19.7%), family history of CVD (67.4% vs. 64.1%), family history of diabetes (46.0% vs. 28.4%), current smoking (8.0% vs. 6.8%), and more adverse glucose homeostasis markers (e.g., mean fasting glucose 115.3 vs. 93.2 mg/dl).

Appendix Table 2 shows baseline characteristics of each of the five states defined by diabetes incidence and statin use. Waist circumference and BMI were higher in groups who developed diabetes but not higher in statin users than in non-users who did not develop diabetes. Physical activity levels (MET-hrs/week) were lower, while family history of diabetes was higher in groups that developed diabetes. Prevalent treated hypertension was also higher in the groups that developed diabetes or used statins compared to their respective counterparts. The biomarker subset indicated that dyslipidemia and dysglycemia was particularly prevalent at baseline in women who developed incident diabetes during follow-up. Compared to the women who did not develop diabetes or use statins, all the groups who developed diabetes were more likely to have markers of insulin resistance (higher fasting glucose and insulin, higher HOMA-IR), irrespective of statin use. This was not seen in women who used statins but did not develop diabetes. Likewise, women who developed incident diabetes had lower HDL and higher triglycerides, regardless of statin use; Women who received statins were distinguished by a higher baseline LDL. Taken together, the data suggest an increased prevalence of metabolic syndrome in these women at baseline.

**Diabetes and ASCVD Outcomes Relative to Statin Use (Table 2)**

During an average of 13.5 years of follow-up, 2,471 (2.1%) women were diagnosed with incident diabetes after taking a statin, 8,518 (7.1%) women developed diabetes before taking a statin, and 109,510 (90.9%) women did not develop diabetes regardless of statin status (Figure 1). The mean and median time to diabetes diagnosis among women without statin use at baseline (n= 10,098) was 393 (SD=198) weeks (median: 393 weeks or 7.6 years), and in women taking statins at baseline (n=891), it was 389 (SD=197) weeks (median: 391 or 7.5 years). The difference in medians was not statistically significant. In multivariable-adjusted analyses, there was a 42% increase in risk of total ASCVD for women with incident diabetes compared to women without diabetes (HR=1.42, 95% CI, 1.28–1.58) among women who did not use statins, and a 39% increase in risk of ASCVD in women with incident diabetes compared to those without diabetes (HR=1.39, 95% CI, 1.12–1.74) among women who used statins. The increased risk of ASCVD associated with diabetes was similar between women with diabetes diagnosis before or after initiating statin use (p=0.89). When we stratified the analyses by waist circumference (<85 cm vs. ≥85 cm, Appendix Table 3) at baseline, the ASCVD risk was markedly increased for the subset with higher waist
circumference in both primary exposure groups shown in Table 2. Conversely, the subgroup with waist circumference <85 cm shows little increased risk for ASCVD.

Similar hazard ratios were observed when MI, stroke, and CVD death were analyzed as separate outcomes. Weighting by propensity score for baseline statin use decreased the ASCVD hazard ratios associated with incident diabetes following statin initiation but these risks did not differ between women whose diabetes developed prior to or after statin use. The four pre-specified sensitivity analyses yielded findings that were materially comparable with the main results (Table 2 and Appendix Table 4).

Additional analyses were conducted attempting to account for duration of statin use (Appendix Table 5). Although these analyses gave higher hazard ratio estimates for diabetes-associated risks of ASCVD, these risks did not differ between women whose diabetes developed prior to or after statin use. Similarly, though the ASCVD risks associated with incident diabetes in women using statins were highest for high potency statins, these risks did not differ significantly from the risks in women using low potency statins (Appendix Table 6).

Based on the multivariable-adjusted Cox regression models derived from our study cohort, we computed absolute 10-year risks (per 1,000 person-years) of ASCVD, MI, stroke, and CVD death for five hypothetical women representing the five states based on incident diabetes and statin use described previously (Figure 3). All groups with incident diabetes had an increased risk of ACVD, MI, stroke, and CVD death. Groups using statins had a lower risk of ASCVD than respective counterpart groups not receiving statins, irrespective of incident diabetes status. The near equal absolute 10-year risks for ASCVD in the last two groups (i.e., d and e) reflect the equal ASCVD effects of incident diabetes regardless of its occurrence before or after initiating statin use. Much of the lower risk of ASCVD associated with statins appeared to be related to stroke risk reduction whereas a reduction in MI was not seen.

DISCUSSION

The major finding in this large prospective observational study on community-dwelling postmenopausal women was that regardless of statin use, postmenopausal women with new-onset diabetes had a significantly increased risk of ASCVD. Similar results were seen for MI, stroke, and CVD death when analyzed as separate endpoints. Whether the diabetes emerged before or after statin use, the magnitude of ASCVD risk associated with incident diabetes was considerably smaller than the previously reported 2–3 fold higher ASCVD risk associated with the diabetes status(1–3). In those previous studies, diabetes may have been present for many years prior to the ASCVD event, while in the present study ASCVD risks were examined during a relatively short period after incident diabetes diagnosis during follow-up for ASCVD events. Importantly, when interpreting the present results, one should be mindful that our observational study analysis does not directly estimate the efficacy of statins on ASCVD risk in those with and without diabetes, for which the clinical trials are a superior source of information. Nevertheless, given the increasing prevalence of diabetes among older adults and the projected growth of this population subgroup, the present
findings highlight the relevance of mitigating diabetes-related ASCVD risk seen with statin use at advanced ages.

Sex-specific risks and benefits for statins have been controversial (26,27). A recent large meta-analysis of clinical trials using individual data found that CVD benefits were driven by baseline risk and LDL reduction, not by sex (28). Given the clinical trial data, 1000 women with a 10% 10-year risk of CVD treated with statins would show an observed net ~20% reduction in CVD event rates, or 20 events (100 minus 80) (26,27). This net reduction would be higher if not for a differential increase in subsequent diabetes-associated risk of ~10% with statin use (6). Assuming that ~100 women would have developed diabetes without statins over 10 years, ~10 extra cases of incident diabetes would be diagnosed after statin use. According to the current study, diabetes would confer a 40% increase in ASCVD compared to no diabetes. Thus, among the 10 extra cases of diabetes, rather than 1 case of ASCVD over 10 years there would be 1.4 cases, i.e., an excess of 0.4 cases with statin use. Hence, the net reduction might have been 20.4 CVD events (20 plus 0.4) were it not for incident diabetes after statin use (26,27). When considered at the population level, this projection has considerable public health relevance as the number of older postmenopausal women increases over coming decades, paralleled by increases in diabetes prevalence and statin use. Statin-associated diabetes would be expected to blunt but not eliminate the CVD benefit observed with statin use. Our findings underscore the importance of prevention, monitoring, and detection of diabetes among post-menopausal women, and perhaps especially among those who take statin medication.

The results of the present study, while complementing findings of some published randomized trials, are also limited by the observational design and lack of detailed data for both statin use patterns and diabetes/glycemic control which complicates interpretation of these findings. We had incomplete baseline data on blood lipids and glucose measures prior to statin initiation or diabetes incidence and no data on these measures during follow-up, and we acknowledge the limitation that blood lipids, glucose and insulin measures were not included in adjusted analyses. Some misclassification of incident diabetes in relation to statin initiation would have occurred, particularly since we considered only cases of diabetes diagnosis and did not take into account diabetes that would have been diagnosed based on blood glucose values only. Given the consistency of findings in our primary analyses and sensitivity models, it is not likely that such misclassification fully accounts for the study results. We were unable to fully account for statin duration, nor for dose and adherence. Pharmacogenomics and interactions were not assessed. However, findings from sensitivity analyses to probe the potential influence of duration and potency of statins did not differ from those for the primary analyses. Finally, we note a limitation that medication use of all CT participants were inventoried on 6 occasions at baseline, year 1, 3, 6, and 9 visits, and during the extension [years 10–15 (median 13.5)]; while in the OS, medication data were collected on only 3 occasions at baseline, year 3, and during the extension. We conducted an additional sensitivity analysis including participants in CT only; results are similar to the main results presented in the manuscript. We, therefore, believe that our results are robust. In addition, the combined sample of CT and OS increased statistical power to detect the associations especially for secondary endpoints: MI, stroke, and CVD death.
Strengths of our study include the large study cohort and lengthy follow-up interval with sufficient endpoint events for the complex multivariable-adjusted and stratified analyses reported herein, and evaluation of statin use among a race-ethnically diverse cohort of postmenopausal women with a relatively wide age range at baseline. The WHI program provides ASCVD outcomes that are centrally adjudicated by a standardized protocol. The use of propensity score analyses and several additional sensitivity and stratified analyses allowed for evaluation of potential confounders and effect modifiers in a comprehensive manner within the constraints of the observational study design and available data.

In conclusion, a similar increase in risk for primary ASCVD events associated with diabetes was seen in older postmenopausal women, regardless of whether incident diabetes diagnosis occurred before or after initiation of statin use. Much of the incident diabetes seems to occur in those with markers of metabolic syndrome at baseline. These findings suggest that mitigating development of diabetes has an important role in the scope of primary ASCVD prevention among older postmenopausal women.

Acknowledgments


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Appendix

Appendix Table 1

Frequency of statin use at baseline and follow-up, Women’s Health Initiative

<table>
<thead>
<tr>
<th>Statin use</th>
<th>N</th>
<th>%</th>
<th>Study Sample Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td></td>
<td></td>
<td>OS and CT</td>
</tr>
<tr>
<td>No</td>
<td>113,879</td>
<td>94.5</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6,620</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>At year 1</td>
<td></td>
<td></td>
<td>CT only</td>
</tr>
<tr>
<td>No</td>
<td>45,322</td>
<td>93.5</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3,141</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>At year 3</td>
<td></td>
<td></td>
<td>OS and CT</td>
</tr>
<tr>
<td>No</td>
<td>93,826</td>
<td>88.4</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12,344</td>
<td>11.6</td>
<td></td>
</tr>
<tr>
<td>At year 6</td>
<td></td>
<td></td>
<td>CT only</td>
</tr>
<tr>
<td>No</td>
<td>36,412</td>
<td>81.2</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8,423</td>
<td>18.8</td>
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### Statin use

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Study Sample Included</th>
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</thead>
<tbody>
<tr>
<td><strong>At year 9</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>7,700</td>
<td>76.2</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2,400</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td><strong>During extension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46,641</td>
<td>60.5</td>
<td></td>
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<tr>
<td>Yes</td>
<td>30,485</td>
<td>39.5</td>
<td></td>
</tr>
</tbody>
</table>

### Appendix Table 2

Baseline characteristics by incident diabetes and statin use states

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes No Statins</th>
<th>Diabetes Not on statin</th>
<th>No Diabetes Statin</th>
<th>Statin Then Diabetes</th>
<th>Diabetes Then Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>113,878</td>
<td>8,095</td>
<td>34,423</td>
<td>2,255</td>
<td>2,969</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Age (Mean(SD))</td>
<td>62.5 (7.2)</td>
<td>61.8 (7.0)</td>
<td>62.4 (6.7)</td>
<td>62.4 (6.5)</td>
<td>60.8 (6.4)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>95,364 (84.0)</td>
<td>5,968 (73.9)</td>
<td>29,580 (86.1)</td>
<td>1,793 (79.7)</td>
<td>2,299 (77.5)</td>
</tr>
<tr>
<td>Black</td>
<td>9,036 (8.0)</td>
<td>1,236 (15.3)</td>
<td>2,185 (6.4)</td>
<td>249 (11.1)</td>
<td>361 (12.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4,566 (4.0)</td>
<td>514 (6.4)</td>
<td>1,061 (3.1)</td>
<td>90 (4.0)</td>
<td>177 (6.0)</td>
</tr>
<tr>
<td>Other</td>
<td>4,629 (4.1)</td>
<td>360 (4.5)</td>
<td>1,526 (4.4)</td>
<td>117 (5.2)</td>
<td>128 (4.3)</td>
</tr>
<tr>
<td>BMI (Mean(SD))</td>
<td>27.5 (5.7)</td>
<td>31.3 (6.6)</td>
<td>27.9 (5.3)</td>
<td>30.7 (5.8)</td>
<td>31.7 (6.2)</td>
</tr>
<tr>
<td>Waist (Mean(SD))</td>
<td>85.2 (13.3)</td>
<td>94.6 (14.7)</td>
<td>86.2 (12.4)</td>
<td>93.6 (12.8)</td>
<td>96.1 (14.1)</td>
</tr>
<tr>
<td>&lt;85 cm</td>
<td>61,581 (54.3)</td>
<td>2,116 (26.2)</td>
<td>17,090 (49.8)</td>
<td>573 (25.5)</td>
<td>638 (21.6)</td>
</tr>
<tr>
<td>≥85 cm</td>
<td>51,889 (45.7)</td>
<td>5,949 (73.8)</td>
<td>17,214 (50.2)</td>
<td>1,677 (74.5)</td>
<td>2,320 (78.4)</td>
</tr>
<tr>
<td>Total MET hours/week (Mean(SD))</td>
<td>13.0 (14.1)</td>
<td>10.0 (12.4)</td>
<td>12.6 (13.3)</td>
<td>10.1 (11.6)</td>
<td>9.3 (11.6)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Never</td>
<td>57,871 (51.5)</td>
<td>4,135 (51.7)</td>
<td>17,257 (50.7)</td>
<td>1,148 (51.5)</td>
<td>1,525 (51.8)</td>
</tr>
<tr>
<td>Past</td>
<td>46,782 (41.6)</td>
<td>3,234 (40.4)</td>
<td>14,542 (42.8)</td>
<td>915 (41.1)</td>
<td>1,204 (40.9)</td>
</tr>
<tr>
<td>Current</td>
<td>7,827 (7.0)</td>
<td>635 (7.9)</td>
<td>2,219 (6.5)</td>
<td>166 (7.5)</td>
<td>216 (7.3)</td>
</tr>
<tr>
<td>Family history of adult diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>74,529 (65.8)</td>
<td>3,978 (49.4)</td>
<td>22,292 (65.1)</td>
<td>1,089 (48.6)</td>
<td>1,413 (47.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>33,850 (29.9)</td>
<td>3,682 (45.7)</td>
<td>10,590 (30.9)</td>
<td>1,052 (47.0)</td>
<td>1,417 (47.9)</td>
</tr>
<tr>
<td>Don’t know</td>
<td>4,923 (4.4)</td>
<td>399 (5.0)</td>
<td>1,384 (4.0)</td>
<td>98 (4.4)</td>
<td>128 (4.3)</td>
</tr>
</tbody>
</table>

*Eur J Epidemiol. Author manuscript; available in PMC 2017 August 01.*
Appendix Table 3

Risks of ASCVD by diabetes diagnosis before taking statin and after taking statin compared to women without diabetes who did not or did take a statin stratified by waist circumference

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes Not on Statin</th>
<th>Diabetes Not on Statin</th>
<th>No Diabetes Statin</th>
<th>Statin Then Diabetes</th>
<th>Diabetes Then Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>113,878</td>
<td>8,095</td>
<td>34,423</td>
<td>2,255</td>
<td>2,969</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>35,452 (31.1)</td>
<td>2,355 (29.1)</td>
<td>9,258 (26.9)</td>
<td>503 (22.3)</td>
<td>819 (27.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>72,762 (65.9)</td>
<td>5,308 (65.6)</td>
<td>2,3658 (68.7)</td>
<td>1,653 (73.3)</td>
<td>2,015 (67.9)</td>
</tr>
<tr>
<td>Don’t know/Missing</td>
<td>5,664 (5.0)</td>
<td>432 (5.3)</td>
<td>1,507 (4.4)</td>
<td>99 (4.4)</td>
<td>135 (4.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hypertension</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
<td>Untreated</td>
<td>Treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>78,033 (72.7)</td>
<td>7,883 (7.3)</td>
<td>21,430 (20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4,494 (59.2)</td>
<td>722 (9.5)</td>
<td>2,371 (31.3)</td>
<td>21,708 (66.9)</td>
<td>2,969</td>
</tr>
<tr>
<td></td>
<td>21,708 (66.9)</td>
<td>2,451 (7.6)</td>
<td>8,291 (25.6)</td>
<td>1,036 (49.5)</td>
<td>1,603 (57.6)</td>
</tr>
<tr>
<td></td>
<td>1,036 (49.5)</td>
<td>184 (8.8)</td>
<td>873 (41.7)</td>
<td>819 (27.6)</td>
<td>2,015 (67.9)</td>
</tr>
<tr>
<td></td>
<td>1,603 (57.6)</td>
<td>261 (9.4)</td>
<td>920 (33.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                  | Glucose (Mean(SD))        |                       |                     |                      |                      |
|                  | 96.2 (19.4)               | 117.4 (41.4)           | 95.0 (13.6)         | 108.5 (24.1)         | 121.8 (43.3)         |

|                  | Insulin (Mean(SD))        |                       |                     |                      |                      |
|                  | 8.6 (6.1)                 | 12.7 (8.6)             | 8.6 (5.7)           | 11.8 (7.1)           | 13.3 (7.9)           |

|                  | HOMA-IR (Mean(SD))        |                       |                     |                      |                      |
|                  | 2.1 (1.9)                 | 3.8 (3.3)              | 2.1 (1.6)           | 3.2 (2.3)            | 4.1 (3.0)            |

|                  | HDL (Mean(SD))            |                       |                     |                      |                      |
|                  | 57.0 (14.7)               | 51.0 (13.3)            | 55.3 (13.7)         | 50.5 (12.4)          | 49.0 (12.0)          |

|                  | LDL (Mean(SD))            |                       |                     |                      |                      |
|                  | 146.9 (37.5)              | 144.8 (36.5)           | 161.9 (36.7)        | 162.3 (40.4)         | 153.7 (35.6)         |

|                  | Triglycerides (Mean(SD))  |                       |                     |                      |                      |
|                  | 138.6 (80.1)              | 164.4 (110.1)          | 156.2 (84.9)        | 183.3 (104.3)        | 178.5 (106.9)        |

1Number adds up to more than total study population because women can change states over the follow-up period Values are expressed as N(%) unless otherwise noted

Appendix Table 3

<table>
<thead>
<tr>
<th></th>
<th>Total N</th>
<th>Events</th>
<th>HR(95% CI)</th>
<th>HR(95% CI)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV adjusted HR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>109,590</td>
<td>6,500</td>
<td>1.42 (1.28–1.58)</td>
<td>1.39 (1.12–1.74)</td>
<td>0.885</td>
</tr>
<tr>
<td>Waist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;85 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>58,875</td>
<td>2,927</td>
<td>1.13 (0.88–1.45)</td>
<td>1.25 (0.76–2.07)</td>
<td>0.715</td>
</tr>
<tr>
<td>≥85 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50,423</td>
<td>3,561</td>
<td>1.49 (1.32–1.67)</td>
<td>1.44 (1.13–1.85)</td>
<td>0.836</td>
</tr>
</tbody>
</table>

<sup>a</sup>P-value for test of no difference between effect of diabetes before statin (if any) and the effect of diabetes after statin.

<sup>b</sup>HRs estimated from PH model with additional terms for age, race/ethnicity, education, region, cigarette smoking, BMI, physical activity, alcohol intake, healthy eating index, medical history of hypertension, systolic blood pressure, family history of cardiovascular disease, hormone therapy use, and study arms.
## Appendix Table 4

### Sensitivity analysis

<table>
<thead>
<tr>
<th></th>
<th>Diabetes before taking statin versus women without diabetes who did not take a statin</th>
<th>Diabetes after taking statin versus women without diabetes who took a statin</th>
<th>p-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCVD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV adjusted HR$^b$</td>
<td>1.42 (1.28–1.58)</td>
<td>1.39 (1.12–1.74)</td>
<td>0.885</td>
</tr>
<tr>
<td>Sensitivity analysis 1</td>
<td>1.43 (1.26–1.63)</td>
<td>1.52 (1.18–1.97)</td>
<td>0.668</td>
</tr>
<tr>
<td>Sensitivity analysis 2</td>
<td>1.43 (1.28–1.60)</td>
<td>1.39 (1.12–1.73)</td>
<td>0.830</td>
</tr>
<tr>
<td>Sensitivity analysis 3</td>
<td>1.42 (1.27–1.57)</td>
<td>1.32 (1.03–1.69)</td>
<td>0.613</td>
</tr>
<tr>
<td>Sensitivity analysis 4</td>
<td>1.42 (1.28–1.58)</td>
<td>1.56 (1.17–2.07)</td>
<td>0.546</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV adjusted HR$^b$</td>
<td>1.38 (1.17–1.62)</td>
<td>1.53 (1.12–2.08)</td>
<td>0.559</td>
</tr>
<tr>
<td>Sensitivity analysis 1</td>
<td>1.35 (1.11–1.62)</td>
<td>1.62 (1.16–2.28)</td>
<td>0.335</td>
</tr>
<tr>
<td>Sensitivity analysis 2</td>
<td>1.44 (1.22–1.72)</td>
<td>1.50 (1.11–2.05)</td>
<td>0.817</td>
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<tr>
<td>Sensitivity analysis 3</td>
<td>1.38 (1.17–1.63)</td>
<td>1.59 (1.14–2.23)</td>
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<tr>
<td>Sensitivity analysis 4</td>
<td>1.38 (1.17–1.63)</td>
<td>1.55 (1.02–2.35)</td>
<td>0.612</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV adjusted HR$^b$</td>
<td>1.31 (1.12–1.53)</td>
<td>1.22 (0.87–1.71)</td>
<td>0.718</td>
</tr>
<tr>
<td>Sensitivity analysis 1</td>
<td>1.38 (1.14–1.68)</td>
<td>1.31 (0.87–1.68)</td>
<td>0.804</td>
</tr>
<tr>
<td>Sensitivity analysis 2</td>
<td>1.27 (1.07–1.51)</td>
<td>1.24 (0.88–1.73)</td>
<td>0.883</td>
</tr>
<tr>
<td>Sensitivity analysis 3</td>
<td>1.30 (1.11–1.52)</td>
<td>1.04 (0.70–1.54)</td>
<td>0.303</td>
</tr>
<tr>
<td>Sensitivity analysis 4</td>
<td>1.31 (1.12–1.54)</td>
<td>1.69 (1.14–2.52)</td>
<td>0.234</td>
</tr>
<tr>
<td><strong>CVD death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV adjusted HR$^b$</td>
<td>1.55 (1.30–1.85)</td>
<td>1.13 (0.74–1.71)</td>
<td>0.161</td>
</tr>
<tr>
<td>Sensitivity analysis 1</td>
<td>1.67 (1.19–2.34)</td>
<td>1.12 (0.52–2.39)</td>
<td>0.335</td>
</tr>
<tr>
<td>Sensitivity analysis 2</td>
<td>1.55 (1.28–1.88)</td>
<td>1.13 (0.74–1.71)</td>
<td>0.166</td>
</tr>
<tr>
<td>Sensitivity analysis 3</td>
<td>1.55 (1.30–1.85)</td>
<td>1.21 (0.78–1.87)</td>
<td>0.297</td>
</tr>
<tr>
<td>Sensitivity analysis 4</td>
<td>1.55 (1.29–1.85)</td>
<td>1.00 (0.56–1.80)</td>
<td>0.159</td>
</tr>
</tbody>
</table>

$^a$P-value for test of no difference between effect of diabetes before statin (if any) and the effect of diabetes after statin.

$^b$HRs estimated from PH model with additional terms for age, race/ethnicity, education, region, cigarette smoking, BMI, physical activity, alcohol intake, healthy eating index, medical history of hypertension, systolic blood pressure, family history of cardiovascular disease, hormone therapy use, and study arms.

Four sensitivity analyses were conducted:

1. censor each subject 3 years after last medication data collection available, so we do not make assumption of statin use for an extended period (i.e., beyond 3 years);
2. censor women in the diabetes no statin group at time of any subsequent statin use; and
3. censor women in the statin groups for non-adherence (i.e., women who reported statin use on one inventory but then no statin on a subsequent inventory);
4. exclude women who were taking a statin at baseline.
### Appendix Table 5

Risks of ASCVD, MI, Stroke and CVD death (CHD death and fatal stroke) by diagnosis of diabetes before taking statins and after taking statins using duration-adjusted data

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Events</th>
<th>Diabetes before taking statin versus women without diabetes who did not take a statin</th>
<th>Diabetes after taking statin versus women without diabetes who took a statin</th>
<th>p-value\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>HR(95% CI)</td>
<td>HR(95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>ASCVD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR\textsuperscript{c}</td>
<td>120,498</td>
<td>4,243</td>
<td>1.87 (1.64–2.14)</td>
<td>1.65 (1.30–2.08)</td>
<td>0.336</td>
</tr>
<tr>
<td>Multivariable adjusted HR\textsuperscript{d}</td>
<td>109,590</td>
<td>3,699</td>
<td>1.68 (1.46–1.95)</td>
<td>1.38 (1.06–1.79)</td>
<td>0.180</td>
</tr>
<tr>
<td><strong>MI</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR\textsuperscript{c}</td>
<td>120,499</td>
<td>1,992</td>
<td>1.89 (1.55–2.30)</td>
<td>1.55 (1.11–2.17)</td>
<td>0.307</td>
</tr>
<tr>
<td>Multivariable adjusted HR\textsuperscript{d}</td>
<td>109,591</td>
<td>1,755</td>
<td>1.68 (1.36–2.07)</td>
<td>1.36 (0.95–1.95)</td>
<td>0.312</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR\textsuperscript{c}</td>
<td>120,498</td>
<td>1,993</td>
<td>1.76 (1.44–2.15)</td>
<td>1.63 (1.16–2.29)</td>
<td>0.699</td>
</tr>
<tr>
<td>Multivariable adjusted HR\textsuperscript{d}</td>
<td>109,590</td>
<td>1,725</td>
<td>1.61 (1.30–2.00)</td>
<td>1.33 (0.90–1.97)</td>
<td>0.388</td>
</tr>
<tr>
<td><strong>CVD death</strong></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Unadjusted HR\textsuperscript{c}</td>
<td>120,499</td>
<td>885</td>
<td>1.56 (1.15–2.13)</td>
<td>1.69 (0.998–2.86)</td>
<td>0.800</td>
</tr>
<tr>
<td>Multivariable adjusted HR\textsuperscript{d}</td>
<td>109,591</td>
<td>755</td>
<td>1.48 (1.07–2.04)</td>
<td>1.08 (0.55–2.11)</td>
<td>0.396</td>
</tr>
</tbody>
</table>

\textsuperscript{a}statin use and diabetes status using revised data to include duration of statin use reported up to 2 years before medication inventory and censored 3.5 years after previous medication inventory, and setting diabetes report back 6 months from form submission.

\textsuperscript{b}P-value for test of no difference between effect of diabetes diagnosis before statin (if any) and the effect of diabetes diagnosis after statin.

\textsuperscript{c}HRs estimated from PH model including factors for statin use, diabetes diagnosis before statins, diabetes diagnosis after statins.

\textsuperscript{d}HRs estimated from PH model with additional terms for age, race/ethnicity, education, region, cigarette smoking, BMI, physical activity, alcohol intake, healthy eating index, medical history of hypertension, systolic blood pressure, family history of cardiovascular disease, hormone therapy use, and study arms.

### Appendix Table 6

Risks of ASCVD by diabetes diagnosis before taking statin and after taking low or high potency statin compared to women without diabetes who did not or did take a statin

<table>
<thead>
<tr>
<th></th>
<th>Diabetes before taking statin versus women without diabetes who did not take a statin</th>
<th>Diabetes after taking statin versus women without diabetes who took a statin</th>
<th>Diabetes after taking statin versus women without diabetes who took a statin</th>
<th>p-value\textsuperscript{e}</th>
<th>p-value\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Events</td>
<td>HR(95% CI)</td>
<td>HR(95% CI)</td>
<td>HR(95% CI)</td>
</tr>
<tr>
<td><strong>ASCVD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Diabetes before taking statin versus women without diabetes who did not take a statin

Diabetes after taking statin versus women without diabetes who took a statin

Diabetes after taking statin versus women without diabetes who took a statin

<table>
<thead>
<tr>
<th></th>
<th>Low potency</th>
<th>High potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV adjusted HRc</td>
<td>Total N</td>
<td>Events</td>
</tr>
<tr>
<td></td>
<td>109,590</td>
<td>6,500</td>
</tr>
</tbody>
</table>

| p-valuea         | 0.162       |
| p-valueb         | 0.273       |

a P-value for test of no difference between effect of diabetes before statin (if any) and the effect of diabetes after statin (low potency).

b P-value for test of no difference between effect of diabetes before statin (if any) and the effect of diabetes after statin (high potency).

c HRs estimated from PH model with additional terms for age, race/ethnicity, education, region, cigarette smoking, BMI, physical activity, alcohol intake, healthy eating index, medical history of hypertension, systolic blood pressure, family history of cardiovascular disease, hormone therapy use, and study arms.

Post hoc test of comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Wald chi-square</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>across 3 diabetes groups</td>
<td>3.4597</td>
<td>2</td>
<td>0.177</td>
</tr>
<tr>
<td>pairwise tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes before statin (if any) and diabetes after statin (low potency)</td>
<td>1.9568</td>
<td>1</td>
<td>0.162</td>
</tr>
<tr>
<td>diabetes before statin (if any) and diabetes after statin (high potency)</td>
<td>1.2013</td>
<td>1</td>
<td>0.273</td>
</tr>
<tr>
<td>diabetes after statin (low potency) and diabetes after statin (high potency)</td>
<td>3.4592</td>
<td>1</td>
<td>0.063</td>
</tr>
</tbody>
</table>

There is no statistical difference between these diabetes groups and risk of ASCVD, after adjustment for multiple comparisons alpha level= 0.017.

References


28. Cholesterol Treatment Trialists C. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. Lancet. 2015
Figure 1. Flowchart for incident diabetes mellitus (DM) analyses using data sets from the Women’s Health Initiative.

1CVD history includes cardiac arrest, CHF, revascularization, carotid artery disease, atrial fibrillation, aortic aneurysm, angina, peripheral vascular disease, stroke, TIA and MI.
2Diabetes (DM) before statin defined as diabetes reported before reported use of statin medication, which includes the case of no reported statin use.
3Diabetes after statin defined as diabetes reported after reported use of statin medication.
Figure 2. Incident diabetes and statin use states for ASCVD risk modeling purposes using datasets from the Women's Health Initiative

- Cox model with time-dependent covariates

\[ \alpha = \log(h_0(t)) \] is the baseline log hazard function of ASCVD

\[ \beta_{\text{stat}} \] is the effect (log hazard ratio) of statin use on ASCVD

\[ \beta_{\text{dbs}} \] and \[ \beta_{\text{das}} \] are the effects of incident diabetes while not on statin (“diabetes before statin”) and incident diabetes while on statin (“diabetes after statin”), respectively.
Figure 3. Absolute 10-year risks of ASCVD, MI, stroke, and CVD death for five hypothetical women representing the five states (a–e)
(a) woman without diabetes and not using a statin
(b) woman with diabetes and not using a statin
(c) woman without diabetes and used a statin
(d) woman who had a diabetes diagnosis after initiating a statin
(e) woman who had diabetes onset before initiating a statin
Table 1

Descriptive table of baseline characteristics by statin use and diabetes reported during follow-up through the end of extension 1 (2010)

<table>
<thead>
<tr>
<th></th>
<th>Statin use</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>No (%)</td>
</tr>
<tr>
<td></td>
<td>120,499</td>
<td>81,067</td>
</tr>
<tr>
<td>Age (Mean(SD))</td>
<td></td>
<td>62.6 (7.2)</td>
</tr>
<tr>
<td>HT Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not randomized to HT</td>
<td>99,520 (82.6)</td>
<td>67,538 (83.3)</td>
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<tr>
<td>E-alone intervention</td>
<td>3,786 (3.1)</td>
<td>2,470 (3.0)</td>
</tr>
<tr>
<td>E-alone control</td>
<td>3,909 (3.2)</td>
<td>2,445 (3.0)</td>
</tr>
<tr>
<td>E+P intervention</td>
<td>6,802 (5.6)</td>
<td>4,532 (5.6)</td>
</tr>
<tr>
<td>E+P control</td>
<td>6,482 (5.4)</td>
<td>4,082 (5.0)</td>
</tr>
<tr>
<td>DM Arm</td>
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<td></td>
</tr>
<tr>
<td>Not randomized to DM</td>
<td>83,309 (69.1)</td>
<td>57,607 (71.1)</td>
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<tr>
<td>Intervention</td>
<td>14,889 (12.4)</td>
<td>9,464 (11.7)</td>
</tr>
<tr>
<td>Control</td>
<td>22,301 (18.5)</td>
<td>13,996 (17.3)</td>
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<tr>
<td>No</td>
<td>51,968 (43.1)</td>
<td>33,023 (40.7)</td>
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<td>68,531 (56.9)</td>
<td>48,044 (59.3)</td>
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<td>Ethnicity</td>
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<td>100,862 (83.9)</td>
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<td>Hispanic/Latino</td>
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<td>Education</td>
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<tr>
<td>Statin use</td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>120,499</td>
<td>81,067</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
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<tr>
<td>&lt; High school</td>
<td>5,512 (4.6)</td>
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<td>High school/GED</td>
<td>20,042 (16.8)</td>
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<tr>
<td>&gt;High school, &lt;4 year college</td>
<td>44,564 (37.3)</td>
<td>29,864 (37.1)</td>
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<tr>
<td>&gt;= 4 year college</td>
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<th>Income</th>
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<td>&lt; $10,000</td>
<td>4,098 (3.6)</td>
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<td>$10,000 to $19,999</td>
<td>12,307 (10.9)</td>
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<td>26,440 (23.5)</td>
<td>17,864 (23.7)</td>
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<td>$35,000 to $49,999</td>
<td>23,346 (20.7)</td>
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<td>$50,000 to $74,999</td>
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<tr>
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<tr>
<td>Northeast</td>
<td>27,683 (23.0)</td>
<td>17,844 (22.0)</td>
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<tr>
<td>South</td>
<td>30,926 (25.7)</td>
<td>21,105 (26.0)</td>
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<tr>
<td>Midwest</td>
<td>26,386 (21.9)</td>
<td>17,487 (21.6)</td>
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<td>West</td>
<td>35,504 (29.5)</td>
<td>24,631 (30.4)</td>
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<table>
<thead>
<tr>
<th>Body-mass Index (kg/m²)</th>
<th>Statin use</th>
<th>Diabetes</th>
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</thead>
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<tr>
<td>(Mean(SD))</td>
<td>Total</td>
<td>No</td>
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<tr>
<td>Underweight (&lt; 18.5)</td>
<td>1,028 (0.9)</td>
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<td>Normal (18.5 – 24.9)</td>
<td>43,428 (36.4)</td>
<td>31,493 (39.2)</td>
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<td>Overweight (25.0 – 29.9)</td>
<td>42,235 (35.4)</td>
<td>27,067 (33.7)</td>
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<td>Obesity I (30.0 – 34.9)</td>
<td>20,815 (17.4)</td>
<td>13,130 (16.3)</td>
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<tr>
<td>Obesity II (35.0 – 39.9)</td>
<td>7,994 (6.7)</td>
<td>5,130 (6.4)</td>
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<tr>
<td>Statin use</td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
<td></td>
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<tr>
<td>Total</td>
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<tr>
<td>N (%)</td>
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<tr>
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<td>N (%)</td>
<td>109,510</td>
<td></td>
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<tr>
<td>N (%)</td>
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<td>Extreme Obesity III (≥40)</td>
<td>3,965 (3.3)</td>
<td>2,655 (3.3)</td>
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<td>Waist (cm) (Mean(SD))</td>
<td>85.4 (13.3)</td>
<td>84.5 (13.4)</td>
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<tr>
<td>&lt;85 cm</td>
<td>64,370 (53.6)</td>
<td>45,681 (56.6)</td>
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<td>≥85 cm</td>
<td>55,696 (46.4)</td>
<td>35,087 (43.4)</td>
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<td>Smoking status</td>
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<td>41,410 (51.7)</td>
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<tr>
<td>Past Smoker</td>
<td>49,606 (41.7)</td>
<td>33,020 (41.3)</td>
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<tr>
<td>Current Smoker</td>
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<td>1,039</td>
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<tr>
<td>Alcohol intake</td>
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<tr>
<td>Non drinker</td>
<td>12,332 (10.3)</td>
<td>8,598 (10.7)</td>
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<tr>
<td>Past drinker</td>
<td>19,571 (16.4)</td>
<td>13,350 (16.6)</td>
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<tr>
<td>&lt;1 drink per month</td>
<td>14,759 (12.3)</td>
<td>9,712 (12.1)</td>
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<tr>
<td>&lt;1 drink per week</td>
<td>25,096 (21.0)</td>
<td>16,457 (20.5)</td>
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<td>1 to &lt;7 drinks per week</td>
<td>32,879 (27.5)</td>
<td>22,072 (27.4)</td>
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<td>7+ drinks per week</td>
<td>14,987 (12.5)</td>
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<td>HT usage status</td>
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<td>67</td>
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<td>Statin use</td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
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<tr>
<td></td>
<td>Total</td>
<td>No (%)</td>
</tr>
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<td>120,499</td>
<td>81,067</td>
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<th>Family history of adult diabetes</th>
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<td>78,655 (65.6)</td>
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<td>36,019 (30.0)</td>
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<tr>
<td>5,213 (4.3)</td>
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<th>Family history of CVD</th>
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<tr>
<td>36,929 (30.6)</td>
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<tr>
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<tr>
<td>77,615 (64.4)</td>
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<tr>
<td>Don't Know/Missing</td>
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<tr>
<td>5,955 (4.9)</td>
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<th>Hypertension</th>
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<tr>
<td>81,568 (71.7)</td>
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<tr>
<td>Untreated hypertensive</td>
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<tr>
<td>8,344 (7.3)</td>
</tr>
<tr>
<td>Treated hypertensive</td>
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<td>23,843 (21.0)</td>
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<tr>
<td>6,744</td>
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<th>Systolic BP (Mean(SD))</th>
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<tr>
<td>&lt;=120</td>
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<td>126.3 (17.4)</td>
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<tr>
<td>120–140</td>
</tr>
<tr>
<td>49.089 (40.8)</td>
</tr>
<tr>
<td>&gt;140</td>
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<tr>
<td>48.648 (40.4)</td>
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<th>Diastolic BP (Mean(SD))</th>
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<td>75.4 (9.1)</td>
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<td>&gt;=90</td>
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<td>112.082 (93.1)</td>
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<td>8,313 (6.9)</td>
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<tr>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
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<tr>
<td></td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>Total MET hours/week</td>
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<tr>
<td>Recreational physical activity minutes/week (Mean(SD))</td>
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<td>Healthy eating index</td>
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<tr>
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<tr>
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<tr>
<td>How many hours of sleep</td>
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<tr>
<td>5 or less hours</td>
</tr>
<tr>
<td>6 hours</td>
</tr>
<tr>
<td>7 hours</td>
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<td>8 hours</td>
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<td>Missing</td>
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<tr>
<td>Depressive symptoms</td>
</tr>
<tr>
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</tr>
<tr>
<td>Yes (CESD&gt;5)</td>
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</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Statin use</strong></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
</tr>
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<td><strong>Glucose (mg/dl)</strong></td>
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<td><strong>Insulin (mU/L)</strong></td>
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<td><strong>HOMA-IR</strong></td>
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<td><strong>HDL (mg/dl)</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>LDL (mg/dl)</strong></td>
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</tr>
<tr>
<td><strong>Triglycerides</strong></td>
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<tr>
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</table>

Values are expressed as N(%) unless otherwise noted.
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Diabetes before taking statin versus women without diabetes who did not take a statin</th>
<th>Diabetes after taking statin versus women without diabetes who took a statin</th>
<th>p-value(^d)</th>
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<tr>
<td><strong>ASCVD</strong></td>
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<td></td>
</tr>
<tr>
<td>Unadjusted HR(^b)</td>
<td>120,498</td>
<td>1.67 (1.52–1.84)</td>
<td>1.64 (1.34–1.99)</td>
<td>0.846</td>
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<tr>
<td>Multivariable adjusted HR(^c)</td>
<td>109,590</td>
<td>1.42 (1.28–1.58)</td>
<td>1.39 (1.12–1.74)</td>
<td>0.885</td>
</tr>
<tr>
<td>MV with PS covariate</td>
<td>109,590</td>
<td>1.42 (1.27–1.57)</td>
<td>1.39 (1.12–1.73)</td>
<td>0.896</td>
</tr>
<tr>
<td>MV weighted by PS</td>
<td>109,590</td>
<td>1.41 (1.25–1.58)</td>
<td>1.19 (0.85–1.69)</td>
<td>0.373</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted HR(^b)</td>
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<td>1.65 (1.41–1.91)</td>
<td>1.75 (1.32–2.32)</td>
<td>0.709</td>
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<tr>
<td>Multivariable adjusted HR(^c)</td>
<td>109,591</td>
<td>1.38 (1.17–1.62)</td>
<td>1.53 (1.12–2.08)</td>
<td>0.559</td>
</tr>
<tr>
<td>MV with PS covariate</td>
<td>109,591</td>
<td>1.38 (1.17–1.62)</td>
<td>1.52 (1.12–2.07)</td>
<td>0.554</td>
</tr>
<tr>
<td>MV weighted by PS</td>
<td>109,591</td>
<td>1.35 (1.12–1.62)</td>
<td>1.46 (0.91–2.35)</td>
<td>0.748</td>
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<tr>
<td><strong>Stroke</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR(^b)</td>
<td>120,498</td>
<td>1.49 (1.29–1.72)</td>
<td>1.45 (1.08–1.94)</td>
<td>0.855</td>
</tr>
<tr>
<td>Multivariable adjusted HR(^c)</td>
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<td>1.31 (1.12–1.53)</td>
<td>1.22 (0.87–1.71)</td>
<td>0.718</td>
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<tr>
<td>MV with PS covariate</td>
<td>109,590</td>
<td>1.30 (1.11–1.52)</td>
<td>1.22 (0.87–1.71)</td>
<td>0.726</td>
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<tr>
<td>MV weighted by PS</td>
<td>109,590</td>
<td>1.24 (1.04–1.48)</td>
<td>0.74 (0.42–1.31)</td>
<td>0.088</td>
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<tr>
<td><strong>CVD death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR(^b)</td>
<td>120,499</td>
<td>1.82 (1.54–2.14)</td>
<td>1.47 (1.03–2.08)</td>
<td>0.269</td>
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<tr>
<td>Multivariable adjusted HR(^c)</td>
<td>109,591</td>
<td>1.55 (1.30–1.85)</td>
<td>1.13 (0.74–1.71)</td>
<td>0.161</td>
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<tr>
<td>MV with PS covariate</td>
<td>109,591</td>
<td>1.55 (1.30–1.85)</td>
<td>1.13 (0.74–1.71)</td>
<td>0.162</td>
</tr>
<tr>
<td>MV weighted by PS</td>
<td>109,591</td>
<td>1.55 (1.27–1.90)</td>
<td>1.11 (0.62–2.02)</td>
<td>0.298</td>
</tr>
</tbody>
</table>

MV=Multivariable; PS=propensity score

\(^a\)P-value for test of no difference between effect of diabetes diagnosis before statin (if any) and the effect of diabetes after statin.

\(^b\)HRs estimated from PH model including factors for statin use, diabetes diagnosis before statins, diabetes after statins.

\(^c\)HRs estimated from PH model with additional terms for age, race/ethnicity, education, region, cigarette smoking, BMI, physical activity, alcohol intake, healthy eating index, medical history of hypertension, systolic blood pressure, family history of cardiovascular disease, hormone therapy use, and study arms.