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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/m²) 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 β_{DBS} was the log hazard ratio primarily comparing the event rates from states (b) to (a). The parameter β_{DAS} was the log hazard

ratio primarily comparing the event rates from states (d) to (c). Group (e) provided additional information for estimating β_{DBS} and β_S . The primary comparison of the two diabetes effects, β_{DBS} and β_{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 incident 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.

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Appendix

Appendix Table 1

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

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

Statin use	N	%	Study Sample Included
At year 9			CT who made it to year 9 before the main study ended
No	7,700	76.2	
Yes	2,400	23.8	
During extension			OS and CT that consented to the Extension
No	46,641	60.5	
Yes	30,485	39.5	

Appendix Table 2

Baseline characteristics by incident diabetes and statin use states

	No Diabetes No Statins	Diabetes Not on statin	No Diabetes Statin	Statin Then Diabetes	Diabetes Then Statin
N^I	113,878	8,095	34,423	2,255	2,969
	N (%)	N (%)	N (%)	N (%)	N (%)
Age (Mean(SD))	62.5 (7.2)	61.8 (7.0)	62.4 (6.7)	62.4 (6.5)	60.8 (6.4)
Ethnicity					
White	95,364 (84.0)	5,968 (73.9)	29,580 (86.1)	1,793 (79.7)	2,299 (77.5)
Black	9,036 (8.0)	1,236 (15.3)	2,185 (6.4)	249 (11.1)	361 (12.2)
Hispanic	4,566 (4.0)	514 (6.4)	1061 (3.1)	90 (4.0)	177 (6.0)
Other	4,629 (4.1)	360 (4.5)	1526 (4.4)	117 (5.2)	128 (4.3)
BMI (Mean(SD))	27.5 (5.7)	31.3 (6.6)	27.9 (5.3)	30.7 (5.8)	31.7 (6.2)
Waist (Mean(SD))	85.2 (13.3)	94.6 (14.7)	86.2 (12.4)	93.6 (12.8)	96.1 (14.1)
<85 cm	61,581 (54.3)	2,116 (26.2)	17,090 (49.8)	573 (25.5)	638 (21.6)
85 cm	51,889 (45.7)	5,949 (73.8)	17,214 (50.2)	1,677 (74.5)	2,320 (78.4)
Total MET hours/week (Mean(SD))	13.0 (14.1)	10.0 (12.4)	12.6 (13.3)	10.1 (11.6)	9.3 (11.6)
Smoking					
Never	57,871 (51.5)	4,135 (51.7)	17,257 (50.7)	1,148 (51.5)	1,525 (51.8)
Past	46,782 (41.6)	3,234 (40.4)	14,542 (42.8)	915 (41.1)	1,204 (40.9)
Current	7,827 (7.0)	635 (7.9)	2,219 (6.5)	166 (7.5)	216 (7.3)
Family history of adult diabetes					
No	74,529 (65.8)	3,978 (49.4)	22,292 (65.1)	1,089 (48.6)	1,413 (47.8)
Yes	33,850 (29.9)	3,682 (45.7)	10,590 (30.9)	1,052 (47.0)	1,417 (47.9)
Don't know	4,923 (4.4)	399 (5.0)	1,384 (4.0)	98 (4.4)	128 (4.3)
Family history of CVD					

	No Diabetes No Statins	Diabetes Not on statin	No Diabetes Statin	Statin Then Diabetes	Diabetes Then Statin
N^I	113,878	8,095	34,423	2,255	2,969
	N (%)	N (%)	N (%)	N (%)	N (%)
No	35,452 (31.1)	2,355 (29.1)	9,258 (26.9)	503 (22.3)	819 (27.6)
Yes	72,762 (63.9)	5,308 (65.6)	2,3658 (68.7)	1,653 (73.3)	2,015 (67.9)
Don't know/Missing	5,664 (5.0)	432 (5.3)	1,507 (4.4)	99 (4.4)	135 (4.6)
Hypertension					
Never	78,033 (72.7)	4,494 (59.2)	21,708 (66.9)	1,036 (49.5)	1,603 (57.6)
Untreated	7,883 (7.3)	722 (9.5)	2,451 (7.6)	184 (8.8)	261 (9.4)
Treated	21,430 (20.0)	2,371 (31.3)	8,291 (25.6)	873 (41.7)	920 (33.1)
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)

^I Number 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

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

			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	
	Total N	Events	HR(95% CI)	HR(95% CI)	p-value ^a
ASCVD					
MV adjusted HR ^b	109,590	6,500	1.42 (1.28–1.58)	1.39 (1.12–1.74)	0.885
Waist					
<85 cm	58,875	2,927	1.13 (0.88–1.45)	1.25 (0.76–2.07)	0.715
85 cm	50,423	3,561	1.49 (1.32–1.67)	1.44 (1.13–1.85)	0.836

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

^bHRs 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

	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	
	HR(95% CI)	HR(95% CI)	p-value ^a
ASCVD			
MV adjusted HR ^b	1.42 (1.28–1.58)	1.39 (1.12–1.74)	0.885
Sensitivity analysis 1	1.43 (1.26–1.63)	1.52 (1.18–1.97)	0.668
Sensitivity analysis 2	1.43 (1.28–1.60)	1.39 (1.12–1.73)	0.830
Sensitivity analysis 3	1.42 (1.27–1.57)	1.32 (1.03–1.69)	0.613
Sensitivity analysis 4	1.42 (1.28–1.58)	1.56 (1.17–2.07)	0.546
MI			
MV adjusted HR ^b	1.38 (1.17–1.62)	1.53 (1.12–2.08)	0.559
Sensitivity analysis 1	1.35 (1.11–1.62)	1.62 (1.16–2.28)	0.335
Sensitivity analysis 2	1.44 (1.22–1.72)	1.50 (1.11–2.05)	0.817
Sensitivity analysis 3	1.38 (1.17–1.63)	1.59 (1.14–2.23)	0.438
Sensitivity analysis 4	1.38 (1.17–1.63)	1.55 (1.02–2.35)	0.612
Stroke			
MV adjusted HR ^b	1.31 (1.12–1.53)	1.22 (0.87–1.71)	0.718
Sensitivity analysis 1	1.38 (1.14–1.68)	1.31 (0.87–1.68)	0.804
Sensitivity analysis 2	1.27 (1.07–1.51)	1.24 (0.88–1.73)	0.883
Sensitivity analysis 3	1.30 (1.11–1.52)	1.04 (0.70–1.54)	0.303
Sensitivity analysis 4	1.31 (1.12–1.54)	1.69 (1.14–2.52)	0.234
CVD death			
MV adjusted HR ^b	1.55 (1.30–1.85)	1.13 (0.74–1.71)	0.161
Sensitivity analysis 1	1.67 (1.19–2.34)	1.12 (0.52–2.39)	0.335
Sensitivity analysis 2	1.55 (1.28–1.88)	1.13 (0.74–1.71)	0.166
Sensitivity analysis 3	1.55 (1.30–1.85)	1.21 (0.78–1.87)	0.297
Sensitivity analysis 4	1.55 (1.29–1.85)	1.00 (0.56–1.80)	0.159

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

^bHRs 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^a

	Total	Events	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	
	N	N	HR(95% CI)	HR(95% CI)	p-value ^b
ASCVD					
Unadjusted HR ^c	120,498	4,243	1.87 (1.64–2.14)	1.65 (1.30–2.08)	0.336
Multivariable adjusted HR ^d	109,590	3,699	1.68 (1.46–1.95)	1.38 (1.06–1.79)	0.180
MI					
Unadjusted HR ^c	120,499	1,992	1.89 (1.55–2.30)	1.55 (1.11–2.17)	0.307
Multivariable adjusted HR ^d	109,591	1,755	1.68 (1.36–2.07)	1.36 (0.95–1.95)	0.312
Stroke					
Unadjusted HR ^c	120,498	1,993	1.76 (1.44–2.15)	1.63 (1.16–2.29)	0.699
Multivariable adjusted HR ^d	109,590	1,725	1.61 (1.30–2.00)	1.33 (0.90–1.97)	0.388
CVD death					
Unadjusted HR ^c	120,499	885	1.56 (1.15–2.13)	1.69 (0.998–2.86)	0.800
Multivariable adjusted HR ^d	109,591	755	1.48 (1.07–2.04)	1.08 (0.55–2.11)	0.396

^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.

^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.

^c HRs estimated from PH model including factors for statin use, diabetes diagnosis before statins, diabetes diagnosis after statins.

^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

			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		
				low potency	high potency		
	Total N	Events	HR(95% CI)	HR(95% CI)	HR(95% CI)	p-value ^a	p-value ^b
ASCVD							

			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		
				low potency	high potency		
	Total N	Events	HR(95% CI)	HR(95% CI)	HR(95% CI)	p-value ^a	p-value ^b
MV adjusted HR ^c	109,590	6,500	1.42 (1.28–1.58)	1.10 (0.78–1.55)	1.68 (1.27–2.23)	0.162	0.273

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

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

^cHRs 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

Comparison	Wald chi-square	df	p-value
across 3 diabetes groups	3.4597	2	0.177
pairwise tests			
diabetes before statin (if any) and diabetes after statin (low potency)	1.9568	1	0.162
diabetes before statin (if any) and diabetes after statin (high potency)	1.2013	1	0.273
diabetes after statin (low potency) and diabetes after statin (high potency)	3.4592	1	0.063

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

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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) through the end of extension 1 (2010).

³Diabetes before statin defined as diabetes reported before reported use of statin medication, which includes the case of no reported statin use.

⁴Diabetes 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 data sets 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

β_{stat} is the effect (log hazard ratio) of statin use on ASCVD

β_{dbs} and β_{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)

	Statin use				Diabetes			
	Total	No	Yes	N (%)	No	Yes	N (%)	N (%)
Total	120,499	81,067	39,432		109,510		10,989	
Age (Mean(SD))	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
	62.6 (7.2)	62.7 (7.4)	62.4 (6.7)		62.7 (7.2)		62.1 (6.9)	
HT Arm								
Not randomized to HT	99,520 (82.6)	67,538 (83.3)	31,982 (81.1)		91,028 (83.1)		8,492 (77.3)	
E-alone intervention	3,786 (3.1)	2,470 (3.0)	1,316 (3.3)		3,252 (3.0)		534 (4.9)	
E-alone control	3,909 (3.2)	2,445 (3.0)	1,464 (3.7)		3,343 (3.1)		566 (5.2)	
E+P intervention	6,802 (5.6)	4,532 (5.6)	2,270 (5.8)		6,073 (5.5)		729 (6.6)	
E+P control	6,482 (5.4)	4,082 (5.0)	2,400 (6.1)		5,814 (5.3)		668 (6.1)	
DM Arm								
Not randomized to DM	83,309 (69.1)	57,607 (71.1)	25,702 (65.2)		76,426 (69.8)		6,883 (62.6)	
Intervention	14,889 (12.4)	9,464 (11.7)	5,425 (13.8)		13,324 (12.2)		1,565 (14.2)	
Control	22,301 (18.5)	13,996 (17.3)	8,305 (21.1)		19,760 (18.0)		2,541 (23.1)	
OS Participant								
No	51,968 (43.1)	33,023 (40.7)	18,945 (48.0)		46,261 (42.2)		5,707 (51.9)	
Yes	68,531 (56.9)	48,044 (59.3)	20,487 (52.0)		63,249 (57.8)		5,282 (48.1)	
Ethnicity								
White	100,862 (83.9)	67,147 (83.0)	33,715 (85.7)		92,649 (84.8)		8,213 (74.9)	
Black	9,543 (7.9)	6,896 (8.5)	2,647 (6.7)		7,951 (7.3)		1,592 (14.5)	
Hispanic/Latino	4,784 (4.0)	3,510 (4.3)	1,274 (3.2)		4,137 (3.8)		647 (5.9)	
Other	5,014 (4.2)	3,302 (4.1)	1,712 (4.4)		4,503 (4.1)		511 (4.7)	
Missing	296	212	84		270		26	
Education								

	Statin use				Diabetes			
	Total		No		Yes		No	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<High school	5,512 (4.6)	3,883 (4.8)	1,629 (4.2)	2,254 (5.6)	109,510	10,989		
High school/GED	20,042 (16.8)	12,983 (16.1)	7,059 (18.0)	15,923 (39.7)				
>High school, <4 year college	44,564 (37.3)	29,864 (37.1)	14,700 (37.5)	30,164 (75.2)				
>= 4 year college	49,496 (41.4)	33,716 (41.9)	15,780 (40.3)	33,716 (83.5)				
Missing	885	621	264	805				
Income								
Less than \$10,000	4,098 (3.6)	3,088 (4.1)	1,010 (2.7)	3,078 (7.6)				
\$10,000 to \$19,999	12,307 (10.9)	8,744 (11.6)	3,563 (9.6)	10,875 (27.0)				
\$20,000 to \$34,999	26,440 (23.5)	17,864 (23.7)	8,576 (23.1)	23,788 (59.0)				
\$35,000 to \$49,999	23,346 (20.7)	15,363 (20.4)	7,983 (21.5)	21,191 (52.5)				
\$50,000 to \$74,999	23,471 (20.8)	15,497 (20.5)	7,974 (21.5)	21,515 (53.5)				
\$75,000 to \$99,999	22,941 (20.4)	14,930 (19.8)	8,011 (21.6)	21,295 (53.0)				
Missing	7,896	5,581	2,315	7,271				
Region								
Northeast	27,683 (23.0)	17,844 (22.0)	9,839 (25.0)	25,324 (62.5)				
South	30,926 (25.7)	21,105 (26.0)	9,821 (24.9)	27,715 (68.8)				
Midwest	26,386 (21.9)	17,487 (21.6)	8,899 (22.6)	24,047 (59.6)				
West	35,504 (29.5)	24,631 (30.4)	10,873 (27.6)	32,424 (80.0)				
Body-mass Index (kg/m²)								
(Mean(SD))	27.6 (5.7)	27.3 (5.8)	28.2 (5.5)	27.2 (5.5)				
Underweight (< 18.5)	1,028 (0.9)	859 (1.1)	169 (0.4)	997 (0.9)				
Normal (18.5 – 24.9)	43,428 (36.4)	31,493 (39.2)	11,935 (30.5)	41,716 (103.5)				
Overweight (25.0 – 29.9)	42,235 (35.4)	27,067 (33.7)	15,168 (38.8)	38,754 (96.0)				
Obesity I (30.0 – 34.9)	20,815 (17.4)	13,130 (16.3)	7,685 (19.6)	17,740 (44.0)				
Obesity II (35.0 – 39.9)	7,994 (6.7)	5,130 (6.4)	2,864 (7.3)	6,390 (15.8)				

	Statin use			Diabetes		
	Total	No	Yes	No	Yes	Yes
	120,499	81,067	39,432	109,510	10,989	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Extreme Obesity III (>=40)	3,965 (3.3)	2,655 (3.3)	1,310 (3.3)	2,967 (2.7)	998 (9.2)	
Missing	1,034	733	301	946	88	
Waist (cm) (Mean(SD))	85.4 (13.3)	84.5 (13.4)	87.0 (12.9)	84.4 (12.9)	94.4 (14.3)	
<85 cm	64,370 (53.6)	45,681 (56.6)	18,689 (47.6)	61,527 (56.4)	2,843 (26.0)	
85 cm	55,696 (46.4)	35,087 (43.4)	20,609 (52.4)	47,586 (43.6)	8,110 (74.0)	
Missing	433	299	134	397	36	
Smoking status						
Never Smoked	61,178 (51.4)	41,410 (51.7)	19,768 (50.7)	55,566 (51.4)	5,612 (51.6)	
Past Smoker	49,606 (41.7)	33,020 (41.3)	16,586 (42.6)	45,216 (41.8)	4,390 (40.4)	
Current Smoker	8,224 (6.9)	5,598 (7.0)	2,626 (6.7)	7,360 (6.8)	864 (8.0)	
Missing	1,491	1,039	452	1,368	123	
Alcohol intake						
Non drinker	12,332 (10.3)	8,598 (10.7)	3,734 (9.5)	10,956 (10.1)	1,376 (12.6)	
Past drinker	19,571 (16.4)	13,350 (16.6)	6,221 (15.9)	17,313 (15.9)	2,258 (20.7)	
<1 drink per month	14,759 (12.3)	9,712 (12.1)	5,047 (12.9)	13,038 (12.0)	1,721 (15.8)	
<1 drink per week	25,096 (21.0)	16,457 (20.5)	8,639 (22.0)	22,704 (20.9)	2,392 (21.9)	
1 to <7 drinks per week	32,879 (27.5)	22,072 (27.4)	10,807 (27.6)	30,552 (28.1)	2,327 (21.3)	
7+ drinks per week	14,987 (12.5)	10,244 (12.7)	4,743 (12.1)	14,155 (13.0)	832 (7.6)	
Missing	875	634	241	792	83	
HT usage status						
Never used	51,852 (43.1)	35,465 (43.8)	16,387 (41.6)	46,595 (42.6)	5,257 (47.9)	
Past user	18,426 (15.3)	12,510 (15.4)	5,916 (15.0)	16,674 (15.2)	1,752 (16.0)	
Current user	50,118 (41.6)	33,025 (40.8)	17,093 (43.4)	46,148 (42.2)	3,970 (36.2)	
Missing	103	67	36	93	10	

	Statin use				Diabetes			
	No		Yes		No		Yes	
	Total	N (%)	No	N (%)	No	N (%)	Yes	N (%)
Family history of adult diabetes	120,499	81,067	39,432	109,510	10,989			
No	78,655 (65.6)	53,624 (66.5)	25,031 (63.8)	73,273 (67.3)	5,382 (49.2)			
Yes	36,019 (30.0)	23,389 (29.0)	12,630 (32.2)	30,994 (28.4)	5,025 (46.0)			
Don't know	5,213 (4.3)	3,619 (4.5)	1,594 (4.1)	4,686 (4.3)	527 (4.8)			
Missing	612	435	177	557	55			
Family history of CVD								
No	36,929 (30.6)	26,386 (32.5)	10,543 (26.7)	33,923 (31.0)	3,006 (27.4)			
Yes	77,615 (64.4)	50,466 (62.3)	27,149 (68.9)	70,208 (64.1)	7,407 (67.4)			
Don't Know/Missing	5,955 (4.9)	4,215 (5.2)	1,740 (4.4)	5,379 (4.9)	576 (5.2)			
Hypertension								
Never hypertensive	81,568 (71.7)	57,121 (74.5)	24,447 (65.8)	75,753 (73.2)	5,815 (56.6)			
Untreated hypertensive	8,344 (7.3)	5,426 (7.1)	2,918 (7.9)	7,365 (7.1)	979 (9.5)			
Treated hypertensive	23,843 (21.0)	14,080 (18.4)	9,763 (26.3)	20,355 (19.7)	3,488 (33.9)			
Missing	6,744	4,440	2,304	6,037	707			
Systolic BP								
(Mean(SD))	126.3 (17.4)	125.5 (17.6)	127.8 (16.9)	125.9 (17.4)	130.5 (17.0)			
<=120	49,089 (40.8)	34,749 (42.9)	14,340 (36.4)	45,818 (41.9)	3,271 (29.8)			
120 – 140	48,648 (40.4)	31,635 (39.1)	17,013 (43.2)	43,622 (39.9)	5,026 (45.8)			
>140	22,675 (18.8)	14,619 (18.0)	8,056 (20.4)	19,992 (18.3)	2,683 (24.4)			
Missing	87	64	23	78	9			
Diastolic BP								
(Mean(SD))	75.4 (9.1)	75.0 (9.2)	76.1 (9.0)	75.2 (9.1)	77.2 (9.1)			
<90	112,082 (93.1)	75,613 (93.4)	36,469 (92.6)	102,133 (93.3)	9,949 (90.7)			
>=90	8,313 (6.9)	5,382 (6.6)	2,931 (7.4)	7,287 (6.7)	1,026 (9.3)			

	Statin use			Diabetes		
	Total	No	Yes	No	Yes	Yes
	120,499	81,067	39,432	109,510	10,989	
Missing	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	104	72	32	90	14	
Total MET hours/week (Mean(SD))	13.0 (14.1)	13.3 (14.4)	12.3 (13.2)	13.3 (14.2)	10.1 (12.3)	
Missing	5,990	3,918	2,072	5,364	626	
Recreational physical activity minutes/week (Mean(SD))	187.4 (182.7)	191.4 (187.0)	179.1 (173.0)	191.1 (183.8)	150.4 (166.5)	
Missing	5,990	3,918	2,072	5,364	626	
Healthy eating index (Mean(SD))	67.2 (10.7)	67.0 (10.8)	67.6 (10.5)	67.4 (10.7)	65.5 (11.0)	
Missing	235	151	84	211	24	
Any Insurance						
No	5,535 (4.6)	4,227 (5.3)	1,308 (3.3)	4,801 (4.4)	734 (6.7)	
Yes	113,833 (95.4)	76,022 (94.7)	37,811 (96.7)	103,685 (95.6)	10,148 (93.3)	
Missing	1,131	818	313	1,024	107	
How many hours of sleep						
5 or less hours	9,067 (7.6)	6,270 (7.8)	2,797 (7.1)	7,997 (7.3)	1,070 (9.8)	
6 hours	32,608 (27.2)	22,078 (27.4)	10,530 (26.8)	29,433 (27.0)	3,175 (29.1)	
7 hours	45,950 (38.3)	30,790 (38.2)	15,160 (38.6)	42,098 (38.6)	3,852 (35.3)	
8 hours	32,262 (26.9)	21,477 (26.6)	10,785 (27.5)	29,432 (27.0)	2,830 (25.9)	
Missing	612	452	160	550	62	
Depressive symptoms						
No	101,192 (85.5)	67,830 (85.3)	33,362 (86.0)	92,348 (85.9)	8,844 (82.4)	
Yes (CESD>5)	17,113 (14.5)	11,698 (14.7)	5,415 (14.0)	15,221 (14.1)	1,892 (17.6)	
Missing	2,194	1,539	655	1,941	253	

	Statin use			Diabetes		
	Total	No	Yes	No	Yes	N (%)
	120,499	81,067	39,432	109,510	10,989	
Biomarkers	N (%)	N (%)	N (%)	N (%)	N (%)	
Glucose (mg/dl) (Mean(SD))	96.3 (19.3)	95.1 (17.9)	98.4 (21.6)	93.2 (11.3)	115.3 (38.2)	
Missing	97,272	66,028	31,244	89,557	7,715	
Insulin (mU/L) (Mean(SD))	8.6 (6.1)	8.3 (6.0)	9.2 (6.2)	8.0 (5.4)	12.4 (8.2)	
Missing	97,868	66,399	31,469	90,078	7,790	
HOMA-IR (Mean(SD))	2.1 (1.9)	2.0 (1.8)	2.3 (1.9)	1.9 (1.4)	3.7 (3.1)	
Missing	97,972	66,469	31,503	90,173	7,799	
HDL (mg/dl) (Mean(SD))	56.8 (14.6)	58.1 (14.9)	54.6 (13.7)	57.9 (14.6)	50.9 (13.1)	
Missing	98,990	67,289	31,701	91,146	7,844	
LDL (mg/dl) (Mean(SD))	146.8 (37.4)	139.0 (35.5)	160.8 (36.5)	146.5 (37.2)	148.7 (38.0)	
Missing	100,404	68,193	32,211	92,379	8,025	
Triglycerides (mg/dl) (Mean(SD))	140.5 (81.4)	130.2 (76.0)	158.9 (87.4)	135.8 (74.9)	169.1 (108.9)	
Missing	97,573	66,328	31,245	89,822	7,751	

Values are expressed as N(%) unless otherwise noted

Table 2

Risks of ASCVD, MI, Stroke and CVD death (CHD death and fatal stroke) by diabetes diagnosis before taking statin and after taking statin compared to women without diabetes who did not or did take a statin

	N	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	
		HR(95% CI)	HR(95% CI)	p-value ^a
ASCVD				
Unadjusted HR ^b	120,498	1.67 (1.52–1.84)	1.64 (1.34–1.99)	0.846
Multivariable adjusted HR ^c	109,590	1.42 (1.28–1.58)	1.39 (1.12–1.74)	0.885
MV with PS covariate	109,590	1.42 (1.27–1.57)	1.39 (1.12–1.73)	0.896
MV weighted by PS	109,590	1.41 (1.25–1.58)	1.19 (0.85–1.69)	0.373
MI				
Unadjusted HR ^b	120,499	1.65 (1.41–1.91)	1.75 (1.32–2.32)	0.709
Multivariable adjusted HR ^c	109,591	1.38 (1.17–1.62)	1.53 (1.12–2.08)	0.559
MV with PS covariate	109,591	1.38 (1.17–1.62)	1.52 (1.12–2.07)	0.554
MV weighted by PS	109,591	1.35 (1.12–1.62)	1.46 (0.91–2.35)	0.748
Stroke				
Unadjusted HR ^b	120,498	1.49 (1.29–1.72)	1.45 (1.08–1.94)	0.855
Multivariable adjusted HR ^c	109,590	1.31 (1.12–1.53)	1.22 (0.87–1.71)	0.718
MV with PS covariate	109,590	1.30 (1.11–1.52)	1.22 (0.87–1.71)	0.726
MV weighted by PS	109,590	1.24 (1.04–1.48)	0.74 (0.42–1.31)	0.088
CVD death				
Unadjusted HR ^b	120,499	1.82 (1.54–2.14)	1.47 (1.03–2.08)	0.269
Multivariable adjusted HR ^c	109,591	1.55 (1.30–1.85)	1.13 (0.74–1.71)	0.161
MV with PS covariate	109,591	1.55 (1.30–1.85)	1.13 (0.74–1.71)	0.162
MV weighted by PS	109,591	1.55 (1.27–1.90)	1.11 (0.62–2.02)	0.298

MV=Multivariable; PS=propensity score

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

^bHRs estimated from PH model including factors for statin use, diabetes diagnosis before statins, diabetes after statins.

^cHRs 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.