BEFORE THE
UNITED STATES JUDICIAL PANEL ON
MULTIDISTRICT LITIGATION

IN RE: Lipitor (Atorvastatin Calcium) Marketing, Sales Practices and Products Liability Litigation (No. II)	MDL 2502

INTERESTED PARTY RESPONSE IN SUPPORT OF PLAINTIFFS' MOTION FOR TRANSFER OF ACTIONS PURSUANT TO 28 U.S.C. § 1407

As with Plaintiff Dianne Christoper, Plaintiff Evalina Smalls agrees the pending Lipitor® actions should be centralized for coordination and consolidated pretrial proceedings pursuant to 28 U.S.C. § 1407 and Rules 6.1 and 6.2 of the Rules of Procedure for the United States Judicial Panel on Multidistrict Litigation. The aforementioned Lipitor® actions are products liability suits brought on behalf of injured individuals alleging substantially similar, if not identical, actions against a common defendant, Pfizer Inc.

Plaintiff files her *Interested Party Response in Support of Plaintiffs' Motion for Transfer of Actions Pursuant to 28 U.S.C. § 1407(a).* There is agreement among the filing plaintiff and the present interested party that consolidation and coordination of these actions is undoubtedly appropriate, and the interested party agrees transfer is appropriate to the United States District Court for South Carolina, Charleston Division. For the reasons discussed herein, Plaintiff respectfully requests the Panel enter an order consolidating and transferring all related actions to the United States District Court for the District of South Carolina, Charleston Division, for coordinated or consolidated pretrial proceedings.

I. BACKGROUND

A. Lipitor/Atorvastatin

Lipitor (also known as atorvastatin calcium) is an HMG-CoA reductase inhibitor and member of the class of drugs known as statins. It is prescribed to reduce the amount of cholesterol and other fatty substances in the blood. In December 1996, Parke-Davis Pharmaceutical Research, a division of Warner-Lambert Company, obtained FDA approval to market Lipitor. Warner-Lambert and Pfizer Inc. entered into a co-marketing agreement and the companies began distributing and selling Lipitor throughout the U.S. in 1997. In June 2000, Pfizer acquired Warner-Lambert and all rights to Lipitor.

In August 2011, FDA's Division of Metabolism and Endocrinology Products requested Pfizer make labeling changes for Lipitor. In February 2012, Pfizer complied with the FDA request and added language to the Warnings and Precautions section of the Lipitor label which stated: "Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including Lipitor." Prior to this February 2012 change, the drug label had never warned patients or physicians of any potential relationship between changes in blood sugar levels and the use of the drug.[1]

B. Lipitor/Atorvastatin Litigation

Plaintiff *Evalina Smalls* filed her action in the District of South Carolina, Charleston Division, on March 25, 2013, naming Pfizer Inc. as Defendant. Plaintiff alleges, inter alia, that the defendant manufactured, marketed, distributed, supplied, promoted and/or sold Lipitor, which is defective and unreasonably dangerous in that it causes diabetes; that the defendant knew or should have known of the risk of diabetes

[1] Plaintiff does not concede that Pfizer Inc.'s actions in placing new language in its label in February 2012 was, in fact, adequate notice to patients and physicians, but merely sets this fact before the panel for historical purposes.

injuries associated with the product; that the defendant marketed, distributed and/or sold the product without adequate warnings concerning its risks; and that as a direct and proximate result of use of the product the plaintiffs suffered serious injury, physical and mental pain and suffering, as well as economic loss.

To date, multiple individual actions have been commenced against Pfizer. See attached Schedule of Actions. Each of these actions asserts substantially similar claims and seeks substantially similar relief. Given the widespread sale and use of Lipitor for over a decade, numerous additional filings are expected.

At the last JPML hearing on July 25th the Chairman of the Panel expressed skepticism about the merits of this litigation stating that there was a "disjunction between the fact" that Lipitor is "a popular drug" that has been on the market for fifteen years and yet at the time of that hearing there were only twenty cases filed. See Transcript of July 25, 2013 JPML hearing re Lipitor, pages 5-6. Although a petition for multidistrict litigation is not generally the place for discussion of the evidence forming the basis of the litigation, in light of the concern expressed by the Court at the prior hearing, Plaintiffs feel it is important to address some of the evidence currently known about this case.

The facts are that the manufacturer of Lipitor, also known as atorvastatin, knew long ago about an increased risk of diabetes with the drug and also knew that it is not effective for women as a prophylactic treatment to prevent cardiovascular disease.[2] However, Pfizer has not disclosed those facts to the public and has refused to warn doctors or patients of the risk of diabetes caused by the use of Lipitor.

[2] The prophylactic use of statins by patients without any evidence of cardiovascular disease is referred to as "primary prevention."

Lipitor's New Drug Application ("NDA") was approved for marketing in 1996. At that time 21 C.F.R. § 201.57 provided that the Warning section of pharmaceutical labeling:

> [S]hall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. (Emphasis supplied).

The clinical trial data that was submitted in support of the NDA demonstrated a statistically significant 3-fold increased incidence of blood glucose more than 1.25 times the upper limit of normal in subjects who used Lipitor/atorvastatin; a level that is diagnostic for diabetes.[3] A statistically significant increased risk of blood glucose levels diagnostic for diabetes is "reasonable evidence of an association of a serious hazard with a drug" and thus the labeling for Lipitor should have warned about the risk of diabetes from the outset of marketing in 1997. Yet even today the Lipitor labeling does not warn about an increased risk of diabetes and it was not until February of 2012 that it even warned about increased blood glucose levels without informing doctors or patients of the magnitude of such increases.[4]

It has long been known that if women do develop diabetes, their risk of cardiovascular problems is higher than in men.[5] But it is only recently that the scientific community has discovered what Pfizer knew or should have known since 1996, that the use of Lipitor increases the risk of diabetes in both men and women. And it is even more

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[3] See Excerpt of FDA Medical Officer's 1996 review of Lipitor NDA, attached as Exhibit A.

[4] By way of comparison, in August 2013 the manufacturer of Crestor, another statin, added a warning to its labeling that increases in blood glucose with that drug "…may exceed the threshold for the diagnosis of diabetes mellitus."

[5] See PowerPoint slide attached as Exhibit B, with data from Kannel WB, Wilson PW. Comparison of Risk Profiles for Cardiovascular Events: Implications for Prevention. Adv Intern Med. 1997;42:39-66.

recently that researchers outside Pfizer have discovered that women using statins have a higher risk of contracting diabetes than men.[6] That is why there were so few cases on file in July of 2013 and why the cases filed to date are only the tip of the iceberg.

Ironically, the clinical trial data submitted by Pfizer in 2004 in support of its Supplemental NDA to receive an indication for Lipitor for primary prevention of cardiovascular disease did not demonstrate that the drug was effective in women for that purpose. Indeed, if anything the data show that women who used Lipitor had a higher risk of cardiovascular disease than the women who took placebos during the study.[7] Thus, the diabetes triggered by use of Lipitor by women as primary prevention for cardiovascular disease was preventable.

II. ARGUMENT

A. These actions are appropriate for transfer and pre-trial coordination under 28 U.S.C. § 1407

Title 28, section 1407(a) of the United States Code provides, "when civil actions involving one or more common questions of fact are pending in different districts, such actions may be transferred to any district for coordinated or consolidated pretrial proceedings." 28 U.S.C. § 1407(a). The Panel "shall" make such transfers when in furtherance of "the convenience of the parties and witnesses" and when transfer "will promote the just and efficient conduct of such actions." *Id.* Because of the number of

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[6] See, e.g., Culver et al. Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative. Arch Intern Med. 2012;172(2):144-52 (attached as Exhibit C); Goodarzi et al. Relationship of Sex to Diabetes Risk in Statin Trials. Diabetes Care. Vol. 36; July 2013 (attached as Exhibit D); Chen et al. Differential Impact of Statins on New-Onset Diabetes in Different Age Groups: A Population-Based Case-Control Study in Women from an Asian Country. PLOS One. August 2013, Vol. 8, Issue 8, e71817 (attached as Exhibit E).

[7] See Excerpt of FDA Medical Officer's Review of 2004 Supplemental NDA, attached as Exhibit F. See also Eisenberg T and Wells M. Statins and Adverse Cardiovascular Events in Moderate-Risk Females: A Statistical and Legal Analysis with Implications for FDA Preemption Claims. Journal of Empirical Legal Studies. Vol. 5, Issue 3, 507-50, September 2008.

current and anticipated Lipitor claims and the existence of common questions of fact, the requirements for transfer under §1407 are easily met here.

Each of the currently pending Lipitor actions involves common questions of fact, including whether the defendants knew or should have known of the dangerous propensity of the product to cause diabetes; whether the warnings were sufficient to alert users of the risk of adverse events; whether the defendants were negligent in marketing, promoting or distributing the product; and whether the product conformed to the defendant's implied warranties. Because of the common issues of fact and the number of current and anticipated claims, these cases are well suited for transfer and pretrial consolidation. Consolidation will foster the just and efficient conduct of these actions by preventing duplicative discovery and preventing inconsistent resolution of pretrial issues.

Finally, the convenience of the parties and witnesses clearly supports transfer and pretrial consolidation. Because of the common defendant, virtually identical issues of law and fact, and the number of current and anticipated claims, transfer and consolidation is most convenient for the parties and potential witness common to these actions.

B. The District of South Carolina is the Appropriate Forum for this Litigation.

The factors considered by this Panel in determining the appropriate MDL forum include: (1) the location of parties, witnesses and documents; (2) the accessibility of the proposed transferee district to parties and witnesses; and (3) the respective caseloads of the proposed transferee district courts. *See In re Corn Derivatives Antitrust Litig.*, 486 F. Supp 929, 93 1-32 (J.P.M.L. 1980). Analysis of each of these factors supports transfer of these actions to the District of South Carolina for consolidated pre-trial proceedings.

Lipitor was used by potentially millions of persons all across the United States. At this juncture, it is impossible to determine if any jurisdiction will emerge as having substantially more Lipitor claims than any other. At this time, however, there is a significant cluster of actions coordinated with the *Smalls* action in front of the Honorable Richard M. Gergel in the District of South Carolina. On May 28, 2013, Judge Gergel entered an order coordinating all cases in the District of South Carolina for pretrial discovery. Since that time, the court has entered a number of orders moving forward with discovery in the cases, including a protective order and initial discovery schedules for both plaintiffs' discovery of Pfizer and Pfizer's discovery in individual plaintiff's cases.[8] Pfizer has begun production of documents in the cases, including the production of portions of the New Drug Application for Lipitor as well as certain custodial files. Thus, the litigation is progressing in the District of South Carolina in coordinated fashion that would clearly benefit the cases pending in other federal districts.

It would not be inconvenient for counsel, witnesses, or the parties to travel to the District of South Carolina for any hearings or other proceedings relating to the MDL. The federal courthouse for the division in which the plaintiffs' cases are pending is located in Charleston, South Carolina, in close proximity to the Charleston International Airport which is serviced by major airlines with direct flights to Nashville, Philadelphia, Cincinnati, Atlanta, Charlotte, Chicago, Dallas, Houston, Boston, Washington, D.C., Detroit, and New York.

Moreover, the District of South Carolina has able jurists, and this Panel has already entrusted this judiciary with previous MDLs: In re L-Tryptophan Products

[8] Currently, the parties are negotiating revisions to the initial protective order and negotiating a protocol for the discovery of Electronically Stored Information.

Liability Litigation MDL-865, In re Safety-Kleen Corp. MDL-1378, In re Laidlaw, Inc. MDL 1397, In re American General Life & Accident Insurance Company Industrial Life Insurance MDL 1429, In re Electrical Receptacle Product Liability Litigation MDL 1595, In re the Thaxton Group, Inc. MDL 1612, In re Bausch & Lomb, Inc. Contact Lens Solution Products Liability Litigation, MDL 1785, In re Household Goods Movers Antitrust Litigation, MDL 1865, and In re MI Windows and Doors, Inc. Products Liability Litigation, MDL 2333. The *Smalls* case is currently pending in the Charleston Division of the District of South Carolina, which has successfully overseen several of the aforementioned MDL proceedings.

Finally, the caseload of the District of South Carolina supports transfer to this district. Data from Federal Court Management Statistics reveals the District of South Carolina is well-suited to provide an efficient disposition of these cases. According to judicial statistics for the twelve-month period ending March 31, 2012, civil cases proceeded to trial in the District of South Carolina in 24.3 months. The median time for filing to disposition other than trial for civil cases was only 8.5 months.

The District of South Carolina, and the Charleston Division in particular, is a perfectly appropriate and logical choice for consolidated pretrial proceedings in this litigation.

III. CONCLUSIONS

Transfer and consolidation for pretrial proceedings of all pending and subsequently filed Lipitor actions will promote the just and efficient conduct of these actions by allowing national coordination of discovery and other pretrial efforts, will prevent duplicative and potentially conflicting pretrial rulings, will reduce the costs of

litigation and allow cases to proceed more efficiently to trial. For all of the foregoing reasons, the plaintiffs respectfully request the Panel enter an order that the related actions be consolidated and transferred to the United States District Court the District of South Carolina, Charleston Division. Plaintiffs further respectfully request this matter be heard at the December 5, 2013 hearing session in Las Vegas, Nevada.

Dated: October 26, 2013.

Respectfully submitted,

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Table 8.8.2. All-completed studies: Median changes from baseline in clinical laboratories

	Placebo	N=110	Atorvastatin	N=2502	Combined HMGRIs	N=736
	Median change	N	Median change	N	Median change	N
Variable (units)						
ALT (U/L)	0	108	3	2483	1	735
AST (U/L)	0	108	1	2483	1	735
Alk Phos (U/L)	0	108	3	2471	0	731
CPK (U/L)	1.5	108	5	2421	3	735
Glucose (mg/dl)	0	106	2	2427	1.4	682
Platelets ($x10^3/mm^3$)	3.5	102	-8	2441	-8	674

Incidence of clinical laboratory abnormalities

The table below summarizes the clinical lab abnormalities, as defined by criteria for clinically meaningful changes, in the placebo-controlled data grouping. Most striking was the incidence of ALT and AST elevations to greater than the upper limit of normal (ULN) that appeared to be dose-related, with 45% of the 80 mg treatment group having at least one ALT value >ULN and 39% having an AST value >ULN.. AST abnormalities paralleled ALT elevations throughout the database. Also of interest is the increased incidence of CPK and glucose elevations in the atorvastatin group.

Table 8.8.3. Placebo-Controlled Data Grouping: Clinical Laboratory Abnormalities [Number (%) of Patients]

Laboratory Parameter	Criteria	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94	Combined* Atorvastatin N = 1122
Alk Phos	>3.00 × ULN	1 (<1)	0 (0)	0 (0)	0 (0)	3 (3)	3 (<1)
ALT	>ULN	31 (11)	139 (16)	4 (11)	27 (34)	42 (45)	219 (20)
AST	>ULN	25 (9)	110 (13)	4 (11)	19 (24)	37 (39)	176 (16)
BUN	>2.00 × ULN	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
CPK	>5.00 × ULN	0 (0)	4 (<1)	0 (0)	1 (1)	1 (1)	6 (1)
Glucose	>1.25 × ULN	3 (1)	30 (3)	2 (6)	1 (1)	4 (4)	37 (3)
Hematocrit	<0.75 × LLN	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Hemoglobin	<0.75 × LLN	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Total Bilirubin	>1.50 × ULN	1 (<1)	9 (1)	0 (0)	1 (1)	2 (2)	15 (1)
WBC	<0.75 × LLN	4 (1)	9 (1)	0 (0)	2 (3)	1 (1)	12 (1)
	>1.50 × ULN	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)
Any Abnormality		44 (16)	214 (25)	8 (22)	33 (42)	50 (53)	314 (28)

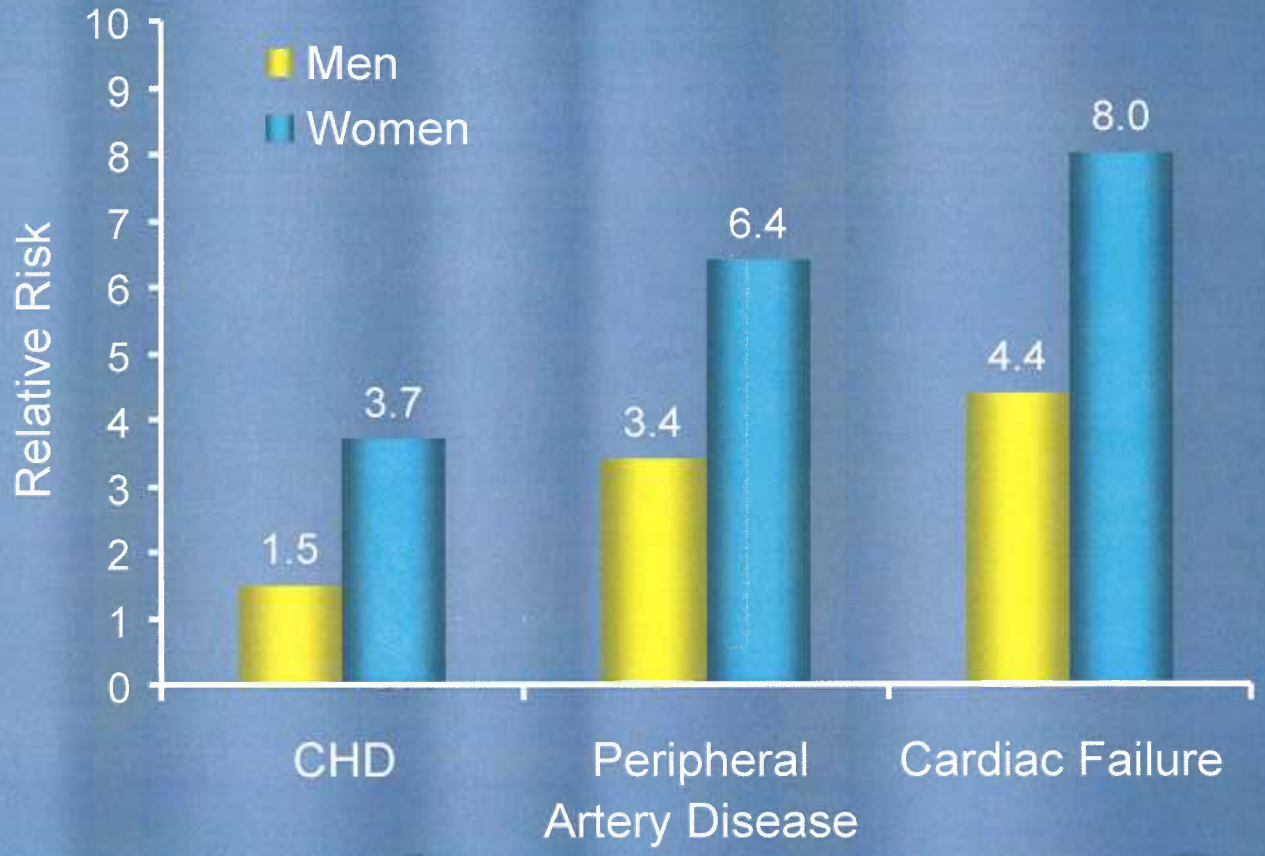
Alk Phos = Alkaline Phosphatase; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BUN = Blood Urea Nitrogen; CPK = Creatine Phosphokinase.

* Contains data for patients who received 2.5 mg (N = 11), 5 mg (N = 26), and 60 mg (N = 13) atorvastatin.

In the **all-completed studies** data grouping, the incidence of lab abnormalities in the combined atorvastatin group was compared to the placebo and to the combined HMGRIs groups. 683/2502 (27%) of atorvastatin patients as compared to 147/742 (20%) and 18/110 (16%) of the combined HMGRIs and placebo groups, respectively, had at least one ALT level >ULN. 1% of both atorvastatin and HMGRI groups had CPK> 5X ULN. Glucose elevation >1.25 X ULN occurred

Diabetes Has a Greater Impact on CVD in Women Than in Men

Age-Adjusted Relative CVD Risk*



*Relative CVD risk for persons with diabetes versus those without

Kannel WB, et al. *Adv Intern Med.* 1997;42:39-66.

tabbies

EXHIBIT B

ORIGINAL INVESTIGATION

ONLINE FIRST

Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative

Annie L. Culver, BPharm; Ira S. Ockene, MD; Raji Balasubramanian, ScD; Barbara C. Olendzki, RD, MPH; Deidre M. Sepavich, MBA; Jean Wactawski-Wende, PhD; JoAnn E. Manson, MD, DrPH; Yongxia Qiao, MD; Simin Liu, MD, ScD; Philip A. Merriam, MSPH; Catherine Rahilly-Tierny, MD, MPH; Fridtjof Thomas, PhD; Jeffrey S. Berger, MD, MS; Judith K. Ockene, PhD, MEd, MA; J. David Curb, MD; Yunsheng Ma, MD, PhD

Background: This study investigates whether the incidence of new-onset diabetes mellitus (DM) is associated with statin use among postmenopausal women participating in the Women's Health Initiative (WHI).

Methods: The WHI recruited 161 808 postmenopausal women aged 50 to 79 years at 40 clinical centers across the United States from 1993 to 1998 with ongoing follow-up. The current analysis includes data through 2005. Statin use was captured at enrollment and year 3. Incident DM status was determined annually from enrollment. Cox proportional hazards models were used to estimate the risk of DM by statin use, with adjustments for propensity score and other potential confounding factors. Subgroup analyses by race/ethnicity, obesity status, and age group were conducted to uncover effect modification.

Results: This investigation included 153 840 women without DM and no missing data at baseline. At baseline, 7.04% reported taking statin medication. There were 10 242 incident cases of self-reported DM over 1 004 466 person-years of follow-up. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83). This association remained after adjusting for other potential confounders (multivariate-adjusted HR, 1.48; 95% CI, 1.38-1.59) and was observed for all types of statin medications. Subset analyses evaluating the association of self-reported DM with longitudinal measures of statin use in 125 575 women confirmed these findings.

Conclusions: Statin medication use in postmenopausal women is associated with an increased risk for DM. This may be a medication class effect. Further study by statin type and dose may reveal varying risk levels for new-onset DM in this population.

Arch Intern Med. 2012;172(2):144-152.
Published online January 9, 2012.
doi:10.1001/archinternmed.2011.625

GIVEN THE SUCCESS OF statins in both primary and secondary prevention of cardiovascular morbidity and mortality,[1-6] their use is progressively increasing, especially among older Americans.[7] With such widespread use, even small risks are apparent alongside benefits. One emerging risk is an increased incidence of diabetes mellitus (DM). There is evidence that incident DM associated with statin use may be more common in the elderly, in women, and in Asians.[8-12] A recent analysis suggests that preexisting metabolic risk factors control incident DM rate with statin medication.[13] It is unclear if this risk varies with individual statins or if this is a dose-driven class effect.[9,14] Although experimental and clinical studies find that individual statins act differently on glucose homeostasis as a function of relative lipophilicity and/or potency of action,[15] other findings differ. A recent meta-analysis of 17 randomized controlled trials by Mills et al[16] found a class effect increase of new-onset DM with statins (odds ratio [OR], 1.09; 95% CI, 1.02-1.16) similar to that reported by Sattar et al.[9] Possibly, the grouping of statins masks the effect variation of individual statins. Still, at some given dose threshold, differences may be overcome, as implied by a meta-analysis of 5 trials comparing intensive to moderate dosing regimens using

See Editor's Note at the end of article

Author Affiliations are listed at the end of this article.

mainly atorvastatin and simvastatin.[13,17] Notably, meta-analysis results display intertrial and intratrial variability in diagnostic and statistical methods and do not consistently consider confounding factors. Moreover, contributing sample sizes do not permit balanced comparison by statin type, sex, race/ethnicity, and age. Similarly, single studies may uncover only part of a greater topography.

As a large part of the aging population, postmenopausal women have not been fully represented in past clinical trials.[16] Sex differences in DM pathogenesis are well recognized.[18,19] Using the Women's Health Initiative (WHI) data, we evaluated the overall effect of statin medication use on incident DM risk and examined these associations by specific statin agent. We stratified analyses by race/ethnicity, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) category, and age group to determine if any associations were modified by these factors. In addition, we conducted subgroup analysis in women with and without self-reported cardiovascular disease (CVD) at baseline to address potential confounding and selection bias.

METHODS

PARTICIPANTS

The WHI recruited 161 808 postmenopausal women aged 50 to 79 years at 40 clinical centers across the United States from 1993 to 1998 and followed consenting participants. Of these women, 68 132 were enrolled in 1, 2, or all 3 of the clinical trial (CT) arms: the Dietary Modification Trial, the Hormone Trial, and the Calcium and Vitamin D Trial. Another 93 676 women were enrolled into a prospective observational study (OS).[20-23] The WHI eligibility criteria included the ability to complete study visits with expected survival and local residency for at least 3 years. Original exclusion criteria addressed conditions that would limit full participation in the study. This analysis used WHI data through 2005. After exclusion for prevalent DM, missing data, and use of cerivastatin (this medication was withdrawn from the market in 2001 for safety reasons), a total of 153 840 women were included (**Figure**).

MEASUREMENT AND CLASSIFICATION OF STATIN MEDICATIONS

The current medication regimens of all CT participants were inventoried at baseline and at years 1, 3, 6, and 9. In the OS, medication data were inventoried at baseline and year 3. At each inventory, the brand or generic name on the medication label was matched to the corresponding item in the Master Drug Data Base (Medi-Span, Indianapolis, Indiana). We sorted for statin use as users or nonusers at baseline and year 3. Given that Sattar et al[9] found a null effect of lipophilicity among statins, and in the absence of dose information, we determined statin categories by relative potency of action to decrease low-density lipoprotein cholesterol. Accordingly, statins were designated as low (fluvastatin, lovastatin, pravastatin) or high (simvastatin, atorvastatin) potency.[24,25]

IDENTIFICATION OF DM

At baseline and at each semiannual (CT) or annual (OS) contact, incident treated DM was identified by questionnaire and was defined as a self-report of a new physician diagnosis of

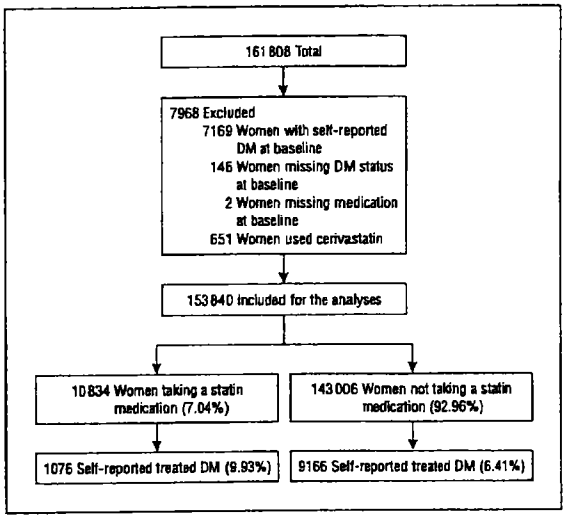


Figure. Flowchart for statin users and diabetes mellitus (DM) analyses using data sets from the Women's Health Initiative.

treated DM. This method of identification of prevalent and incident DM has been used in prior publications by the WHI investigators.[18,26-28] The accuracy of self-reported DM in the WHI trials has been assessed using medication and laboratory data, and self-reported DM was found to be reliable.[29]

COVARIATES

Baseline questionnaires ascertained demographic and health history information, including race/ethnicity, age, educational attainment, family history of DM, family history of depression, self-report of CVD, hormone therapy use, and smoking status. Baseline self-report for CVD has been previously validated in the WHI[30,31] and found to have reasonable agreement with hospital discharge *International Classification of Diseases, Ninth Revision (ICD-9)* codes.

The metabolic equivalents of physical activities and average daily nutrient intake were computed, using detailed methods described elsewhere.[32,33] Trained and certified clinic staff measured height using a fixed stadiometer and weight by a calibrated balance-beam scale. Relative weight as BMI was calculated from these values. Blood was analyzed for glucose and insulin for the random 6% WHI-CT blood subsample at baseline, year 1, year 3, year 6, and year 9. Fasting glucose was analyzed using the hexokinase method with interassay coefficients of variation less than 2%.[26] Insulin was measured by enzyme-linked immunosorbent assay. The WHI used the homeostasis model assessment of insulin resistance (HOMA-IR), which was developed for application in large epidemiologic investigations as an alternative to the glucose clamp. HOMA-IR = fasting plasma insulin (μIU/mL) × fasting plasma glucose (mmol/L)/22.5.[34]

STATISTICAL ANALYSIS

Cox proportional hazards (PH) models were used to estimate hazard ratios (HRs) of DM by statin medication use. The dependent variable was time to occurrence of DM determined by self-report (ie, time to event). The time to event was calculated as the interval between enrollment date and the earliest of the following: (1) date of annual medical history update when new DM was ascertained (observed outcome) and (2) date of the last annual medical update during which DM status was

ascertained (censored outcome). The primary independent variable in these analyses was statin use at baseline, coded as a binary variable. We present 3 Cox PH models to examine the association between baseline statin use and DM: model 1 estimates the unadjusted HRs (and associated 95% CIs) of the effects of statin use on incident DM; model 2 presents age- and race/ethnicity–adjusted HRs; and model 3 presents HRs adjusted for all potential confounding variables at baseline (age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arm, and self-report of CVD). Similar analyses were conducted for specific type of statin medication use at baseline, categorized as low vs high potency.

Since individuals using statins may have different underlying conditions that could put them at elevated risk for DM, we conducted several subgroup analyses to control confounding by indication. First, we conducted subgroup analyses by age, race/ethnicity, and BMI categories to examine whether the associations of statin use and onset of DM differed by categories of these variables. Age was categorized into 3 groups (50-59 years, 60-69 years, and ≥70 years). Race/ethnicity was assessed according to 4 major groups (white, African American, Hispanic, Asian). Body mass index was categorized into 3 groups (<25.0, 25.0-29.9, ≥30.0). Second, we conducted similar analyses in 2 subgroups of women either with or without self-reported CVD at baseline. Finally, propensity score analysis[35] was performed to reduce the confounding effects of other factors in the evaluation of the association between statin use and DM risk within an observational study setting. Participant-specific propensity scores were estimated from a logistic regression model to predict the probability of statin prescription. Covariates considered for inclusion into the logistic regression model included age, BMI, self-report of hypertension, self-report of CVD, family history of DM, smoking status, and physical activity. The final propensity score model retained all covariates noted herein with the exception of physical activity, which was an insignificant predictor of statin use. The association between statin use and DM risk was evaluated in Cox PH models after adjusting for the estimated propensity score.

After exclusion for cases of DM before year 3 (146 women), use of cerivastatin (651 women), and missing medication data at year 3 (2 women), our longitudinal analyses were conducted in a subset of 125 575 women from the OS and the CT arm at baseline and year 3 visits. Statin use was sorted into 4 categories: (1) never took statin; (2) use at both baseline and at the year 3 visit, (3) use only at baseline; and (4) use only at the year 3 visit. The HRs for DM by statin use were estimated similarly based on Cox PH models.

RESULTS

PARTICIPANTS' CHARACTERISTICS

Participant characteristics are listed in **Table 1**. At baseline, the mean (SD) age of women included in our sample was 63.2 (7.3) years. Approximately 16.30% of the women were from racial/ethnic groups other than white, of which the largest representation was African American (8.32%). Only 2.56% (3922 women) were Asian. At baseline, 7.04% of participants took statin medication. Of these, 30.29% took simvastatin; 27.29%, lovastatin; 22.52%, pravastatin; 12.15%, fluvastatin; and 7.74%, atorvastatin. Comparison between statin users and nonusers showed significant differences in baseline characteristics.

STATIN USE AT BASELINE AND DM INCIDENCE

A total of 10 242 incident cases of DM were reported over 1 004 466 person-years of follow-up. **Table 2** presents results regarding the association between statin use at baseline and risk of incident DM. In unadjusted models, statin use at baseline was significantly associated with an increased DM risk (HR, 1.71; 95% CI, 1.61-1.83) when compared with nonuse. This association was decreased but remained significant after adjusting for potential confounders (HR, 1.48; 95% CI, 1.38-1.59). This association was observed for all types of statin. Similar risk associations were found in use of either high- or low-potency statins, with multivariate-adjusted HRs of 1.45 (95% CI, 1.36-1.61) and 1.48 (95% CI, 1.36-1.61) compared with nonusers, respectively. **Table 3** shows subgroup analyses by race/ethnicity, BMI category, and age group. In both unadjusted and adjusted models, statin use was consistently associated with increased risk of DM across subgroups by age. We observed significantly increased risk of DM by statin use within subgroups of white, Hispanic, and Asian women in both unadjusted and adjusted models. In adjusted models, we observed HRs of 1.49 (95% CI, 1.38-1.62), 1.18 (95% CI, 0.96-1.45), 1.57 (95% CI, 1.14-2.17), and 1.78 (95% CI, 1.32-2.40) among whites, African Americans, Hispanics, and Asians, respectively. Statin use was also associated with a significantly increased risk of DM within 3 subgroups according to BMI (<25.0, 25.0-29.9, ≥30.0). Moreover, a significantly increased risk of DM associated with statin use was observed among women with BMI lower than 25.0 when compared with women with BMI of 30.0 or higher after adjusting for all potential confounders. In adjusted models, the HRs were 1.89 (95% CI, 1.57-2.29), 1.66 (95% CI, 1.48-1.87), and 1.20 (95% CI, 1.09-1.33) within the groups of women with BMI of less than 25.0, 25.0 to 29.9, and 30.0 or higher, respectively.

STATIN USE AT BASELINE AND RISK OF DM AMONG POSTMENOPAUSAL WOMEN WITH AND WITHOUT HISTORY OF CVD

To address potential confounding and selection bias, we conducted subgroup analyses among postmenopausal women with and without a history of CVD (**Table 4**). Among a subset of 24 842 women who self-reported CVD at baseline, we found that statin use was associated with an increased risk of DM (HR, 1.52; 95% CI, 1.36-1.71). These associations remained significant after adjusting for potential confounders (HR, 1.46; 95% CI, 1.29-1.65). Similar findings were observed among women without CVD at baseline.

PROPENSITY SCORE ANALYSES

In unadjusted models, statin use was significantly related to DM risk (HR, 1.71; 95% CI, 1.61-1.83). When the propensity score was included, the estimated HR attenuated to 1.38 (95% CI, 1.29-1.47). On inclusion of other confounders in the model, the HR was essentially unaltered (HR, 1.40; 95% CI, 1.31-1.51). Propensity score

Table 1. Characteristics of 153 840 Study Participants, Women's Health Initiative[a]

Variable	Total (N = 153 840)	Statin Users (n = 10 834)	Non–Statin Users (n = 143 006)	*P* Value
Age, y	63.17 (7.25)	65.66 (6.48)	62.98 (7.27)	<.001
BMI	27.77 (5.81)	28.56 (5.32)	27.70 (5.84)	<.001
Dietary variable				
Energy intake, kcal/d	1625.24 (711.56)	1541.81 (690.42)	1631.56 (712.75)	<.001
Carbohydrate, % of energy	50.34 (9.37)	52.12 (9.34)	50.21 (9.36)	<.001
Protein, % of energy	16.71 (3.21)	17.06 (3.31)	16.68 (3.20)	<.001
Fat, % of energy	32.53 (8.39)	30.79 (8.37)	32.66 (8.38)	.81
Saturated fat, % of energy	10.84 (3.33)	9.94 (3.15)	10.91 (3.34)	<.001
Trans fat, g/d	4.29 (3.22)	4.02 (3.08)	4.31 (3.23)	<.001
Fiber, g/d	15.88 (7.14)	15.63 (7.07)	15.90 (7.14)	.18
Alcohol intake, g/d	5.32 (10.58)	4.47 (9.44)	5.38 (10.65)	<.001
Physical activity				
Minutes of recreational physical activity per week[b]	183.40 (180.53)	177.50 (167.28)	183.86 (181.52)	<.001
Categorical variable, No. (%)				
Race/ethnicity				
Asian or Pacific Islander	3922 (2.56)	401 (3.71)	3521 (2.47)	<.001
African American	12 772 (8.32)	862 (7.97)	11 910 (8.35)	
Hispanic/Latino	5978 (3.90)	322 (2.98)	5656 (3.96)	
European American, not of Hispanic origin	128 458 (83.71)	9065 (83.87)	119 393 (83.69)	
Education				
<High school	7711 (5.05)	651 (6.05)	7060 (4.97)	<.001
High school/GED	25 955 (17.0)	2241 (20.83)	23 714 (16.71)	
>High school, <4 y college	57 740 (37.81)	4205 (39.08)	53 535 (37.72)	
≥4 y college	61 285 (40.14)	3663 (34.04)	57 622 (40.60)	
Smoking status				
Never	77 364 (50.94)	5178 (48.48)	72 186 (51.13)	<.001
Former	63 893 (42.07)	4858 (45.49)	59 035 (41.81)	
Current	10 605 (6.98)	644 (6.03)	9961 (7.06)	
Hormone therapy use				
Never	49 198 (32.94)	3654 (34.42)	45 544 (32.83)	<.001
Former	34 430 (23.05)	2633 (24.80)	31 797 (22.92)	
Current	65 720 (44.0)	4330 (40.78)	61 390 (44.25)	
Family history of DM				
Yes	47 329 (30.93)	3653 (33.91)	43 676 (30.70)	<.001
No	98 686 (64.48)	6599 (61.26)	92 087 (64.73)	
Type of statin medication use at baseline				
Lovastatin	2957 (27.29)	2957 (27.29)	NA	NA
Simvastatin	3282 (30.29)	3282 (30.29)	NA	NA
Fluvastatin	1316 (12.15)	1316 (12.15)	NA	NA
Atorvastatin	839 (7.74)	839 (7.74)	NA	NA
Pravastatin	2440 (22.52)	2440 (22.52)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GED, general educational development; HR, hazard ratio; NA, not applicable.

[a] Data are continuous variables given as means (SDs) except where noted. Numbers and percentages may not add up to 153 840 and 100% owing to missing data.

[b] Geometric means (SDs) were presented.

adjusted models yielded HRs of 1.38 (95% CI, 1.23-1.54) and 1.40 (95% CI, 1.29-1.53) for respective increased risk with either high- or low-potency statin use at baseline compared with nonuse.

LONGITUDINAL MEASURES OF STATIN USE AND RISK OF DM

When compared with those who never received statin therapy, unadjusted HRs of 1.82 (95% CI, 1.65-2.00), 1.75 (95% CI, 1.43-2.14), and 1.81 (95% CI, 1.67-1.97) were observed for the groups of women who reported statin use at both baseline and at the year 3 visit, reported statin use only at baseline, and reported statin use only at the year 3 visit, respectively (**Table 5**). The risk associations remained significant after adjusting for age, race/ethnicity, other potential confounders, and propensity score. The multivariate adjusted HRs were 1.47 (95% CI, 1.32-1.64), 1.44 (95% CI, 1.15-1.80), and 1.60 (95% CI, 1.47-1.75), respectively.

SENSITIVITY ANALYSIS

A sensitivity analysis was conducted on a subset of 3706 women without DM at baseline and enrolled in the WHI CT for whom fasting glucose measurements were available at baseline and at least 1 additional follow-up visit. Diabetes mellitus was identified based on fasting glucose levels of 126 mg/dL (6.99 mmol/L) or higher. In unadjusted models, statin use at baseline was not significantly related to DM risk (HR, 1.06; 95% CI, 0.61-1.86). However, using baseline through year 6 data in the CT arm,

Table 2. Association Between Diabetes Mellitus (DM) Risk and Statin Use Status at Baseline in 153 840 Participants

Variable	Patients, No.	Cases of New-Onset DM	Unadjusted HR	Age- and Race/Ethnicity-Adjusted HR[a]	Multivariate-Adjusted HR[b]
Taking statin medications at baseline					
Yes	10 834	1076 (9.93)	1.71 (1.61-1.83)	1.69 (1.58-1.80)	1.48 (1.38-1.59)
No	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Years of statin medication use					
<1.0	3614	360 (9.96)	1.74 (1.57-1.94)	1.71 (1.54-1.90)	1.46 (1.30-1.64)
1.0-2.9	3650	365 (10.00)	1.72 (1.55-1.91)	1.67 (1.51-1.86)	1.42 (1.26-1.59)
≥3.0	3570	351 (9.83)	1.68 (1.51-1.87)	1.68 (1.51-1.87)	1.57 (1.40-1.77)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Type of statin medications at baseline					
Lovastatin					
Yes	2949	281 (9.53)	1.52 (1.35-1.71)	1.51 (1.33-1.70)	1.35 (1.19-1.55)
Other statins	7885	795 (10.08)	1.85 (1.72-1.99)	1.82 (1.69-1.97)	1.56 (1.43-1.69)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Simvastatin					
Yes	3247	310 (9.55)	1.71 (1.52-1.92)	1.72 (1.53-1.93)	1.41 (1.25-1.61)
Other statins	7587	766 (10.10)	1.77 (1.64-1.91)	1.73 (1.61-1.87)	1.54 (1.41-1.67)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Fluvastatin					
Yes	1313	145 (11.04)	1.99 (1.69-2.35)	1.90 (1.61-2.24)	1.61 (1.35-1.92)
Other statins	9521	931 (9.78)	1.72 (1.60-1.84)	1.71 (1.59-1.83)	1.48 (1.37-1.60)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Atorvastatin					
Yes	839	79 (9.42)	1.99 (1.58-2.49)	1.99 (1.58-2.49)	1.61 (1.26-2.06)
Other statins	9995	997 (9.97)	1.74 (1.63-1.86)	1.72 (1.61-1.84)	1.49 (1.39-1.61)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Pravastatin					
Yes	2423	256 (10.57)	1.87 (1.65-2.13)	1.83 (1.61-2.07)	1.63 (1.43-1.87)
Other statins	8411	820 (9.75)	1.71 (1.59-1.84)	1.70 (1.58-1.83)	1.46 (1.34-1.58)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Potency of statin at baseline					
Low potency: lovastatin, fluvastatin and pravastatin	6701	682 (10.18)	1.68 (1.56-1.82)	1.64 (1.52-1.78)	1.48 (1.36-1.61)
High potency: simvastatin and atorvastatin	4133	394 (9.53)	1.74 (1.58-1.93)	1.75 (1.58-1.93)	1.45 (1.36-1.61)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: HR, hazard ratio; PH, proportional hazards.
[a] The HRs were estimated from Cox PH models adjusting for age and race/ethnicity.
[b] The HRs were estimated from Cox PH models, adjusting for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, and self-report of cardiovascular disease at baseline.

we found that the statin users had higher fasting glucose levels and HOMA-IR compared with non–statin users, with increasing values from baseline to year 6 follow-up.

COMMENT

The results of this study imply that statin use conveys an increased risk of new-onset DM in postmenopausal women. In keeping with the findings of other studies,[9,13,36] our results suggest that statin-induced DM is a medication class effect and not related to potency or to individual statin. However, the data set contains unequal representation of statins that may have influenced the outcomes. In addition, women who took statins may have changed statin type prior to incident DM. Results may actually reflect a changing market and demand and include those statins that were not available at baseline. For example, rosuvastatin was not available until 2003, after the baseline and year 3 capture points, and may affect follow-up results. Rosuvastatin was associated with increased risk for DM in the postmenopausal women in the JUPITER trial (HR, 1.49; 95% CI, 1.11-2.01).[10] In the absence of dose information, we could not explore further comparisons.

Women with a BMI lower than 25.0 were at greater risk for new-onset DM than those with BMI of 30.0 or higher, who seem to be at lowest relative risk among BMI categories. Given no other reports of this incidence pattern in other studies, we can only speculate that differences in phenotype, such as weight distribution, may contribute to this finding. Native hormonal changes in menopause permit a redistribution of weight in favor of visceral fat that may be independent of BMI as a risk factor for DM.[37] Weight gain within a BMI category may also increase risk for DM.[38] Alternatively, there may be some paradoxical protection against DM among postmenopausal women, akin to that reported for recurrent coronary artery events. This may in fact be a sign of index event bias.[15] This is an area to explore further.

Overlaps in 95% CIs erase significant ethnic differences, although the trend for greater risk among Asian women compared with others agrees with evidence for increased sensitivity to statin effects in this group.[8,12,34,35] Our sample size urges cautious interpretation.

Table 3. Association Between Diabetes Mellitus (DM) Risk and Statin Use Status at Baseline, Within Age, Race/Ethnicity, and BMI Subgroups in 153 840 Participants

Variable	Patients, No.	Cases of New-Onset DM, No. (%)	Unadjusted HR[a]	Multivariate-Adjusted HR[b]
Age, y				
50-59				
Statin users	1936	205 (10.59)	1.82 (1.58-2.09)	1.50 (1.29-1.76)
Nonusers	49 685	3169 (6.38)	1 [Reference]	1 [Reference]
60-69				
Statin users	5641	566 (10.03)	1.66 (1.52-1.81)	1.47 (1.34-1.62)
Nonusers	63 035	4145 (6.58)	1 [Reference]	1 [Reference]
≥70				
Statin users	3257	305 (9.36)	1.65 (1.46-1.86)	1.47 (1.29-1.68)
Nonusers	30 286	1852 (6.12)	1 [Reference]	1 [Reference]
Race/ethnicity				
White				
Statin users	9065	814 (8.98)	1.82 (1.69-1.96)	1.49 (1.38-1.62)
Nonusers	119 393	6534 (5.47)	1 [Reference]	1 [Reference]
African American				
Statin users	862	128 (14.85)	1.26 (1.05-1.50)	1.18 (0.96-1.45)
Nonusers	11 910	1546 (12.98)	1 [Reference]	1 [Reference]
Hispanic				
Statin users	322	51 (15.84)	1.64 (1.23-2.18)	1.57 (1.14-2.17)
Nonusers	5656	617 (10.91)	1 [Reference]	1 [Reference]
Asian or Pacific Islander				
Statin users	401	59 (14.71)	2.12 (1.59-2.81)	1.78 (1.32-2.40)
Nonusers	3521	264 (7.50)	1 [Reference]	1 [Reference]
BMI				
<25.0				
Statin users	2824	144 (5.10)	2.50 (2.11-2.98)	1.89 (1.57-2.29)
Nonusers	52 446	1208 (2.30)	1 [Reference]	1 [Reference]
25.0-29.9				
Statin users	4367	391 (8.95)	1.91 (1.71-2.12)	1.66 (1.48-1.87)
Nonusers	49 048	2561 (5.22)	1 [Reference]	1 [Reference]
≥30.0				
Statin users	3549	532 (14.99)	1.23 (1.13-1.35)	1.20 (1.09-1.33)
Nonusers	40 239	5306 (13.19)	1 [Reference]	1 [Reference]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; PH, proportional hazards.
[a] The HRs were estimated from Cox PH models.
[b] The HRs were estimated Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, and self-report of cardiovascular disease at baseline. Age was excluded in models within age subgroups. Similarly, race and BMI were individually excluded in models fitted within race/ethnicity and BMI subgroups.

Table 4. Risk of Diabetes Mellitus (DM) by Statin Use Among Women With and Without Medical History of Cardiovascular Disease (CVD) at Baseline

	Women With CVD (n = 24 842)		Women Without CVD (n = 120 173)	
Description	Statin Users	Nonusers	Statin Users	Nonusers
Participants, No.	3338	21 504	7089	113 084
Incident DM cases, No.	369	1695	645	6786
Cumulative incidence rate, %	11.05	7.88	9.10	6.0
Unadjusted HR (95% CI)[a]	1.52 (1.36-1.71)	1 [Reference]	1.65 (1.52-1.79)	1 [Reference]
Age- and race/ethnicity–adjusted HR (95% CI)[b]	1.52 (1.36-1.70)	1 [Reference]	1.61 (1.49-1.75)	1 [Reference]
Multivariate adjusted HR (95% CI)[c]	1.46 (1.29-1.65)	1 [Reference]	1.48 (1.36-1.62)	1 [Reference]

Abbreviations: HR, hazard ratio; PH, proportional hazards.
[a] The HRs were estimated from Cox PH models.
[b] The HRs were estimated Cox PH models, adjusted for age and race/ethnicity.
[c] The HRs were estimated from Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, body mass index, physical activity, alcohol intake, energy intake, family history of DM, and hormone therapy use.

Overlapping 95% CIs indicate similar risk for incident DM with statin use for women with CVD (adjusted HR, 1.46; 95% CI, 1.29-1.65) and without CVD (adjusted HR, 1.48; 95% CI, 1.36-1.62). Given that specific indications for statin use was not available among all women, and that our analysis did not include cardiovascular outcomes, we could not compare risk and benefit for statins in primary or secondary prevention in

Table 5. Risk of Diabetes Mellitus (DM) by Statin Use at Baseline and 3-Year Follow-up in 125 575 Participants

Description	Statin Use Only at Baseline	Statin Use Only at 3-y Follow-up	Statin Use at Baseline and 3-y Follow-up	Never Use
Participants, No.	1531	9571	7076	107 397
Incident DM cases, No.	98	644	442	4294
Cumulative incidence rate, %	6.40	6.73	6.25	4.00
Unadjusted HR (95% CI)[a]	1.75 (1.43-2.14)	1.81 (1.67-1.97)	1.82 (1.65-2.00)	1 [Reference]
Adjusted HR (95% CI)				
Age and race/ethnicity[b]	1.65 (1.35-2.01)	1.79 (1.65-1.95)	1.81 (1.64-2.00)	1 [Reference]
Multivariate[c]	1.49 (1.19-1.86)	1.65 (1.51-1.81)	1.56 (1.41-1.74)	1 [Reference]
Propensity score[d]	1.49 (1.20-1.85)	1.63 (1.49-1.78)	1.43 (1.28-1.58)	1 [Reference]
Multivariate, including propensity score[e]	1.44 (1.15-1.80)	1.60 (1.47-1.75)	1.47 (1.32-1.64)	1 [Reference]

Abbreviations: BMI, body mass index; HR, hazard ratio; PH, proportional hazards.
[a] The HRs were estimated from Cox PH models.
[b] The HRs were estimated Cox PH models, adjusted for age and race/ethnicity.
[c] The HRs were estimated from Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, and self-report of CVD at baseline.
[d] The HRs were estimated from Cox PH models, adjusted for propensity score.
[e] The HRs were estimated from Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, self-report of CVD at baseline, and propensity score.

this population. Current and impending guidelines for cardiometabolic risk assessment and statin therapy include monitoring for DM and DM risk,[39,40] which seems prudent.

Several strengths are worth noting: the WHI includes a large, racially diverse cohort of postmenopausal women, and its prospective design enables an examination of temporal associations. When the WHI began, statin use in women with CHD risk factors was not prevalent, allowing comparative study of statin use and nonuse in women with similar risk factors. Our study was also uniform in terms of ascertainment of DM and consistent with data collection for confounders and risk factors over several years.

There are several limitations. First, as this was a observation study, we could not control all confounding factors. While our subgroup analyses in women either with or without CVD found that statin use remains a significant risk for DM, we cannot rule out variations in health care. The sensitivity analyses also attempt to discover and resolve detection and/or selection bias, but it is possible that such biases remain. Second, we did not have data on blood lipid, C-reactive protein, or hemoglobin A_{1c} levels to distinguish if those using statins were at higher risk than those not using statins. Third, although incident DM in older women is likely of the type 2 variety, the WHI question did not specify for type.[26,27,29] Despite a lower sensitivity in self-reports for newly incident DM, statin users and nonusers should have a similar bias of underreporting.[41,42] Fourth, the inability to track intermittent or inconsistent medication use limits analysis.[43] We cannot reliably say that women who reported statin use at 1 or both collection points continued therapy in a way that was likely to provide the intended effect. Moreover, the WHI data up to 2005 reveal that only 7.4% of women used statins, and this proportion may not reflect attributable risk patterns of greater use. Finally, we could not measure drug-drug or drug-disease interactions.

Clearly, statins address the cardiovascular consequences of DM, and current American Diabetes Association guidelines for primary and secondary prevention should not change.[44] The Cholesterol Treatment Trialists' Collaboration found that statins significantly benefit vascular mortality and morbidity and all-cause mortality in diabetic populations with rates comparable with those without DM.[45] Likewise, guidelines for statin use in nondiabetic populations should not change.[39,40] However, the consequences of statin-induced DM have not been specifically defined and deserve more attention. Given the wide use of statins in the aging population, further studies among women, men, and diverse ethnicities will clarify DM risk and risk management to optimize therapy.

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EDITOR'S NOTE

ONLINE FIRST

Increased Diabetes Mellitus Risk With Statin Use

Tipping the Balance

In this issue of the *Archives*, Culver et al report an association between use of statins and increased risk of developing diabetes mellitus in a large cohort of women enrolled in the Women's Health Initiative. These data confirm and extend associations previously demonstrated among participants in randomized trials. Although observational data are potentially susceptible to bias by indication, we thought it was noteworthy that the increased risk of diabetes mellitus with statin use was similar among women with and without a history of cardiovascular disease, a finding that may have important implications for the balance of risk and benefit of statins in the setting of primary prevention in which previous meta-analyses show no benefit on all-cause mortality.

Kirsten L. Johansen, MD

OBSERVATIONS

Relationship of Sex to Diabetes Risk in Statin Trials

Statins appear to modestly increase the risk of incident diabetes. While an early trial (the West of Scotland Coronary Prevention Study [WOSCOPS]) suggested possible protection against diabetes (1), the JUPITER study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) documented a 25% increase in diabetes risk with statin treatment (3 vs. 2.4%, $P = 0.01$) (2). A meta-analysis of 13 statin trials (>91,000 subjects) documented a statistically significant 9% increased risk for incident diabetes (3). Women may be more susceptible than men to develop diabetes while taking statins. While the overall increase in diabetes incidence was 25% in JUPITER, sex stratification revealed that the risk was increased by 49% in women and by only 14% in men (4). A retrospective analysis of the Women's Health Initiative (WHI) found that statin use was associated with a 71% increased risk of diabetes (95% CI, 1.61–1.83); after adjustment for potential confounders, the hazard ratio (HR) remained significant at 1.48 (1.38–1.59) (5). The effect of sex on incident diabetes has not been evaluated in recent meta-analyses (3).

To explore the relationship between the proportion of women in statin trials and diabetes risk, we obtained from the literature (3,6) the odds ratios (ORs) (and 95% CIs) of new-onset diabetes from 13 placebo-controlled statin trials (WOSCOPS, Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS], Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID], Heart Protection Study [HPS], Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm [ASCOT-LLA], Scandinavian Simvastatin Survival Study [4S], Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Heart Failure [GISSI HF], Controlled Rosuvastatin in Multinational Trial in Heart Failure [CORONA], JUPITER, Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial [ALLHAT-LLT], Prospective Study of Pravastatin in the Elderly at Risk [PROSPER], Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese [MEGA]) and reviewed the index publications to obtain the percent of women in each. Using SAS version 9.1, we conducted a random-effects meta-regression analysis between natural log-transformed OR of

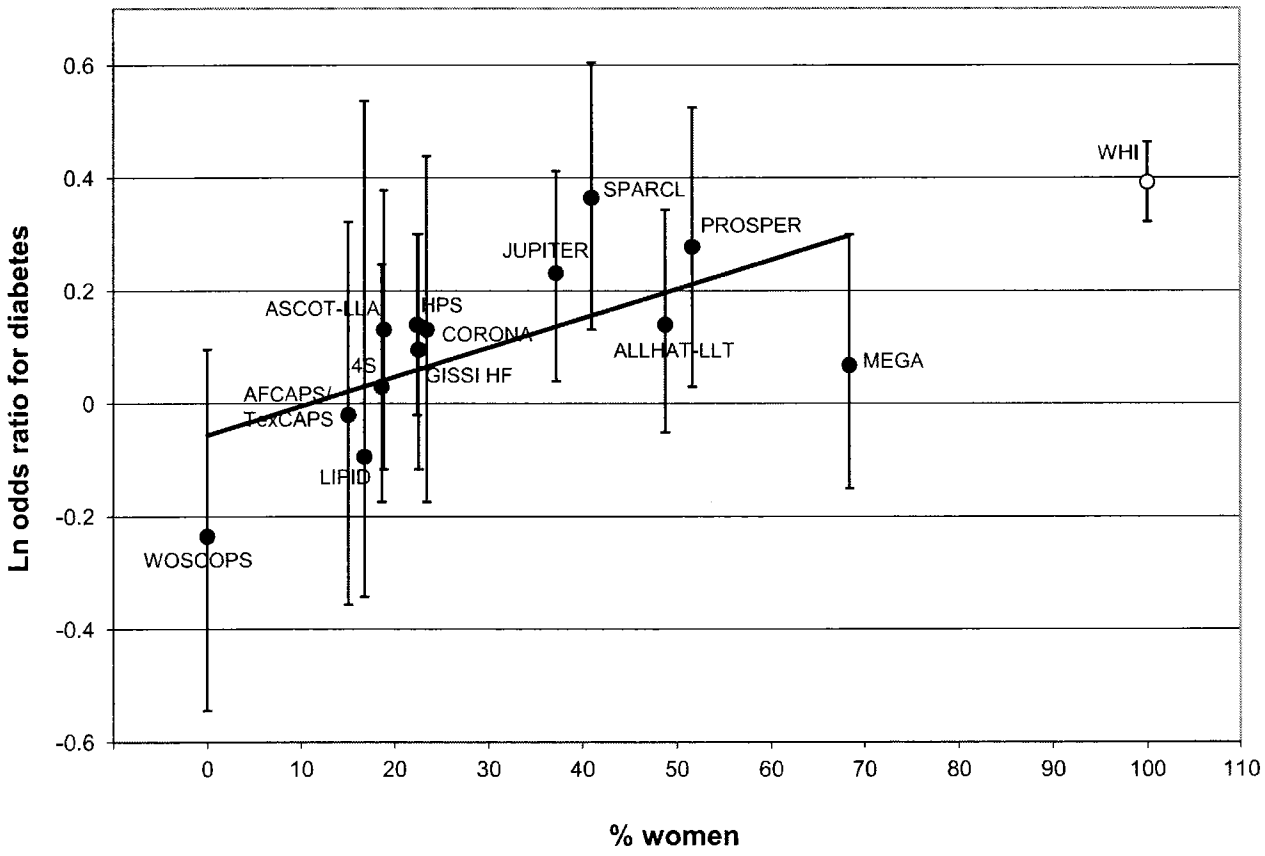

Figure 1—*Meta-regression of percent of women on OR for incident diabetes. Only trials examining statin vs. nonstatin placebo or control arms are represented. The percent of women in each trial was obtained from the index publications. When available, the percent of nondiabetic women was used (HPS, LIPID); otherwise, the percent of women in the trial as a whole was used. ORs (natural log-transformed, ln) for diabetes were obtained from the Sattar et al. meta-analysis (3) and from Waters et al. for SPARCL (6). The error bars represent the 95% CIs. The adjusted HR for diabetes from the WHI is plotted for comparison (open circle); its data were not used in the regression calculation.*

diabetes and proportion of females. A P value <0.05 for the likelihood ratio test for sex was considered statistically significant. We found a significant relationship ($r = 0.6$, $P = 0.036$) between the percent of women in statin trials and the OR of diabetes (Fig. 1). The three trials (JUPITER, PROSPER, SPARCL) that individually had significant rates of diabetes had higher proportions of women (>35%) than usually included in statin trials (<25%), while the one trial (WOSCOPS) suggesting reduced diabetes consisted only of men.

We found a provocative association of female sex with increased odds of diabetes. While the risk of statin-induced diabetes seen in WHI must be interpreted cautiously because it is an observational study, Fig. 1 reveals that the WHI HR for diabetes is consistent with the regression line derived from randomized trials. The possible greater risk of statin-induced diabetes in women is of substantial importance given that women tend to have lower cardiovascular risk than men (4), yet may be prescribed a statin based on lipid levels alone without calculation of cardiovascular risk. If this leads to statin administration to low-risk women, the risk of incident diabetes may outweigh the cardiovascular benefit.

As a meta-regression analysis, our findings are hypothesis generating. One possibility for higher risk in women is smaller body mass and hence greater effective statin dosage. Possibly, the effect of statins on diabetes has been noticed only recently because women have previously been underrepresented in statin trials. Appropriate monitoring for glycemic deterioration and encouragement of preventive lifestyle measures in patients commencing statin therapy may be particularly relevant for women.

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M.O.G. collected data and wrote the manuscript. X.L. analyzed data and edited the manuscript. R.M.K., J.I.R., and Y.-D.I.C. reviewed and edited the manuscript. M.O.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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PLOS ONE

Differential Impact of Statin on New-Onset Diabetes in Different Age Groups: A Population-Based Case-Control Study in Women from an Asian Country

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Abstract

Background: Statins reduce cardiovascular risks but increase the risk of new-onset diabetes (NOD). The aim of this study is to determine what effect, if any, statins have on the risk of NOD events in a population-based case-control study. An evaluation of the relationship between age and statin-exposure on NOD risks was further examined in a female Asian population.

Method: In a nationwide case-controlled study, the authors assessed 1065 female NOD patients and 10650 controls with matching ages, genders and physician visit dates. The impact of statin-exposure on NOD was examined through multiple logistic regression models. Subgroup analysis for exploring the risk of NOD and statin-exposure in different age groups was performed.

Results: Statin-exposure was statistically significantly associated with increased new-onset diabetes risks using multivariate analysis. Interaction effect between age and statin-exposure on NOD risk was noted. For atorvastatin, the risk of cDDDs>60 was highest among the 55–64 year-olds (adjusted odds ratio [OR], 8.0; 95% confidence interval [CI], 2.57–24.90). For rosuvastatin, the risk of cDDDs>60 was highest among the 40–54 year-olds (adjusted OR, 14.8; 95% CI, 2.27–96.15). For simvastatin, the risk of cDDDs>60 was highest among the 55–64 year-olds (adjusted OR, 15.8; 95% CI, 5.77–43.26). For pravastatin, the risk of cDDDs>60 was highest among the 55–64 year-olds (adjusted OR, 14.0; 95% CI, 1.56–125.18).

Conclusions: This population-based study found that statin use is associated with an increased risk of NOD in women. The risk of statin-related NOD was more evident for women aged 40–64 years compared to women aged 65 or more, and was cumulative-dose dependent. The use of statins should always be determined by weighing the clinical benefits and potential risks for NOD, and the patients should be continuously monitored for adverse effects.

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Introduction

There is no doubt using statins can effectively reduce cardiovascular events and mortality [1,2]. Yet, the Jupiter trial, a cornerstone study into using statins in primary prevention, found that apart from potential benefits in cardiovascular outcomes, statins also increased the risk in new onset diabetes (NOD) [3]. In this study, the use of rosuvastatin, in comparison with a placebo, showed a 25% of higher risk of NOD. Later, a meta-analysis showed statin therapy was associated with a 9% increase in the risk of incident diabetes [4]. Even though many studies concluded that the cardiovascular and mortality benefits of statin therapy outweighed the diabetes hazard, statin-related NOD is still a concern [5,6].

In a pooled analysis of data from 5 statin trials, intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared to moderate-dose statin therapy [7]. Data from a SPARCL trial also demonstrated that high-dose atorvastatin treatment, compared to placebos, is associated with a 19% increased risk of NOD [8]. The study also demonstrated that baseline fasting glucose levels and the features of metabolic syndrome are predictive of new-onset Type II diabetes [8]. The finding was consistent with post-hoc analysis from the Jupiter trial,

which found that the risk factors of statin-related NOD included metabolic syndrome, impaired fasting glucose, a BMI of 30 kg/m^2, or HbA1c greater than 6%[5]. There was still no consensus about the relationship between age and statin-related NOD. Statin-related NOD may be related to younger ages as shown by an IDEAL trial [8], and older ages [4,9,10].

However, most studies showed no relationship or only an insignificant trend for younger age predisposing to statin-related NOD [6,7,11]. Data also revealed lipid lower therapy cannot reduce total or cardiovascular mortality for women without cardiovascular disease. [12] Also, in the Women's Health Initiative study, statin use at baseline was associated with an increased risk of DM (hazard ratio [HR]: 1.71; 95% CI: 1.61–1.83) and, even after adjusting for potential confounders, the multivariate adjusted HR for developing DM was 1.48 (95% CI: 1.38–1.58) [13]. Statin use for primary prevention in women continues to be controversial based on lacking of net clinical benefit[14]. So, it is very important to evaluate the risk of NOD in female patients. We conducted a retrospective cohort study by using the Taiwan National Health Insurance Research Database (NHIRD) to evaluate the relationship between age and statin-related NOD in a female Asian population.

Materials and Methods

Ethics Statements

This study was initiated after being approved by the Institutional Review Board of Buddhist Dalin Tzu Chi General Hospital, Taiwan. The identification numbers and personal information of the individuals included in the study were not included in the secondary files,the review board approved that written consents from patients were not required.

Database

Taiwan implemented its National Health Insurance program in 1995, which provides compulsory universal health insurance. The program includes up to 99% of Taiwan's citizens and has contracts with 97% of all medical providers. The database contains comprehensive information on insured subjects, including dates of clinical visits, diagnostic codes, and details of prescriptions and expenditures. This study used the Longitudinal Health Insurance Dataset for 2004–2006 released by the Taiwan Nation Health Research Institute. The patients in this dataset did not statistically significantly differ from the larger cohort in age, gender, or healthcare costs, as reported by the Taiwan National Health Research Institute (www.nhri.org.tw).

Study Population

For this study, cases were female patients with incident new-onset diabetes diagnosed between Jan 1st 2004 and Dec 31st 2006 due to our preliminary data (Appendix S1) showing that the association between NOD and statins were more obvious in women. New-onset diabetes patients with diagnosis codes (International Classification of Diseases, 9th revision - Clinical Modification [ICD-9-CM] 250.00–250.93) with 4 or more outpatient visits or who had been hospitalized for further treatment were included in the study [15]. By using these criteria, the accuracy of the diabetes diagnoses was more than 92%. Patients with diabetes diagnosed before 2004 were excluded.

Each new-onset diabetes patient was matched with 10 match controls from the Longitudinal Health Insurance Database between Jan 1st 2004 and Dec 31st 2006. The controls were matched to cases based on propensity scores, which in turn was derived from gender, age, and year of the patient's physician visit, and comorbidities (history of hypertension, coronary artery disease, and hyperlipidemia). A SAS macro was applied to implement Greedy matching on the basis of their propensity scores. Individuals younger than 40 and patients were excluded. In the end, there were 1065 NOD patients and 10650 matched controls in our study.

Definition of Exposure and Covariate Adjustment

The dosage, date of prescription, duration, and total number of statin pills dispensed from the outpatient pharmacy prescription database were recorded. In accordance with the Anatomic Therapeutic Chemical Classification System of drugs, atrovastatin, rosuvastatin, simvastatin andpravastatin were selected. The cumulative DDD was calculated according to the following formula: (total amount of drug/DDD amount of drug). To examine the dose-effect relationship, we categorized statin use into four groups in our series (0, 1–27, 28–60, >60 cDDDs).

Other medications were included for analysis, including nonstatin lipid-lowering medications (i.e., cholestyramine, colestipol, colextran, neceritrol, nicrofuranose, acipimox, probucol, and ezetimibe), aspirin, angiotensin-converting enzyme inhibitors (i.e. captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, benazepril, cilazapril, and fosinopril), triglyceride-lowering medications (i.e. bezafibrate, clofibriate, etofibriate, fenofibrate, gemfibrozil, and simifibrate) and hormone replacement therapy. The patients' ages, genders, comorbidities (history of hypertension, coronary artery disease, diabetes, hyperlipidemia, atrial fibrillation, chronic kidney disease, obesity, and peripheral arterial disease), monthly income levels as a proxy of socioeconomic status, levels of urbanization, and geographic regions of residence were also recorded. The individuals were classified into three groups: (1) low SES: lower than US$571 per month (New Taiwan Dollar (NT$) 20,000); (2) moderate SES: between US$571–1,141 per month (NT$20,000–40,000); and (3) high SES: US$1,142 per month (NT$40,001) or more [16]. The geographic regions and urbanization of the areas of residence were classified as previously described [17,18].

Statistical Analysis

SPSS version 15 (SPSS Inc., Chicago, IL) was used for data analysis. Pearson's chi-square test was used for categorical variables, demographic characteristics (age group and gender), comorbidities (history of hypertension, coronary artery disease, diabetes, hyperlipidemia, atrial fibrillation, chronic kidney disease, obesity, and peripheral arterial disease), and medications. The multiple logistic regression model was used to examine whether statin use was an independent risk factor of NOD after adjusting for age, gender, comorbidities (history of hypertension, coronary artery disease, diabetes, hyperlipidemia, atrial fibrillation, chronic kidney disease, obesity and peripheral arterial disease), level of urbanization, and region of residence, socioeconomic status, and use of medication. A p-value of <0.05 was considered statistically significant.

Results

Demographic Data

1065 female patients with new-onset diabetes and 10650 controls with date-matched ages, selected comorbidities and physician visits were recruited. The distribution of demographic characteristics between the two groups is shown in Table 1. In comparison with controls, the NOD patients were more likely to be of low socioeconomic status, to reside in southern Taiwan, and

Table 1. Demographic characteristics and co-morbidities of the primary diabetes(DM) and control groups in Taiwan, 2009 (n = 11715).

Characteristic	With diabetes (n = 1065)		Controls (n = 10650)		P value
	Number	(%)	Number	(%)	
Age (mean ±SD)	61.32±11.69		61.13±13		0.593
40–54 year of age	362	(34)	3583	(36)	0.801
55–64 year of age	293	(27)	3012	(28)	
65–74 year of age	263	(25)	2685	(25)	
≥75 year of age	147	(14)	1370	(13)	
Gender					-
Male	0	(0)	0	(0)	
Female	1065	(100)	10650	(100)	
Hypertension					1.000
Yes	44	(4)	440	(4)	
No	1021	(96)	10210	(96)	
Coronary heart disease					1.000
Yes	47	(4)	470	(4)	
No	1018	(96)	10180	(96)	
Hyperlipidemia					1.000
Yes	82	(8)	820	(8)	
No	983	(92)	9830	(92)	
Atrial fibrillation					0.943
Yes	7	(1)	72	(1)	
No	1058	(99)	10578	(99)	
Chronic kidney disease					0.852
Yes	9	(1)	96	(1)	
No	1056	(99)	10554	(99)	
Obesity					NA
Yes	0	(0)	0	(0)	
No	1065	(100)	10650	(100)	
Peripheral arterial disease					0.761
Yes	2	(0.2)	25	(0.2)	
No	1063	(99.8)	10625	(99.8)	
Socioeconomic status					0.028
Low	547	(52)	5236	(49)	
Medium	450	(42)	4485	(42)	
High	68	(6)	929	(9)	
Urbanization level of residence					0.735
Urban	301	(28)	3132	(29)	
Suburban	444	(42)	4377	(41)	
Rural	320	(30)	3141	(30)	
Geographic region of residence					0.001
Northern	525	(49)	5876	(55)	
Central	212	(20)	1904	(18)	
Southern	295	(28)	2647	(25)	
Eastern	33	(3)	223	(2)	
Statin					<0.001
Yes	163	(15)	268	(3)	
No	902	(85)	10382	(97)	
Non-statin lipid lowering medications					0.088
Yes	5	(0.5)	22	(0.2)	

Table 1. Cont.

Characteristic	With diabetes (n = 1065)		Controls (n = 10650)		P value
	Number	(%)	Number	(%)	
No	1060	(99.5)	10628	(99.8)	
Aspirin					<0.001
Yes	249	(23)	693	(7)	
No	816	(77)	9957	(97)	
Angiotensin-converting ezeyme inhibitors					<0.001
Yes	186	(18)	193	(2)	
No	879	(82)	10457	(98)	
Triglyceride-lowering medications					<0.001
Yes	80	(7)	100	(1)	
No	985	(93)	10550	(99)	
Progesterone alone					0.043
Yes	30	(3)	435	(4)	
No	1035	(97)	10215	(96)	
Estrogen alone					0.557
Yes	55	(5)	596	(6)	
No	1010	(95)	10054	(94)	
Estrogen-progesterone combination					0.180
Yes	12	(1)	178	(2)	
No	1053	(99)	10472	(98)	

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to use asprin, statin, anigotensin-converting enzyme inhibitors and triglyceride-lowering medications.

The Effect of Statins on New-onset Diabetes Risks

Statin-exposure was statistically significantly associated with increased new-onset diabetes risks using multivariate analysis (Table 2).

Table 2 also shows an inverse relationship between the risk of NOD and age. After adjusting for other factors, increased age was associated with a decreased risk of NOD. In individuals aged 65–74 years and ≥75 years ($p = 0.001$ and <0.001, respectively), compared with those aged 40–54 years, the risk of NOD was reduced by 28% and 37% respectively.

In order to clarify the effect of age on the relationship between new-onset diabetes and statins, subgroup analysis was further performed. Table 3 shows that the NOD risk was increased as statin cDDDS increased, and the effect was more significant between the age groups of 40–54 years and 55–64 years. For atorvastatin, the risk of cDDDs>60 was highest among the 55–64 year-olds (adjusted odds ratio [OR], 8.0; 95% confidence interval [CI], 2.57–24.90) (Figure 1a). For rosuvastatin, the risk of cDDDs>60 was highest among the 40–54 year-olds (adjusted OR, 14.8; 95% CI, 2.27–96.15) (Figure 1b). For simvastatin, the risk of cDDDs>60 was highest among the 55–64 year-olds (adjusted OR, 15.8; 95% CI, 5.77–43.26) (Figure 1c). For pravastatin, the risk of cDDDs>60 was highest among the 55–64 year-olds (adjusted OR, 14.0; 95% CI, 1.56–125.18) (Figure 1d). Table 3 also showed higher cumulative dose of statins carries higher risk of NOD.

In summary, statin-exposure is associated with NOD. The risk of NOD was more evident for women aged 40–64 years.

Discussion

This population-based study implies that statin use is associated with an increased risk of new-onset diabetes in women. In addition, the effect of NOD for statin-exposurre varied according to the age when the individuals took statins, and the risk was more evident for women aged 40–64 years compared to those aged 65 or more. The population of women between ages 40 and 64 are more likely to be exposed to Hormone Therapy (HT) drugs. Table 1 showed there is no additional risk for NOD when HT drugs are used conjointly with statins. Among the different statin drugs, rosuvastatin resulted in the highest level of risk ofNOD in women aged 40–54 years and other three statins(atorvastatin, simvastatin and pravastatin) in women age 55–64. The impact of age on statin-related NOD is a controversial issue. Most studies support the hypothesis that patients with a higher risk of diabetes, such as metabolic syndrome, obesity or higher A1Ccarry a higher risk of statin related NOD [5,6,8,19,20]. It is known that the elements of metabolic syndrome correlate with age [21]. Therefore, it is reasonable to conclude that older patients may have a higher risk of suffering from statin-related NOD, a conclusion supported by some studies [4,9,10]. This is different from our findings. Only one report produced results similar to our finding [8]. These findings have yet to be explained. However, this finding prompted us to pay more attention to the prescription of statins to younger female patients, to look for a possible higher risk of developing diabetes mellitus, or other diabetes-related complications over a lifetime. Further study to verify the age effect on statin-related NOD is warranted.

The strengths of our study are based on the fact that it was a large population-based case-control study (n = 11715), with nearly complete follow-up information regarding any drug prescriptions among the whole study population (99%), as well as the fact that

Table 2. Adjusted odds ratio for diabetes with different statins exposure and age -response analyses (n = 11715).

Female	Adjusted odds ratio	(95% CI)	P value
Age group			
40–54 year of age	1		
55–64 year of age	0.86	(0.72–1.02)	0.082
65–74 year of age	0.72	(0.59–0.87)	0.001
≥75 year of age	0.63	(0.49–0.80)	<0.001
Atorvastatin			
Yes	2.80	(1.74–4.49)	<0.001
No	1		
Rosuvastatin			
Yes	4.69	(2.78–7.92)	<0.001
No	1		
Simvastatin			
Yes	4.09	(2.52–6.64)	<0.001
No	1		
Pravastatin			
Yes	3.41	(1.66–7.04)	0.001
No	1		

Abbreviation: 95% CI, 95% confidence interval.
*Adjustments are made for patient's gender, hypertension, coronary heart disease, diabetes, hyperlipidemia, atrial fibrillation, chronic kidney disease, obesity, peripheral arterial disease, non-statin lipid lowering medications, aspirin, angiotensin-converting enzyme inhibitors, triglyceride-lowering medications, hormone therapy, socioeconomic status, geographic region and urbanization level of residence.
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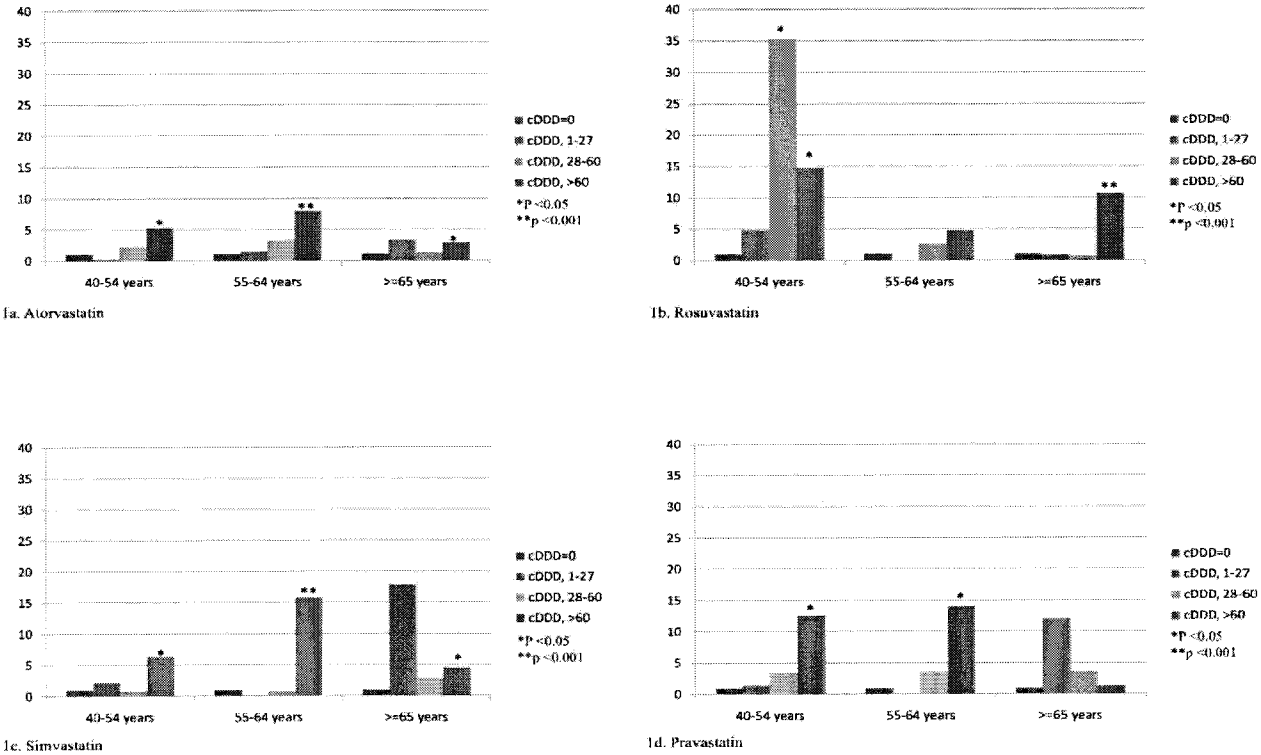
the dataset is routinely monitored for diagnostic accuracy by the National Health Insurance Bureau of Taiwan. Dose-response effects on diabetes risks were observed in atorvastatin, rosuvastatin, simvastatin, and pravastatin. This observation further strengthened the association between statin-exposure and new-onset diabetes.

Recent data showed that different types and doses of statins show different potentials in terms of increasing the risk of new-onset diabetes [22]. This is still a controversial issue. Pravastatin has been shown to reduce the risk of NOD in men aged 65 years by 30% in the WOSCOP study [23]. In one study, simvastatin significantly increased insulin and leptin levels and decreased adiponectin levels and insulin sensitivity, while pravastatin significantly increased adiponectin levels and insulin sensitivity but did not change insulin and leptin levels [24]. Compared to atorvastatin, pravastatin has a favorable effect on pancreatic beta cell function [25]. Koh hypothesized that pravastatin increases the expression of adiponectin mRNA, enhances adiponectin secretion, increases plasma levels in adiponectin, and enhances insulin sensitivity, which results in a favorable effect regarding NOD, compared to other statins [26]. Baker stated that statins do not appear to demonstrate a 'class effect' on insulin sensitivity in patients without diabetes, based on meta-analysis of 16 trials comparing pravastatin, simvastatin, atorvastatin and rosuvastatin to placebo or controls in non-diabetic patients [27]. Navarese et al also found that 40 mg/day of pravastatin was associated with the lowest risk of NOD compared to placebo (odds ratio 1.07, 95% credible interval 0.86 to 1.30). 20 mg/day of rosuvastatin was numerically associated with a 25% increased risk of diabetes compared to placebos (odds ratio 1.25, 95% credible interval 0.82 to 1.90). 80 mg/day of atorvastatin appeared to produce an intermediate impact on NOD compared to placebo (odds ratio 1.15, 95% credible interval 0.90 to 1.50) [22]. Ma et al found that



1a. Atorvastatin

1b. Rosuvastatin

1c. Simvastatin

1d. Pravastatin

Figure 1. The adjusted odds ratio for new-onset diabetes for artorvastatin (a), rosuvastatin (b), simvastatin (c), and pravastatin (d).
doi:10.1371/journal.pone.0071817.g001

Table 3. Adjusted odds ratio for diabetes with dose-response analyses (n = 11715).

cDDD	Female (n = 11715)		Group					
			40–54years (n = 3945)		55–64years (n = 3305)		≥65years (n = 4465)	
	Event/total(%)	Odds radio (95% CI)	Event/total(%)	Odds radio (95% CI)	Event/total (%)	Odds radio (95% CI)	Event/total (%)	Odds radio (95% CI)
Atorvastatin								
cDDD = 0	1002/11574(9)	1	346/3912(9)	1	274/3270(8)	1	382/4392(9)	1
cDDD, 1–27	5/13(39)	1.56 (0.33–7.38)	1/5(20)	0.23 (0.004–14.81)	3/4(75)	1.39 (0.07–28.17)	1/4(25)	3.26 (0.25–43.29)
cDDD, 28–60	11/37(30)	1.75 (0.66–4.63)	3/8(38)	2.26 (0.11–46.78)	2/8(25)	3.22 (0.39–26.40)	6/21(29)	1.26 (0.34–4.72)
cDDD, >60	47/91(52)	3.50** (1.95–6.27)	12/20(60)	5.22* (1.31–20.74)	14/23(61)	7.99** (2.57–24.90)	21/48(44)	2.85* (1.22–6.65)
Rosuvastatin								
cDDD = 0	1019/11616(9)	1	347/3923(9)	1	279/3278(9)	1	393/4415(9)	1
cDDD, 1–27	2/12(17)	1.83 (0.25–13.54)	1/3(33)	4.85 (0.15–161.39)			1/9(22)	0.84 (0.04–18.32)
cDDD, 28–60	18/45(40)	2.88* (1.27–6.53)	6/9(67)	35.38* (2.81–445.79)	10/17(59)	2.57 (0.60–11.11)	2/19(11)	0.69 (0.11–4.27)
cDDD, >60	26/42(62)	9.81** (4.53–21.24)	8/10(80)	14.76* (2.27–96.15)	4/10(40)	4.74 (0.79–28.55)	14/22(64)	10.64** (3.47–32.60)
Simvastatin								
cDDD = 0	1010/11581(9)	1	348/3910(9)	1	277/3269(9)	1	385/4402(9)	1
cDDD, 1–27	4/12(33)	3.95 (0.91–17.15)	2/7(29)	2.10 (0.22–20.56)	0/2(0)	–	2/3(67)	17.88 (0.88–363.72)
cDDD, 28–60	13/43(30)	1.95 (0.76–5.05)	2/12(17)	0.81 (0.05–12.71)	4/12(33)	0.76 (0.06–10.38)	7/19(37)	2.83 (0.75–10.64)
cDDD, >60	38/79(48)	5.99** (3.28–10.96)	10/16(63)	6.24* (1.33–29.22)	12/22(55)	15.80** (5.77–43.26)	16/41(39)	4.49* (1.76–11.43)
Pravastatin								
cDDD = 0	1037/11665(9)	1	353/3932(9)	1	281/3288(9)	1	403/4445(9)	1
cDDD, 1–27	5/7(71)	9.23 (0.97–87.40)	1/2(50)	1.41 (0.01–154.10)	2/2(1)	–	2/3(67)	12.04 (0.59–247.05)
cDDD, 28–60	10/20(50)	2.89 (0.90–9.23)	2/3(67)	3.36 (0.18–62.39)	5/8(63)	3.48 (0.54–22.65)	3/9(33)	3.61 (0.46–28.21)
cDDD, >60	13/23(57)	4.67* (1.58–13.75)	6/8(75)	12.54* (1.58–99.30)	5/7(71)	13.96* (1.56–125.18)	2/8(25)	1.34 (0.16–11.38)

Abbreviation: 95% CI, 95% confidence interval.

*<0.05 **<0.001.

*Adjustments are made for patient's gender, hypertension, coronary heart disease, diabetes, hyperlipidemia, atrial fibrillation, chronic kidney disease, obesity, peripheral arterial disease, non-statin lipid lowering medications, aspirin, angiotensin-converting enzyme inhibitors, triglyceride-lowering medications, hormone therapy, socioeconomic status, geographic region and urbanization level of residence.

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for elderly hypertensive and dyslipidemic patients who took lovastatin (HR 1.38; 95% CI 1.26, 1.50) or simvastatin (HR 1.30; 95% CI 1.14, 1.48) were at a higher risk of developing NOD than non-users, and those who took pravastatin and fluvastatin were not associated with an increased risk of NOD [11]. Another study by Ma found a different result, where patients with hypertension and dyslipidemia taking fluvastatin, lovastatin and rosuvastatin were at a lower risk of NOD, while those who took pravastatin were at a greater risk. Simvastatin and atorvastatin seemed to have a neutral effect [9]. Culver et. al. found that statin use in post-menopausal women is still associated with an increased risk of NOD, and the phenomenon may be a medication class effect [13]. This was similar to our finding. In our study, we also focused on women, and found that all 6 statins carry a risk for NOD, which differs from some of the previous reports mentioned above.

Based on the findings of table 3, statin-related NOD is possibly cumulative-dose dependent. Higher accumulated doses result in a higher risk of NOD. Some reports also supported this finding. Exposure to higher doses of statin resulted in higher risks of NOD [7,9,22]. Many mechanisms for statin-related DM have been proposed but this is still a controversial issue [28]. Xia et. al. (2008) indicated that chronic inhibition of cholesterol synthesis (in mouse and human pancreatic islets) impairs insulin secretion and pancreatic beta-cell function. They argued that dysregulation of cellular cholesterol may cause impairment of beta-cell function which may in turn lead to the development of type 2 diabetes[29]. Based on this hypothesis, exposure to any kind of statins would result in NOD. As our data showed, every statin carries risk of

NOD. This study also provided an information of dose-dependent effect on NOD which is a finding from real-world practice. Yet,we still need a conclusive mechanism to explain this finding, in order to reduce the risk of statin-related NOD.

There are several limitations to this study. First, diagnoses of NODand any other comorbid conditions were completely dependent on ICD-9-CM codes. However, the National Health Insurance Bureau of Taiwan conducts randomized reviews of the charts and interviews patients to verify the accuracy of these diagnoses. Hospitals with outlier charges or practices are subject to auditing, and heavy penalties are levied if malpractice or discrepancies are found. Furthermore, the accuracy of the National Health Insurance Research Database when recording the diagnosis of NOD using above mentioned criteria is $\geq$ 92% [15]. Second, the database does not contain information on smoking, dietary habits, and body mass index. Hence, obesity, an important risk factor for statin related NOD, cannot be analyzed in this study. Third, due to subgroup analysis for interaction effect of age and statin-exposure on DM risk, some estimates w1lith wide 95% confidence interval were noted. Further studies linking large administrative data and primary hospitalization information are warranted.

In conclusion, based on this population-based case-control study, statin use is associated with an increased risk of NOD in women. All types of statins have the potential for NOD. The risk of statin-related NOD was more evident for women aged 40–64 years compared with those aged 65 or more, and was cumulative-dose-dependent. Use of statins should always be judged by weighing the clinical benefit and potential risk for NOD for all age-groups, especially for younger female patients.

Supporting Information

Appendix S1 Adjusted odds ratio for diabetes for men and women.
(DOC)

Acknowledgments

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Author Contributions

Conceived and designed the experiments: CWC CCL PFC. Analyzed the data: CCL PFC PC. Wrote the paper: CWC TCC KYH PC PFC CCL.

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The sponsor reported no significant interactions with treatment for any of the subgroups, however FDA analyses revealed a significant interaction for gender by treatment with a p-value of 0.078 and borderline significant results (p=0.14) for diabetics/non-diabetics.

The gender differences in treatment effects are clearly illustrated in the following two figures.

Figure 6.1.9.1.1.1: Kaplan Meier Plot of Primary Endpoint For Females

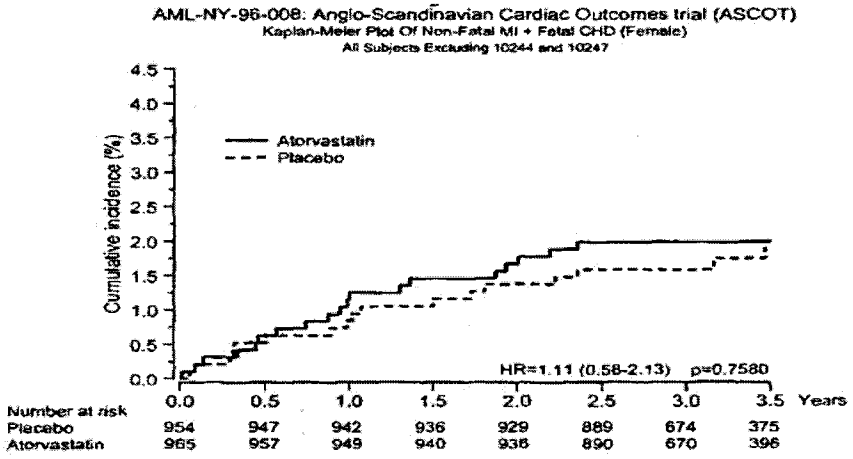
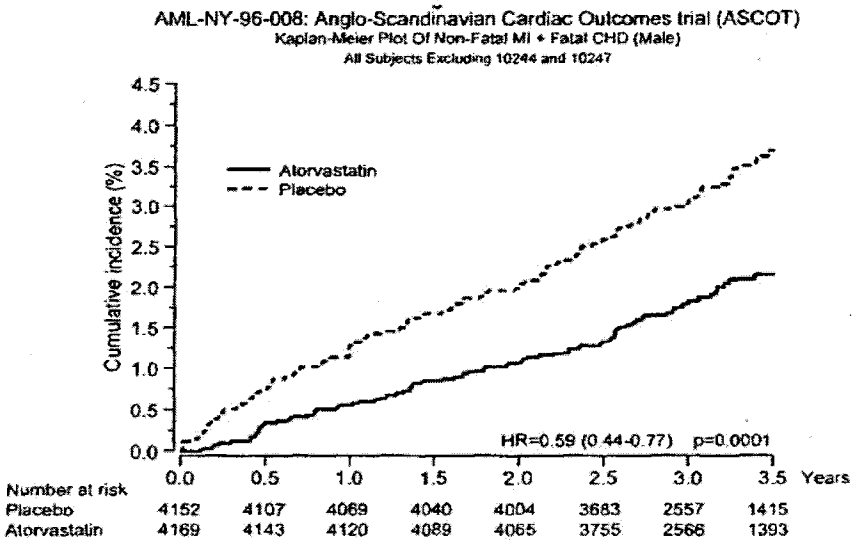


Figure 6.1.9.1.1.2: Kaplan-Meier Plot of Primary Endpoint for Males



For men, the incidence of the primary endpoint appears lower in the atorvastatin group (compared to placebo) almost throughout the study period, with very significant separation nearing the end of the study. For women, however, the incidence of the primary endpoint actually appears lower in the placebo group throughout most of the study until study cessation (at 3.3 yrs), when the incidence lines appear to suddenly converge.

The overall small number of events seen for females may explain the lack of a treatment effect. To examine the gender issue further, the results for secondary endpoints by gender are summarized below. Only the results for cardiovascular procedures show a strong effect for atorvastatin in females; these results drive the results seen for the composite endpoint; total cardiovascular events plus procedures. Overall the results for females are not strong and suggest that a comment in the labeling is warranted.

Table 6.1.9.1.1.2 Secondary Endpoint Results for Males and Females

	Atorva	Placebo	HR (CI)	Int. p-value
NFMI+Fatal CHD				
Males	1.94% (81/4169)	3.30% (137/4152)	0.59 (0.44, 0.77)	
Females	1.97% (19/965)	1.78% (17/954)	1.11 (0.58, 2.13)	0.078
Total CV+Proc				
Males	7.68% (320/4169)	9.61% (399/4152)	0.79 (0.69, 0.92)	
Females	7.15% (69/965)	8.81% (84/954)	0.81 (0.59, 1.11)	0.30
Total Coronary				
Males	3.60% (150/4169)	5.18% (215/4152)	0.69 (0.56, 0.85)	
Females	2.90% (28/965)	3.35% (32/954)	0.87 (0.52, 1.44)	0.42
CV Mortality				
Males	1.37% (57/4169)	1.69% (70/4152)	0.81 (0.57, 1.15)	
Females	1.76% (17/965)	1.26% (12/954)	1.41 (0.67, 2.94)	0.19
All Cause Mortality				
Males	3.53% (147/4169)	4.38% (182/4152)	0.81 (0.65, 1.00)	
Females	3.94% (38/965)	3.14% (30/954)	1.26 (0.78, 2.03)	0.10
CV Procedures				
Males	1.63% (68/4169)	2.58% (107/4152)	0.63 (0.47, 0.86)	
Females	0.62% (6/965)	2.10% (20/954)	0.30 (0.12, 0.74)	0.12