New-Onset Diabetes After Statin Exposure in Elderly Women

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Published in:
Drugs and Aging

DOI:
10.1007/s40266-017-0435-0

New onset diabetes after statin exposure in elderly women: The Australian Longitudinal Study on Women's Health

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Word count: 2894 (main text); 298 (abstract)

This is a post-peer-review, pre-copyedit version of an article published in Drugs and Aging. The final authenticated version is available online at: https://doi.org/10.1007/s40266-017-0435-0

Abstract

Introduction: Extensive clinical research has consistently shown statins lower risk of cardiovascular events and mortality. Some studies also suggest statins increase the risk of new onset diabetes. Research to date has rarely included elderly women hence little is known on risk of diabetes after statin exposure in this population.

Objectives: To evaluate and estimate the risk of new onset diabetes associated with statin exposure in a cohort of elderly Australian women.

Methods: Analysis of a population based longitudinal cohort study with data linkage to national death index, national databases of non-hospital episodes of medical care and prescription medications dispensing was performed. Participants included 8,372 Australian women born between 1921 and 1926, alive at January 1 2003, free of diabetes, and eligible for data linkage. Statin exposure was ascertained based on prescriptions dispensed between 1 July 2002 and 31 August 2013.

Results: Over 10 years of follow up, 49% of the cohort had filled a prescription for statins and 5% had initiated treatment for new onset diabetes. Multivariable Cox regression showed statin exposure was associated with higher risk of treatment for new onset diabetes (hazard ratio 1.33, 95% CI: 1.04 to 1.70, P=0.024). This equates to a number needed to harm (NNH) of 131 (95% CI: 62, 1079) for 5 years of exposure to statins. Risk increased with increasing dose of statin from the hazard ratio of 1.17 (95% CI: 0.84, 1.65) for the lowest dose to 1.51 (95% CI: 1.14, 1.99) for the highest dose.

Conclusion: The dose-response for statins on new onset of diabetes suggests elderly women should not be exposed to higher doses of statins. Elderly women currently taking statins should be carefully and regularly monitored for increased blood glucose to ensure early detection and appropriate management of this potential adverse effect, including consideration of de-prescribing.

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Key points

Over 10 years, almost 50% of Australian elderly women had filled a prescription for statins.

During that time, 5% of women had initiated treatment for new onset diabetes.

There was a 33% increased risk of new onset diabetes associated with statin exposure.

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1. Introduction

Statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) are a class of drugs used for cholesterol lowering that target the reduction of low-density lipoprotein cholesterol (LDL-C). They have been shown in clinical trials to reduce cardiovascular events and mortality in secondary prevention[1], including meta-analysis of subgroups in the elderly[2]. The effects appear to be similar in men and women[3]. However the majority of participants in trials of statins have been males, with females and especially elderly females under-represented[4]. Statin use in primary prevention is controversial[5-7]. A recent meta-analysis of elderly patients showing evidence of reduced risk of myocardial infarction and stroke but not mortality[8].

Previous studies, including meta-analyses of clinical trials, have shown an association between statin use (or higher potency statins) and onset of diabetes[9-13]. Diabetes is a serious and increasingly common chronic disease hence it is important to quantify the risk of this potential unintended effect of statin therapy. The World Health Organisation (WHO) recently reported the global prevalence of diabetes had almost doubled in the past 24 years from 4.7% in 1980 to 8.5% in 2014[14]. WHO predicts diabetes to be the seventh leading cause of death by 2030[14]. Diabetes has moved from 10th to 7th leading cause of death in Australian women in the 10 years from 2001 to 2011[15]. A recent study has shown the increased risk of type 2 diabetes associated with statins may be at least partially explained by an association between diabetes and 3-hydroxy-3-methylglutaryl-CoA reductase inhibition, which is the intended drug target[16].

In the present study we have investigated the association of new onset diabetes with statin exposure in a unique Australian national cohort of elderly women with longitudinal data linkage.

2. Methods

The cohort used for this study consisted of a sample of Australian women born between 1921 and 1926 who have been surveyed every 3 years since 1996[17]. The sample was randomly generated from the national universal public health insurance database with a higher proportion of women living in rural and remote areas included using stratified random sampling. For more details on the

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Australian Longitudinal Study on Women's Health cohort, see Dobson, et al[18]. The study was approved by Ethics Committees at the University of Queensland and University of Newcastle.

Drug exposure information was obtained through linkage to the Australian Pharmaceutical Benefits Scheme (PBS) with data available from 1 July 2002 to 31 August 2013. Through this scheme all Australian residents are able to obtain subsidised anti-lipemic drugs if they meet certain criteria[19]. The data included dates of prescription of drugs as well as dates when prescriptions (including repeats) were dispensed. The cohort was also linked to the Medicare Benefits Schedule (MBS) data[20], which covers non-hospital services (predominantly general practitioner visits) subsidised by the Australian government, with data available from 1996 to 2013. In addition, linkage to the National Death Index (NDI)[21], was used to obtain cause and date of death (up to October 2012). Women reporting diagnosis or treatment for diabetes based on survey responses to the first three waves of the survey undertaken in 1996, 1999, and 2002 were excluded. Our primary outcome was new onset diabetes defined as a record of a participant being dispensed a new prescription for insulin or analogues or other blood glucose lowering drugs according to the linked PBS database between January 1, 2003 and August 31, 2013. To help ensure previous cases were not included, women dispensed these medications between July 1 and December 31, 2002 and also women with a MBS record of consulting medical practitioners for diabetes care or testing (glucose tolerance or quantitation of HbA1c) up to December 31, 2002 were excluded. Furthermore, we assigned treatment for new onset diabetes cases within eight months of initiating statin treatment as associated with no exposure. This was to allow for a possible delay in treatment for newly diagnosed cases of diabetes (who may have initially undertaken lifestyle changes only) and to allow sufficient time to elapse for statin use to affect risk of diabetes. To assess the impact of this decision we conducted sensitivity analysis where we varied the assumed lag from initial diagnosis of diabetes to treatment from zero to 12 months. We classified participants into six groups of equivalent dosages of statins[22] (Table 1). Prescriptions of ezetimibe (another medication to treat high cholesterol)

were identified for 2% of participants, almost all of whom also took a statin. Recent research suggests ezetimibe does not increase risk of new-onset diabetes when used in combination with a statin[23]. Hence these participants were not excluded from the study.

Cox regression was used for analysis where statin exposure was included as a time-dependent variable based on the first prescription for new users after December 31, 2002. Participants with any prescription between July 1 and December 31 2002 were classified as existing statin users (typically prescriptions are filled monthly). The use of a time-dependent exposure variable for statin use avoids immortal time bias[24]. Analyses were conducted for existing users and new users as separate exposure groups as well as for all statin users as a combined exposure group. The survival time was from 1 January, 2003 until treatment for new onset diabetes or death (a competing risk) or the end of the study period. Competing risks analysis was conducted using the method of Fine and Gray[25]. We used competing risks analysis to account for expected differences in mortality risks between participants exposed and not exposed to statins. Analyses were adjusted for potential confounding variables baseline age, smoking, physical functioning, self-rated health status, education, alcohol use, body mass index, and hypertension. We also adjusted for four additional time-dependent variables based on PBS data. These variables were dispensing of a prescription for (1) renin-angiotensin system agents, (2) beta-blockers, (3) antithrombotic medications, and (4) diuretics. These variables were included because they were considered to be potentially associated with statin exposure and risk of diabetes, either directly, or through the conditions they are prescribed for, such as hypertension.

To further examine the association of statin exposure with new onset diabetes we conducted sub-group analyses by dose, BMI group and whether the participant had a routine blood test during the follow up period. For the dose subgroup analysis we collapsed the bottom two doses into one group and top two doses into one group due to low numbers in the lowest and highest dose groups. The latter subgroup analysis was undertaken to investigate whether diagnosis of diabetes was more

common in those having a routine blood test, and whether this could have led to higher risk of diagnosis for statin users. To investigate possible confounding by indication, effects for two other medication classes (proton pump inhibitors and anti-arthritic drugs) expected to have no association with new onset diabetes (i.e. negative controls) are reported. In a secondary analysis we investigated new onset diabetes using an alternative definition based on the survey question: *in the last 3 years have you been diagnosed with or treated for diabetes (high blood sugar)?* Women answering yes to the question were classified as having diabetes; women answering no were classified as not having diabetes; and women not answering the question were dropped from the analysis. Analysis was conducted at three follow up survey waves in 2005, 2008 and 2011 using multivariable logistic regression (adjusting for the same variables that were included in the Cox models).

We estimated number needed to harm (NNH) by multiplying the overall hazard ratio for statin exposure by the rate of treatment for new onset diabetes for each unexposed participant year to obtain the rate of treatment for new onset diabetes for each exposed participant year. We then subtracted the rates to obtain the absolute increased rate per patient year. This value was then inverted and divided by 5 to obtain the NNH for 5 years of exposure to statins.

We have followed the STROBE guidelines in preparing this manuscript[26].

3. Results

The figure shows a flowchart of participant numbers from the baseline survey in 1996 to the beginning of follow up for the present study in January 1, 2003 when the women were aged 76 to 82 years. After removing those screened or treated for diabetes, there were 8,372 women included in the analysis. Baseline characteristics for the 8,372 women in 1996 when the women were aged 70-75 years are compared between participants with and without statin exposure in Table 2. As expected, statin users were more likely to have hypertension and heart disease. All other baseline characteristics were clinically similar for the two groups. The amount of missing data ranged from 0

to 8% for the individual baseline variables however in multivariable analysis, 23% of participants with one or more missing covariates were not included.

Over more than 10 years of follow up, 49% of the cohort had filled a prescription for a statin (27% existing users and 22% new users). The mean (SD) duration of statin therapy was 6.5 (3.9) years. Each woman could have had multiple types and dosages over time. Types of statin dispensed, at any time during the period, were fluvastatin for 44 participants, rosuvastatin for 588 participants, pravastatin for 682 participants, atorvastatin for 2228 participants, and simvastatin for 1653 participants. Many participants changed type and dose of statin over time with changes in dose more frequently to a higher level than a lower level (Tables 3 and 4). It was not possible to determine precisely how many users stopped statins completely but the percentage of users who did not fill a prescription for statins in the last 6 months prior to death or end of follow up was 37%, and for the last 12 months was 29%.

A total of 383 (5%) participants were dispensed new prescriptions for insulin or analogues or other blood glucose lowering drugs between January 1, 2003 and 31 August 2013. Multivariable competing risks Cox regression showed statin exposure was associated with higher risk of treatment for new onset diabetes (hazard ratio [HR] 1.33, 95% CI: 1.04 to 1.70, P=0.024). This equates to a number needed to harm (NNH) of 131 (95% CI: 62, 1079) for 5 years of exposure to statins. Varying the assumed lag from onset of diabetes to treatment had a large effect on the result; from HR = 1.80 [1.40, 2.31] assuming no lag, to 1.60 [1.24, 2.05] assuming a lag of six months, and 1.29 [1.00, 1.65] for a lag of 12 months. Stratification by existing and new users of statins showed a stronger association in new users (HR 1.56 [1.12, 2.17]) compared to existing users (HR 1.22 [0.93, 1.61]).

In subgroup analysis there appeared to be a dose response effect of statin exposure on treatment for new onset diabetes (Table 5). The overall association was apparent for overweight (HR: 1.41 [0.96, 2.07]) and healthy or underweight participants (HR: 1.49 [0.98, 2.28]) but not for obese participants (HR: 0.89 [0.53, 1.50]). Having a standard blood test during the follow up period was

associated with higher incidence of treatment for new onset diabetes (7% vs 4%) but the effect of statin exposure was lower in those with a blood test (HR: 1.15 [0.79, 1.66]) compared to those without a blood test (HR: 1.44 [1.03, 2.01]). The negative controls showed insufficient evidence of association: proton pump inhibitors (HR: 0.91 [0.70, 1.17]); and anti-arthritic medications (HR: 1.11 [0.85, 1.44]). And finally the incidence of self-reported diabetes (rather than diabetes inferred from prescription data) was 2%, 3%, and 5% in 2005, 2008, and 2011 respectively with multivariable logistic regression showing evidence of association with statin exposure at all time-points: 2005 (odds ratio[OR] 2.50 [1.67, 3.73]); 2008 (OR: 1.74 [1.20, 2.51]); and 2011 (OR: 3.11 [2.01, 4.82]).

4. Discussion

In an elderly cohort of over 8,000 Australian women, followed longitudinally since 1996, around half had been exposed to statins over a 10 year period between 2003 and 2013 and 5% began treatment for diabetes. We found evidence that statins were associated with a 33% increased risk of treatment for new onset diabetes. Furthermore the association was stronger in new users of statins compared to existing users and there was a dose response effect. However, varying the assumed lag from diagnosis to treatment for diabetes had a large effect on the estimate. Typically patients diagnosed with diabetes will be given three months to determine whether lifestyle changes alone are sufficient to control blood glucose hence we believe a six month lag is appropriate. However data analysis showed a spike in cases with onset of treatment for diabetes between six and eight months after initial statin exposure. This suggests a lag of eight months is required to ensure cases associated with statins were truly diagnosed after statin exposure.

Subgroup analysis by BMI group showed similar effects in participants of healthy weight and those overweight however there appeared to be no effect in obese participants, an unexpected finding without an obvious explanation. Insufficient evidence of an effect in two negative controls suggests the finding for statins may not be explained by confounding by indication where participants who are more likely to consult medical practitioners and be prescribed medical interventions are

healthier and less prone to diseases such as diabetes. Higher risk of treatment for new onset diabetes in statin users did not appear to be associated with more frequent blood testing leading to more incidental diagnoses. And finally, consistent results were obtained using self-reported diabetes at three follow up surveys.

The finding of increased risk of onset of diabetes after statin exposure is consistent with other observational studies and meta-analyses of clinical trials. For example meta-analysis of 17 randomised trials showed a 9% increased odds of diabetes[13]. Another meta-analysis of randomised studies showed a 9% increased odds of diabetes overall, with risk highest in trials of older participants [11]. Observational studies have also shown increased risk of new onset diabetes[9, 10] with 48% increased risk in women[12]. A recent observational study of men suggested the increased risk of diabetes may be attributable to statins decreasing insulin sensitivity and secretion[27]. Consistent with a study showing the intended mechanism of action of statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibition) is associated with higher prevalence of diabetes[16], we found an increased risk of treatment for new onset diabetes after statin exposure. The size of the effect in this study (33% increased risk) is larger than reported in meta-analysis of clinical trials (9% increased odds). This could be due to a number of factors including our study population which was elderly women. Previous research has shown larger effects in older participants[11] and women[12]. Furthermore there appeared to be an increasing risk of diabetes with increasing dose. This combined with participants tending to increase dose over time may help to explain the large effect size. Follow up for our study was for 10 years, much longer than in clinical trials where follow up ranged from <1 to 6 years[13]. Unlike previous studies, we accounted for the competing risk of death. This reduces the estimated cumulative incidence of diabetes because deaths are not censored at the time of death. Because mortality is expected to be less in the statin exposed group compared to the unexposed group the reduction in cumulative incidence is expected

to be less in statin exposed compared to unexposed groups. This tends to increase the hazard ratio estimate compared to standard Cox regression.

The women in our study would have been aged 86-92 years at the end of follow-up and, depending upon reason for initial prescribing, primary or secondary prevention, serious consideration could perhaps now be recommended for statin de-prescribing in women of this age[28, 29]. In our study, around a third of users did not fill a prescription for statins in the last 6 months prior to death or end of follow up. This still leaves significant numbers exposed to statins and suggests ongoing risk/benefit assessment could be critical to ensure optimal health outcomes and quality of life in older women.

Limitations

This is an observational study where comparisons between exposed and non-exposed participants tend to be at higher risk of bias compared to randomised studies. We did not classify participants who had stopped statins as unexposed because it was difficult to determine when statins had been permanently stopped or what time lags would be appropriate and we did not have access to reasons for stopping. Furthermore the effect of stopping statins on temporal pattern of risk of adverse events remains unclear[30]. It is likely that some of the participants in the unexposed group previously used statins and statin exposure was based on electronic records of filled prescriptions hence it is uncertain whether an individual in fact took the medication. Multivariable analysis was only conducted on 77% of the participants due to missing covariate data however we did conduct analyses after multiple imputation of missing covariates and results were similar (data not shown).

Conclusions

In a large cohort of nationally representative Australian elderly women (aged 76 to 82 years at baseline) followed for 10 years we have found evidence of an increased risk of new onset diabetes associated with statin exposure. The dose-response effect of statin use on new onset of diabetes suggests elderly women should not be exposed to higher doses of statins. It is recommended that

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elderly women currently taking statins be carefully and regularly monitored for increased glucose levels to ensure early detection and appropriate management of this potential adverse effect. In elderly women, consideration should be given to de-prescribing of statins.

Acknowledgements

Contributors: MJ drafted the protocol, conducted the analysis and drafted the manuscript. All other authors contributed to the study design, interpretation of results and provided critical input to the writing of the protocol and manuscript.

Funding: The Australian Longitudinal Study on Women's Health is funded by the Australian Department of Health. MJ and GDM are funded by the Australian National Health and Medical Research Council (APP1000986). The funding bodies had no role in the collection, analysis, and interpretation of data; the writing of the manuscript, or the decision to submit the manuscript for publication.

Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work apart from that described above; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Table 1: Equivalent dosages by type of statin

Dosage level*	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
1	-	20 mg	10 mg	10 mg	-	5 mg
2	-	40 mg	20 mg	20 mg	-	10 mg
3	10 mg	80 mg	40 mg	40 mg	5 mg	20 mg
4	20 mg	-	80 mg	80 mg	5-10 mg	40 mg
5	40 mg	-	-	-	10-20 mg	80 mg
6	80 mg	-	-	-	40 mg	-

*For subgroup analysis we collapsed the bottom two doses into one group and top two doses into one group due to low numbers in the lowest and highest dose groups

Table 2: Baseline (1996) characteristics of included participants

Characteristic*	Missing data N (%)	No Statin exposure N=4261 N (%)	Statin exposure N=4082 N (%)	P-value
Heart disease	29 (<1)	733 (17)	1294 (32)	<0.0001
Hypertension	18 (<1)	2043 (48)	2577 (63)	<0.0001
Stroke	27 (<1)	281 (7)	334 (8)	0.006
Cancer	57 (1)	535 (13)	431 (11)	0.004
Hormone replacement therapy	78 (1)	619 (15)	663 (16)	0.034
Smoking: current	556 (7)	316 (8)	240 (6)	0.019
ex-smoker		1158 (29)	1131 (30)	
never		2519 (63)	2452 (64)	
Alcohol: risky	297 (4)	155 (4)	143 (4)	0.18
moderate		2618 (64)	2607 (66)	
none		1334 (32)	1218 (31)	
Health: excellent	259 (3)	331 (8)	264 (7)	0.057
very good		1241 (30)	1171 (29)	
good		1637 (40)	1646 (41)	
fair		819 (20)	809 (20)	
poor		109 (3)	86 (2)	
Adequate exercise^	292 (4)	2999 (73)	2958 (75)	0.036
Education: tertiary	437 (5)	665 (16)	589 (15)	0.13
high school#		555 (14)	498 (13)	
other		2835 (70)	2793 (72)	
BMI: mean (SD)	638 (8)	24.8 (4.4)	25.2 (4.0)	0.0001
Age: mean (SD)	0 (0)	72.7 (1.5)	72.4 (1.5)	<0.0001
Physical functioning~: mean (SD)	449 (5)	66.2 (26)	66.8 (24)	0.28

*Self-reported by participants

^Moderate-to-high versus sedentary-to-low level of exercise

#Completed high school

~Based on SF36 physical functioning scale ranging from 0-100

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Table 3: Changes in type of statin prescribed over time; N (%)

	Subsequent type of statin			
Initial type of statin	**Atorvastatin**	**Simvastatin**	**Pravastatin**	**Rosuvastatin**
Atorvastatin	1820 (82)	126 (6)	66 (3)	216 (10)
Simvastatin	267 (16)	1189 (72)	52 (3)	145 (9)
Pravastatin	160 (23)	59 (9)	374 (55)	89 (13)
Rosuvastatin	29 (5)	10 (2)	9 (1)	540 (92)

*Please note 44 participants prescribed fluvastatin not included in the analysis due to low numbers

Table 4: Changes in dose of statin prescribed over time; N (%)

	Subsequent dose* of statin			
Initial dose* of statin	**Low**	**Mid**	**High**	**Very high**
Low	256 (27)	329 (35)	217 (23)	130 (14)
Mid	140 (6)	984 (46)	663 (31)	371 (17)
High	69 (3)	211 (10)	1269 (62)	499 (24)
Very high	41 (3)	109 (8)	0 (0)	1154 (88)

*Low = equivalent dosage 1-2; Mid = equivalent dosage 3; High = equivalent dosage 4; Very high = equivalent dosage 5-6 (See Table 1 for further details)

Table 5: Treatment for new onset diabetes by statin exposure dosage

Statin dosage	**Hazard ratio with 95% confidence interval***	**P-value**
Low	1.17 [0.84, 1.65]	0.35
Mid	1.26 [0.97, 1.63]	0.077
High	1.46 [1.12, 1.89]	0.005
Very high	1.51 [1.14, 1.99]	0.004

*Compared to non-use of statins

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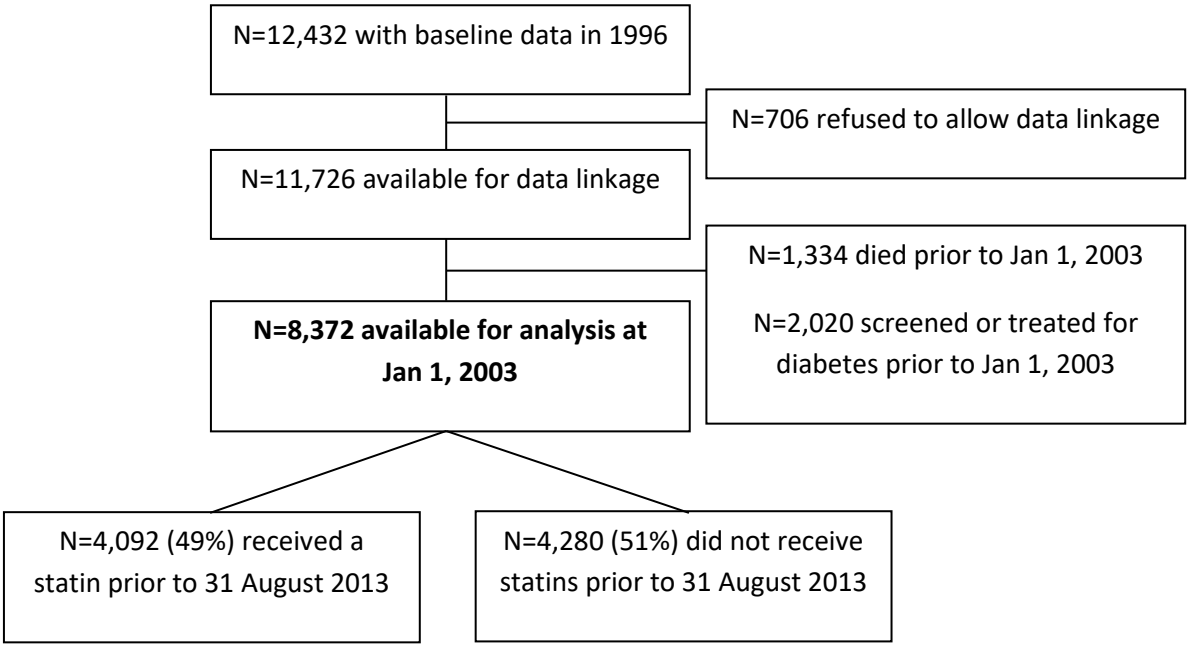
Figure: Flowchart of participants in the study



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