Assessing Potential Population Impact of Statin Treatment for Primary Prevention of Atherosclerotic Cardiovascular Diseases in the United States: Population-Based Modeling Study

Supplemental Material

Appendix

Estimating age-sex-race/ethnicity specific ASCVD death rates by the treatment eligible groups

We estimated age-sex-race/ethnicity specific ASCVD death rates by the treatment eligible groups using data derived from the 2010 Multiple Cause of Death files, the 2010 US Census, NHANES III Linked Mortality Files (1988-2006), and NHANES 2005-2010. The denominators of age-sex-race/ethnicity specific ASCVD death rates were derived from 2010 US Census data. To estimate age-sex-race/ethnicity specific ASCVD death rates by the statin treatment eligible groups, we followed the following steps and estimated the treatment group-specific ASCVD rates for men and women separately:

1. We estimated the age-specific prevalence of each statin treatment group and the reference groups among participants aged 40-75 years using NHANES 2005-2010 (we could not get stable estimate of age- and race/ethnicity specific prevalence because of the limited sample size). To estimate age-sex-race/ethnicity specific ASCVD death rates by the treatment eligible groups, we also included the participants with ASCVD at baseline in NHANES 2005-2010 (n = 518), because the baseline total ASCVD death rates were a weighted average of all treatment group-specific death rates. We then applied four prevalence rates (treatment eligibility groups 1 and 2, participants with ASCVD at baseline, and remaining participants aged 40-75 years) to calculate the age- and race/ethnicity specific number in the overall population (age-specific prevalence multiplied by the total population derived from the 2010 US Census), denoting these numbers as

$N_{ij,}$ where i = 1, 2, 3, and 4 for each of four treatment groups and j = 1 to 16 for each of the 16 age-race/ethnicity combinations.

2. We used NHANES III Linked Mortality Files (1988-2006, n=8941 including 1,136 ASCVD deaths during a median of 14-years follow-up) to estimate sex and treatment groups specific relative risk (RR) of ASCVD mortality by comparing statin treatment eligibility group 1, group 2, and those with ASCVD at baseline to the rest of participants 40-75 years of age (reference group). We denote these RRs as RR_t, where t = 1, 2, and 3. Cox proportional hazards regression was used to estimate the adjusted hazard ratios (HRs) for sex and treatment group-specific ASCVD mortality adjusting for age and race/ethnicity, and assumed that the adjusted HRs apply to each age, sex, and race/ethnicity stratum in US population.

3. Denoting the age- and race/ethnicity specific total number of ASCVD deaths as TD_j, j = 1 to 16 for the age-race/ethnicity combinations, using N_{ij}, and RR_t, we can calculate the age- and race/ethnicity specific number of ASCVD deaths for each treatment group:

$$D_{3j} = TD_j / (1 + [RR_1 * N_{1j}/N_{3j}] + [RR_2 * N_{2j}/N_{3j}] + [RR_3 * N_{4j}/N_{3j}])$$

$$D_{1j} = (RR_1 * N_{1j} * D_{3j}) / N_{3j}$$

$$D_{2j} = (RR_2 * N_{2j} * D_{3j}) / N_{3j}$$

$$D_{4j} = (RR_3 * N_{4j} * D_{3j}) / N_{3j}$$

where D_{ij} = the treatment group-specific number of ASCVD deaths (D_{3j} = reference, D_{1j} = with diabetes, D_{2j} = without diabetes, D_{4j} = with ASCVD at baseline, and j = 1 to 16 age-race/ethnicity combinations. We can calculate the treatment group-specific and age- and race/ethnicity specific ASCVD death rates by (D_{ij} / N_{ij}).

4. These age-sex-race/ethnicity specific ASCVD death rates were the weighted average among individuals who were currently taking a statin and those who were not. We obtained the age- and race/ethnicity specific ASCVD death rates for non-statin users using

$$DD_{ij} = (D_{ij} / N_{ij}) / ([P_{ij} * 0.83 + (1 - P_{ij})])$$

where DD_{ij} = the age- and race/ethnicity specific ASCVD death rates among non-statin users for statin treatment eligibility groups *i*, P_{ij} = the age- and race/ethnicity specific prevalence of current statin use for each treatment group, and 0.83 is the RR of ASCVD mortality comparing statin users with non-users for primary prevention.[5] To estimate DD_{ij}, we have approximated the observed RR by the causal RR estimates from the RCTs.

Table A1 Data Sources and Calculation of Population Impact of Statin Use for Primary Prevention of ASCVD*

Data/Measurements	Explanation and Calculation
Data sets	
NHANES 2005-2010	We used NHANES 2005-2010 data to estimate • the prevalence of adults aged 40-75 years who met the ACC/AHA's new guidelines for statin treatment for primary prevention of ASCVD, and • the prevalence of current statin use by age, sex, and race-ethnicity (n = 3,178).
Age-sex-race/ethnicity specific population and eligible population by statin treatment eligibility groups	We estimated age-specific prevalence by statin treatment eligibility groups and the reference group using NHANES 2005-2010. We included participants with ASCVD at baseline (n = 518) for prevalence estimate. Age-sex-race/ethnicity specific populations and the eligible population by statin treatment groups were obtained by multiplying the age-specific prevalence of non-statin users in each statin treatment eligibility group by the total number of the noninstitutionalized population derived from the Current Population Surveys (CPS). We used the midpoint CPS population of each survey cycle, and combined them as follows: 1/3 (NHANES 2005-2006 population totals) + 1/3 (NHANES 2007-2008 population totals) + 1/3 (NHANES 2009-2010 population totals) to get a population total for 2005-2010 (http://www.cdc.gov/nchs/tutorials/nhanes/NHANESAnalyses/AgeStandardization/Info2.htm).
CDC Wonder	We used CDC Wonder to estimate the annual age-sex-race/ethnicity specific number of ASCVD deaths, and calculated annual ASCVD death rates for those aged 40-75 years in 2010. We used 2010 US Census data as denominators for the annual ASCVD death rates (https://wonder.cdc.gov/ucd-icd10.html).

NHANES III Linked Mortality Files (1988-2006)	We used the NHANES III Linked Mortality Files (1988-2006) to estimate the adjusted RRs comparing participants in treatment eligible group 1 (with diabetes), in treatment eligible group 2 (without diabetes but with an estimated 10-year risk of ASCVD ⩾7.5%), with ASCVD at baseline with the participants with an estimated 10-year risk of ASCVD <7.5% (reference group) among participants 40-75 years of age by sex. These adjusted RRs were used to estimate age-sex-race/ethnicity specific ASCVD mortality by statin treatment eligibility groups for primary prevention of ASCVD.
Age-sex-race/ethnicity specific ASCVD mortality by statin treatment eligibility groups	We estimated age-sex-race/ethnicity specific ASCVD death rates by statin treatment eligibility group 1 and 2 (i.e., with diabetes (group 1) and without diabetes but with an estimated 10-year ASCVD risk ≥7.5% (group 2)) using age-sex-race/ethnicity specific population information, age-sex-race/ethnicity specific ASCVD deaths (derived from CDC Wonder), RRs of ASCVD associated with diabetes and with an estimated 10-year ASCVD risk ≥7.5% (derived from NHANES III Linked Mortality Files 1988-2006), age-sex-race/ethnicity specific prevalence of current statin use.
Population impact measures	
Annual number of ASCVD deaths prevented	The age- and race/ethnicity specific number of annual ASCVD deaths prevented by statin treatment eligibility groups by sex: $\sum[POP_{ij}*DDij - ((1-P_i)* POP_{ij}*DD_{ij} + P_i* POP_{ij}*DD_{ij}*RR)]$ where POP_{ij}=age-race/ethnicity specific eligible population (non-current statin users); DD_{ij}=treatment group-specific ASCVD death rates, i=1 to 4 groups, and j=1 to 16 age and race/ethnicity groups; P_i=proportion of population eligible for statin treatment complied with the statin therapy in treatment group i (assuming 100% statin use in primary analysis); RR =0.83 (95% CI, 0.72-0.96), estimated RR of statin use on ASCVD mortality.
Annual number of additional cases of diabetes	Annual number of additional cases of diabetes = ∑(excess incidence of diabetes associated with statin use * eligible population). The excess incidence of diabetes is estimated to be 1 per 1000 patients per year.[9] We assumed that those who died within 1 year contributed 0.5 person year.

Annual number of additional myopathy cases	Number of additional cases of myopathy = ∑(excess incidence of myopathy associated with statin use * eligible population). We estimated 2 sets of the annual number of excess myopathy cases by using results from a meta-analysis of RCTs and a population-based cohort study with more than 2 million patients in the QResearch database[7 8] For the RCT-based estimate, the excess incidence of myopathy or rhabdomyolysis was 0.0628 (95% CI, 0.167-0.292) per 1000 patient-years.[8] For the population-based estimate, myopathy included diagnosed myopathy or rhabdomyolysis or a raised upper limit of normal creatine kinase concentration ≥4, as the presence of these conditions likely resulted in treatment discontinuation.[7] For treatment group 1, the excess incidence of myopathy was 2.176 (95% CI, 1.769-2.655) and 0.791 (95% CI, 0.545-1.100) per 1000 patient-years for men and women, respectively. For treatment group 2, the corresponding numbers were 1.864 (95% CI, 1.515-2.282) and 0.632 (95% CI, 0.436-0.880), respectively.

Abbreviations: ASCVD, atherosclerosis cardiovascular diseases; CDC, Centers for Disease Control and Prevention; NHANES, National Health and Nutritional Examination Surveys; RR, relative risk.

[*] ASCVD includes ischemic heart diseases (ICD-10 I20-I25); cerebrovascular diseases excluding hemorrhagic cerebrovascular disease (ICD-10 I63-I69); atherosclerosis (ICD-10 I70) and other peripheral artery diseases (ICD-10 I73.9).

Table A2 Estimated Statin Eligible Population (100000), and ASCVD Deaths (per 1000) by Treatment Groups Among Participants Aged 40-75 Years—NHANES 2005-2010

Population*	With ASCVD (n = 518)			With Diabetes (n = 520)			Without diabetes, but with predicted 10yr ASCVD Risk ≥7.5% and LDL 70mg/dL ≥ to ≤189mg/dL (n = 784)			Remainder of Population Aged 40-75 Years (n = 1874)	
	Population (100000) *	Eligible population (100000) †	ASCVD deaths per 1000	Population (100000) *	Eligible population (100000) †	ASCVD deaths per 1000	Population (100000) *	Eligible population (100000) †	ASCVD mortality per 1000	Population (100000) *	ASCVD mortality per 1000
Total	134.3	72.2	4.99	123.5	77.0	1.89	206.2	164.8	1.93	721.9	0.29
Age group											
40-49	28.9	22.0	1.48	27.5	21.1	0.73	13.7	13.7	0.64	370.0	0.18
50-59	32.8	20.0	3.66	44.7	28.7	1.58	52.7	46.4	1.46	260.5	0.36
60-69	50.3	20.5	5.60	33.1	16.9	2.20	90.0	70.1	1.78	80.9	0.48
70-75	22.3	9.7	10.14	18.1	10.4	3.88	49.7	34.6	3.08	10.6	0.96
Men	73.3	34.2	6.49	66.3	41.6	2.15	139.6	113.7	1.96	292.2	0.41
Women	61.0	38.1	3.19	57.2	35.4	1.60	66.6	51.1	1.88	429.8	0.21
Race/ethnicity											
Non-Hispanic white	101.0	53.5	5.06	92.1	57.0	1.91	158.4	126.1	1.93	516.6	0.30
Non-Hispanic black	13.5	7.6	7.28	12.7	8.0	2.85	19.5	15.7	2.93	81.3	0.45
Hispanic	12.4	7.0	3.31	11.8	7.6	1.22	17.6	14.3	1.39	80.3	0.16
Other	7.4	4.1	2.75	6.9	4.3	1.04	10.8	8.7	1.14	43.7	0.15
Men											

Non-Hispanic white											
40-49	8.2	4.5	2.52	11.9	8.7	1.00	7.9	7.9	0.76	121.2	0.29
50-59	12.5	8.0	5.10	19.3	12.8	2.02	36.3	32.3	1.53	74.3	0.58
60-69	25.2	9.3	6.40	13.1	6.5	2.53	45.9	35.4	1.92	11.0	0.73
70-75	10.3	4.0	12.05	5.4	2.9	4.76	17.2	11.5	3.62	2.6	1.37
Non-Hispanic black											
40-49	1.3	0.7	3.33	1.9	1.4	1.32	1.2	1.2	1.00	19.2	0.38
50-59	1.7	1.1	7.52	2.6	1.7	2.97	4.8	4.3	2.26	9.9	0.86
60-69	2.7	1.0	10.00	1.4	0.7	3.95	4.9	3.8	3.01	1.2	1.14
70-75	1.1	0.4	17.68	0.6	0.3	6.99	1.8	1.2	5.31	0.3	2.01
Hispanic											
40-49	1.6	0.9	1.20	2.4	1.7	0.48	1.6	1.6	0.36	24.3	0.14
50-59	1.6	1.0	3.25	2.5	1.6	1.28	4.7	4.1	0.98	9.5	0.37
60-69	2.4	0.9	5.12	1.3	0.6	2.02	4.4	3.4	1.54	1.1	0.58
70-75	0.9	0.4	10.30	0.5	0.3	4.07	1.6	1.0	3.10	0.2	1.17
Women											
Non-Hispanic white											
40-49	11.6	10.5	0.86	7.0	5.8	0.39	1.6	1.6	0.31	132.2	0.09
50-59	11.8	6.8	2.11	13.9	8.4	0.96	3.1	2.4	0.76	118.4	0.22
60-69	14.1	6.6	3.86	12.6	6.6	1.75	24.4	19.4	1.39	51.2	0.40
70-75	7.3	3.7	7.08	8.8	5.2	3.21	22.0	15.7	2.54	5.7	0.74
Non-Hispanic black											
40-49	2.2	2.0	1.67	1.3	1.1	0.76	0.3	0.3	0.60	24.9	0.17
50-59	1.8	1.1	4.42	2.2	1.3	2.00	0.5	0.4	1.59	18.5	0.46
60-69	1.9	0.9	7.30	1.7	0.9	3.31	3.2	2.5	2.62	6.7	0.76
70-75	0.9	0.5	11.53	1.1	0.6	5.23	2.7	2.0	4.15	0.7	1.21
Hispanic											

40-49	2.1	1.9	0.41	1.3	1.1	0.19	0.3	0.3	0.15	24.4	0.04
50-59	1.5	0.9	1.40	1.8	1.1	0.63	0.4	0.3	0.50	14.9	0.15
60-69	1.5	0.7	3.22	1.3	0.7	1.46	2.6	2.0	1.16	5.4	0.34
70-75	0.7	0.4	5.91	0.9	0.5	2.68	2.1	1.5	2.12	0.6	0.62

Abbreviations: ASCVD, atherosclerotic cardiovascular diseases; LDL, low density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; NNH, number needed to harm; NNT, number needed to treat.

* Population = number of adults aged 40-75 years by statin treatment groups in 100000.

† Eligible population = number of adults aged 40-75 years in each statin treatment group * (1 - prevalence of statin use).

Table A3 Estimated Annual ASCVD Deaths Prevented and Additional Cases of Myopathy From Statin Use Among Participants Aged 40-75 Years With Diabetes Assuming 80% Eligible Take Statin With 80% Adherence—NHANES 2005-2010[*]

Characteristic	Population[†] (100 000)	Eligible Population[‡] (100 000)	Estimated Annual ASCVD Deaths	ASCVD Deaths Prevented (95% CI)	RCT-Based Excess Number Myopathy[§] (95% CI)	Population-Based Excess Number Myopathy (95% CI)[‖]
Total	123.5	61.6	23380	1609 (379-2651)	308 (0-1433)	7553 (5921-9546)
Women	57.2	28.3	9150	622 (146-1025)	142 (0-659)	1783 (1231-2482)
Age group						
40-49	10.3	6.8	410	38 (9-63)	34 (0-160)	432 (298-601)
50-59	19.0	9.2	1930	136 (32-225)	46 (0-215)	581 (401-809)
60-69	16.5	6.9	3050	188 (44-310)	34 (0-160)	434 (299-603)
70-75	11.3	5.4	3760	260 (61-428)	27 (0-124)	334 (231-465)
Race/ethnicity						
Non-Hispanic white	42.5	20.9	6660	452 (106-745)	104 (0-486)	1315 (907-1830)
Non-Hispanic black	6.3	3.1	1660	114 (27-187)	16 (0-73)	198 (136-275)
Hispanic	5.2	2.7	561	38 (9-63)	13 (0-62)	169 (116-235)
Men	66.3	33.3	14230	987 (232-1625)	167 (0-774)	5769 (4690-7064)
Age group						
40-49	17.2	10.1	1600	133 (31-220)	51 (0-235)	1750 (1422-2142)
50-59	25.7	13.7	5130	394 (93-649)	69 (0-319)	2379 (1934-2914)
60-69	16.6	6.6	4250	251 (59-414)	33 (0-152)	1136 (923-1391)
70-75	6.7	2.9	3240	208 (49-343)	14 (0-67)	500 (406-612)

Race/ethnicity						
Non-Hispanic white	49.6	24.8	10950	757 (178-1248)	124 (0-575)	4288 (3486-5251)
Non-Hispanic black	6.4	3.3	1950	137 (32-226)	16 (0-76)	564 (459-691)
Hispanic	6.6	3.4	880	61 (14-101)	17 (0-80)	593 (482-726)

Abbreviations: ASCVD, atherosclerotic cardiovascular diseases; NHANES, National Health and Nutrition Examination Survey

* Assumes 80% of eligible population take statins with an adherence rate of 80%.

† Population = number of adults aged 40-75 years with diabetes in 100000.

‡ The age- and race/ethnicity specific annual number of ASCVD deaths prevented is calculated as follows: $\sum[POP_{ij}*DD_{ij} - ((1-P_i)* POP_{ij}*DD_{ij} + P_i* POP_{ij}*DD_{ij}*RR)]$, where POP_{ij} = age- and race/ethnicity --specific eligible population (non-statin users); P_t = proportion of eligible population for statin treatment complied with the statin therapy; *RR* = relative risk of statin use on CVD mortality (0.83; 95% CI, 0.72-0.96).[5] We used the 95% CI of the *RR* to estimate the lower and upper limit of annual number of ASCVD deaths prevented.

§ The estimated excess number of myopathy cases was based on a meta-analysis of RCTs estimate of the excessive incidence of myopathy, 0.0628 per 1000 patient-years.[8]

‖ Estimated additional myopathy cases were based on a population-based cohort study with >2 million patients.[7] The excess incidence of myopathy was 1.864 (95% CI, 1.515-2.282) and 0.632 (95% CI, 0.436-0.880) per 1000 patient-years for men and women, respectively.

Table A4 Predicted Annual ASCVD Deaths Prevented and Additional Adverse Events by Statin Use Among Participants 40-75 Years, With ≥7.5% 10-Year ASCVD Risk Assuming 80% Eligible Take Statin With 80% Adherence —NHANES 2005-2010[*]

Characteristic	Population [†] (100 000)	Eligible Population [‡] (100 000)	Estimated Annual ASCVD Deaths	ASCVD Deaths Prevented (95% CI)	Excess Number Diabetes (95% CI)	RCT-Based Excess Number Myopathy (95% CI)[§]	Population-Based Excess Number Myopathy (95% CI)[‖]
Total	206.2	131.9	39880	3472 (817-5718)	10500 (3150-16 800)	660 (0-3,066)	15554 (12392-19387)
Women	66.6	40.9	12500	1063 (250-1751)	3259 (978-5215)	205 (0-952)	2060 (1422-2867)
Age group							
40-49	2.3	1.9	73	8 (2-13)	148 (44-237)	9 (0-43)	94 (65-130)
50-59	4.2	2.7	340	30 (7-50)	212 (64-339)	13 (0-62)	134 (92-186)
60-69	31.9	20.2	4670	418 (98-688)	1609 (483-2574)	101 (0-470)	1017 (702-1415)
70-75	28.2	16.1	7420	607 (143-1000)	1276 (383-2042)	80 (0-373)	807 (557-1122)
Race/ethnicity							
Non-Hispanic white	51.1	31.3	9270	787 (185-1296)	2494 (748-3991)	157 (0-728)	1576 (1088-2194)
Non-Hispanic black	6.7	4.1	2070	177 (42-291)	330 (99-528)	21 (0-96)	209 (144-290)
Hispanic	5.4	3.3	777	66 (16-109)	267 (80-426)	17 (0-78)	168 (116-234)
Men	139.6	91.0	27380	2409 (567-3968)	7241 (2172-11 585)	455 (0-2,114)	13494 (10971-16521)
Age group							
40-49	11.4	9.1	807	88 (21-145)	729 (219-1166)	46 (0-213)	1358 (1104-1662)
50-59	48.5	34.5	7350	725 (170-1193)	2749 (825-4399)	173 (0-803)	5124 (4166-6273)
60-69	58.1	35.8	11320	988 (233-1628)	2838 (852-4541)	178 (0-829)	5290 (4301-6476)

70-75	21.5	11.5	7900	608 (143-1002)	902 (270-1442)	57 (0-263)	1680 (1366-2057)
Race/ethnicity							
Non-Hispanic white	107.3	69.6	21230	1865 (439-3071)	5540 (1662-8864)	348 (0-1,618)	10325 (8394-12 641)
Non-Hispanic black	12.8	8.4	3640	323 (76-532)	668 (201-1070)	42 (0-195)	1246 (1013-1525)
Hispanic	12.2	8.1	1670	147 (35-242)	647 (194-1034)	41 (0-189)	1205 (980-1475)

Abbreviations: ASCVD, atherosclerotic cardiovascular diseases; NHANES, National Health and Nutrition Examination Survey; RCT, randomized clinical trial.

[*]Assumes 80% of eligible population take statins with an adherence rate of 80%.

[†] Population = number of adults aged 40-75 years without diabetes but with ≥7.5% 10-year ASCVD risk in 100000.

[‡] The age- and race/ethnicity specific annual number of ASCVD prevented is calculated as follows: $\sum[POP_{ij}*DD_{ij} - ((1-P_i)* POP_{ij}*DD_{ij} + P_i* POP_{ij}*DD_{ij}*RR)]$, where POP_{ij} = age-race/ethnicity specific eligible population (non-current statin users; we assume 80% of eligible are taking statin in the sensitivity analysis); P_t = percent of eligible population taking statin (we assumed 80% in the sensitivity analysis); *RR* = relative risk of statin use on CVD mortality (0.83 (95% CI, 0.72-0.96)).[5] We used the 95% CI of *RR* to estimate the lower and upper limit of annual number of ASCVD prevented.

[§] The estimated excess number of myopathy cases was based on a meta-analysis of RCTs estimate of the excessive incidence of myopathy, 0.0628 per 1000 patient-years.[8]

[‖] The estimated additional myopathy cases were based on a population-based cohort study with >2 million patients.[7] The excess incidence of myopathy were 1.864 (95% CI, 1.515-2.282) and 0.632 (95% CI, 0.436-0.880) per 1000 patient-years for men and women, respectively.