BMJ Open Diabetes Research & Care

Baseline hemoglobin A1c and risk of statin-induced diabetes: results of Veterans Affairs Database analysis

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To cite: Ziganshina AP, Gemoets DE, Kaminsky LS, *et al*. Baseline hemoglobin A1c and risk of statin-induced diabetes: results of Veterans Affairs Database analysis. *BMJ Open Diab Res Care* 2022;10:e002554. doi:10.1136/bmjdrc-2021-002554

LSK since deceased.

Received 17 August 2021
Accepted 7 December 2021

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Development of new-onset diabetes mellitus (NODM) is one of the side effects of statin therapy.[1] Since the absolute risk of statin-induced diabetes is small, it remains unclear if there are any specific factors that might predispose to hyperglycemia following statin initiation. Conditions such as metabolic syndrome, hypertension, and/or low exercise tolerance[2] have been proposed as potential risk factors based on relatively small prospective trials or observational studies that were not initially designed for evaluating of statin-induced NODM. The goal of this study was to determine if baseline level of hemoglobin A1c (HbA1c) is a significant and independent risk factor that increases the risk of statin-induced diabetes.

This was a retrospective nationwide cohort study of US Veterans without prior diagnosis of diabetes started on most commonly used in Veterans Healthcare Administration system statins (atorvastatin, simvastatin, pravastatin). Between January 2011 and December 2018, we identified 152 358 patients using the following inclusion criteria: availability of full demographic and clinical information, baseline HbA1c <6.5%, no International Classification of Diseases, Ninth Version (ICD-9) diagnosis of diabetes or use of diabetes medications except metformin (as it can be used in the management of pre-diabetes), baseline calculated low-density lipoprotein cholesterol (LDL-C) value, and adequate adherence to statins (determined based on proportion of days covered ≥80%)[3] (table 1). Baseline HbA1c values were stratified into three categories: ≤5.6%, 5.7%–5.9% and 6.0%–6.4%. The risk of statin-induced NODM was assessed in the whole cohort and according to the above baseline HbA1c categories using Cox proportional hazards model adjusted for case-mix. Covariates for risk adjustment included: age, gender, ethnicity, obesity, hypertension, coronary artery disease, baseline LDL-C level, cerebrovascular disease, and metformin use. Effect size measures of omega squared for continuous variables and Cramer's V for categorical variables quantified degree of possible confounding.

Mean study follow-up was 6.89 (SD 2.26) years in non-statin users and 3.85 (SD 2.29) years in statin users. The rate of statin-induced NODM was similar to prior observations (1,2), with an estimate of 224.5 additional cases of diabetes per 10 000 patients during 4-year study period compared with non-users. We found that in the adjusted models, statin-induced NODM risk was inversely related to baseline HbA1c (table 1). In overall statin users' group, HRs were 2.08 (1.85 to 2.35), 1.57 (1.40 to 1.75) and 1.03 (0.93 to 1.15) for HbA1c groups of ≤5.6%, 5.7%–5.9% and 6.0%–6.4%, respectively (p<0.0001 for decreasing trend in HRs). This trend persisted when either atorvastatin, simvastatin and pravastatin were analyzed individually or all statins were grouped based on the LDL-C-lowering potency (table 1). There was no significant difference in diabetogenic risk among different statin groups. The body mass index changes in the statin users throughout the observation period did not alter their diabetogenic risks regardless of A1c category (data not shown).

The results of this largest to date analysis of the diabetogenic risk in statin and non-statin users closely matched for baseline characteristics suggest that the rate of statin-induced NODM may have reverse association with baseline HbA1c. We hypothesize that our findings can be explained by the fact that HbA1c between 6.0% and 6.4% is by itself associated with high diabetes development risk and thus additional risks from statin therapy are no longer significant. In one systematic review, Zhang *et al* showed that

Table 1 Summary of the results: HR with 95% CIs of diabetes risk in statin users and non-users

	Total cohort (N=152 358)		Statin non-users			Statin users			
	Statin non-users N=143 505	Statin users N=8853	≤5.6% (N=83 593)	5.7%–5.9% (N=36 771)	6.0%–6.4% (N=23 141)	≤5.6% (N=4594)	5.7%–5.9% (N=2731)	6.0%–6.4% (N=1528)	Effect size or p value*
Mean age (SD), year	51.5 (16.8)	57.9 (11.6)	47.3 (16.8)	55.6 (15.4)	59.7 (14.0)	56.0 (12.3)	59.5 (10.5)	60.7 (10.3)	0.096
Gender, male, n (%)	126 868 (88.0)	8284 (94.0)	72 178 (86.0)	33 253 (90.0)	21 437 (93.0)	4281 (93.0)	2559 (94.0)	1444 (95.0)	0.087
Ethnicity, n (%)									0.090
Caucasian	110 647 (77.0)	7450 (84.0)	67 455 (81.0)	27 366 (74.0)	15 826 (68.0)	4000 (87.0)	2289 (84.0)	1161 (76.0)	
African American	27 919 (19.0)	1159 (13.0)	13 166 (16.0)	8185 (22.0)	6568 (28.0)	472 (10.0)	367 (13.0)	320 (21.0)	
Other	4939 (3.0)	244 (3.0)	2972 (4.0)	1220 (3.0)	747 (3.0)	122 (3.0)	75 (3.0)	47 (3.0)	
Mean follow-up (SD), years	6.9 (2.3)	3.8 (2.3)	7.3 (1.8)	6.8 (2.2)	5.5 (3.0)	3.9 (2.3)	3.9 (2.3)	3.7 (2.3)	0.167
Mean BMI (SD), kg/m^2	28.5 (5.4)	28.9 (5.2)	27.9 (5.1)	28.8 (5.5)	29.9 (5.9)	28.6 (5.0)	29.1 (5.2)	29.9 (5.5)	0.018
Mean HbA1c (SD), %	5.6 (0.4)	5.6 (0.3)	5.3 (0.3)	5.8 (0.1)	6.1 (0.1)	5.3 (0.2)	5.8 (0.1)	6.1 (0.1)	0.695
Hypertension, n (%)	48 475 (34.0)	4406 (50.0)	22 736 (27.0)	14 272 (39.0)	11 467 (50.0)	2112 (46.0)	1414 (52.0)	880 (58.0)	0.191
Mean LDL-C, (SD), mg/dL	101.8 (30.9)	114.4 (31.9)	100.6 (30.7)	104.0 (31.0)	103.0 (31.4)	113.4 (31.6)	114.9 (32.0)	116.4 (32.5)	0.012
Cerebrovascular disease, n (%)	2525 (2.0)	253 (3.0)	1252 (1.0)	692 (2.0)	601 (3.0)	139 (3.0)	70 (3.0)	44 (3.0)	0.034
Coronary artery disease, n (%)	5772 (4.0)	501 (6.0)	2227 (3.0)	1744 (5.0)	1801 (8.0)	207 (5.0)	165 (6.0)	129 (8.0)	0.095
Metformin use, n (%)	2532 (2.0)	209 (2.0)	849 (1.0)	663 (2.0)	1020 (4.0)	72 (2.0)	77 (3.0)	60 (4.0)	0.090
Type of statin									
Atorvastatin, n (%)	–	4394 (50.0)	–	–	–	2387 (52.0)	1285 (47.0)	722 (47.0)	
Simvastatin, n (%)	–	3189 (36.0)	–	–	–	1599 (35.0)	999 (37.0)	591 (39.0)	
Pravastatin, n (%)	–	1270 (14.0)	–	–	–	608 (13.0)	447 (16.0)	215 (14.0)	
Unadjusted HR of NODM compared with A1c ≤5.6% in non-users	1.00 (ref)	1.68 (1.58 to 1.80)	1.00 (ref)	2.6 (2.5 to 2.8)	9.3 (8.9 to 9.7)	2.5 (2.2 to 2.8)	4.6 (4.1 to 5.2)	9.7 (8.7 to 10.8)	<0.0001
Unadjusted HR of NODM for all statin users compared with respective A1c category in non-users	1.00 (ref)	1.68 (1.58 to 1.80)	1.00 (ref)	1.00 (ref)	1.00 (ref)	2.50 (2.22 to 2.82)	1.75 (1.56 to 1.96)	1.04 (0.94 to 1.16)	<0.0001
Adjusted HR of NODM for all statin users compared with respective A1c category in non-users	1.00 (ref)	1.40 (1.31 to 1.50)	1.00 (ref)	1.00 (ref)	1.00 (ref)	2.08 (1.85 to 2.35)	1.57 (1.40 to 1.75)	1.03 (0.93 to 1.15)	<0.0001
Adjusted HR of NODM for individual statin groups									
Atorvastatin			1.00 (ref)	1.00 (ref)	1.00 (ref)	2.28 (1.91 to 2.71)	1.85 (1.56 to 2.19)	1.21 (1.03 to 1.41)	<0.0001
Simvastatin			1.00 (ref)	1.00 (ref)	1.00 (ref)	2.05 (1.72 to 2.46)	1.45 (1.22 to 1.72)	0.98 (0.84 to 1.15)	0.015
Pravastatin			1.00 (ref)	1.00 (ref)	1.00 (ref)	1.69 (1.23 to 2.32)	1.30 (0.98 to 1.71)	0.78 (0.58 to 1.04)	0.13
Adjusted HR of NODM for statin intensity groups									
High intensity			1.00 (ref)	1.00 (ref)	1.00 (ref)	2.62 (1.94 to 3.54)	1.93 (1.43 to 2.61)	1.30 (0.99 to 1.71)	0.21
Moderate intensity			1.00 (ref)	1.00 (ref)	1.00 (ref)	1.92 (1.64 to 2.27)	1.61 (1.38 to 1.87)	0.99 (0.86 to 1.14)	<0.0001

Continued

Table 1 Continued

	Total cohort (N=152 358)		Statin non-users			Statin users			
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Low intensity			1.00 (ref)	1.00 (ref)	1.00 (ref)	1.96 (1.49 to 2.57)	1.19 (0.91 to 1.56)	0.78 (0.60 to 1.03)	0.71

*Effect sizes for baseline characteristics to assess confounding or p values for testing significance in the HR trends between non-users and statin users across A1c ranges.
BMI, body mass index; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; NODM, new-onset diabetes mellitus.

the highest risk of developing type 2 diabetes is in the individuals with HbA1c ≥6.0%.[4] Among statin non-users with baseline HbA1c 6.0%–6.4%, unadjusted HR for NODM was 9.3, consistent with findings in the systematic review by Zhang *et al*; of note, this risk was not significantly different from the risk of NODM in the statin users (table 1). Our hypothesis is supported by the findings from the trials where higher incidence of statin-induced NODM was reported in subjects with mean baseline HbA1c <6.0%[5] and the studies that demonstrated lower incidence of NODM when baseline dysglycemia was more pronounced.[6]

Our study has limitations. It was a retrospective analysis conducted in the government-funded healthcare system and majority of the patients were white and male. The strengths are that we tried to match all subjects as close as possible and included only patients who adhered to the statin treatment. The results of this retrospective observational trial with DM risk as the primary outcome can be particularly clinically relevant because older patients with pre-diabetes may have high cardiovascular (CV) risk and are often candidates for statin therapy. Providers and patients may perceive the risk of statin-induced diabetes as a negative factor in decision to initiate statin therapy. Our results suggest that individuals with HbA1c between 6.0% and 6.4% who may have significant baseline CV risk may in fact not be at higher risk of developing diabetes which should alleviate concerns of new-onset dysglycemia from statin use in clinical practice. We also suggest that the A1c value at the time of a patient–provider shared decision-making session should be included to discuss diabetogenic risks of statin therapy.

Acknowledgements This material is the result of work supported with resources and the use of facilities at the Stratton VAMC, Albany, New York, USA.

Contributors APZ researched data and wrote the manuscript. DEG analyzed data and contributed to the discussion. LSK contributed to the discussion. ARG contributed to the study design, cohort development, data interpretation and reviewed/edited the manuscript. All authors participated in drafting the article and revising it critically for important intellectual content. All authors provided their approval of this version of the manuscript for publication. ARG 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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The opinions expressed in this paper are those of the authors and do not represent the views of the Department of Veterans Affairs or the US Government.

Competing interests DEG, LSK, and ARG are employees of the US Department of Veterans Affairs. ARG serves as an Associate Editor of the *BMJ Open Diabetes Research & Care* and *Journal of Clinical and Translational Endocrinology*. The other authors declare no competing interests.

Patient consent for publication Not required.

Ethics approval The study was approved by the Stratton Veterans Affairs Medical Center Institutional Review Board, Albany, New York, USA.

Provenance and peer review Not commissioned; externally peer reviewed.

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