RISK OF TYPE-2 DIABETES ASSOCIATED WITH STATIN THERAPY AMONG ELDERLY PATIENTS – A NESTED CASE-CONTROL STUDY

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BACKGROUND

HMG-COA reductase inhibitors, commonly known as statins, lower cholesterol levels, thereby preventing cardiovascular events among high-risk patients. There is some evidence in the literature indicating that statin therapy is associated with an increased risk of type-2 diabetes (odds ratio [OR]: 1.09; 95% Confidence Interval [CI]: 1.02–1.17).[1,2] In 2012, the Food and Drug Administration (FDA) issued labeling changes for this class of medications indicating that statins may potentially increase the risk of developing type-2 diabetes.

OBJECTIVES

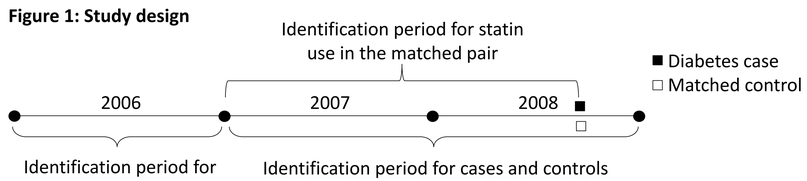
1. To investigate the impact of statin therapy on the risk of type-2 diabetes in elderly patients enrolled in Medicare; and
2. To evaluate whether this relationship is related to treatment intensity.

METHODOLOGY

Data Source: *2006-2008* 5% national sample of Medicare beneficiaries
Study Design: A nested case-control study design was used (Figure 1).

- A cohort of Medicare beneficiaries in 2006 was identified using the following inclusion criteria: (a) 65 years or older in age; (b) no managed care enrollment in any of the months in the study period; (c) no claim for statin medications in 2006 (statin-naïve); (d) no diagnosis of type-2 diabetes (indicated by absence of ICD-9-CM diagnosis code 250.x0 or 250.x2) in 2006.
- Of these, patients who developed type-2 diabetes (ICD-9-CM diagnosis code 250.x0 or 250.x2 along with at least one claim for an oral hypoglycemic agent within 90 days from the date of diagnosis) in 2007 or 2008 were identified as cases. The first date of their diabetes diagnosis was set as the index date. Patients who did not develop diabetes in this period were identified as controls.
- Each case was matched with a control on age and gender; controls were assigned the index date of corresponding cases.
- Beneficiaries who were prescribed statin medications (listed in Table 1) before the index date were then identified as statin users. Furthermore, statin therapy was classified into low-dose, moderate-dose, and intensive-dose on the basis of the type of statin and dose (Table 1).[3]
- Conditional logistic regression stratified on matched pairs was used to address study objectives.

Figure 1: Study design



RESULTS

Table 1: Classification of statin medications based on intensity (adopted from Barac et al.)[3]

Statin	Intensity		
	Low	Moderate	Intensive
Simvastatin	<20 mg	20-40 mg	>40 mg
Lovastatin	<20 mg	20-80 mg	>80 mg
Atorvastatin	<20 mg	20 mg	>20 mg
Rosuvastatin	<20 mg	20 mg	>20 mg
Pravastatin	<20 mg	20-80 mg	>80 mg
Fluvastatin	<20 mg	20-80 mg	>80 mg

- Significant differences were observed between cases and controls in terms of statin use, statin intensity, use of concomitant drugs, and medical comorbidities in the matched sample (Table 2).
- In the multivariable model (Table 3), statin users had a significantly higher likelihood of developing type-2 diabetes compared to non-users (OR: 1.396; 95% CI: 1.308 – 1.491).
- Compared to non-users, patients on intensive statin therapy had the highest odds of developing type-2 diabetes followed by moderate- and low-intensity statin therapy (Table 3).

Table 3: Odds ratio estimates for the effect of statin use and intensity on the risk of type-2 diabetes.*

Characteristics	Odds Ratio	95% Confidence Intervals
Statin use		
Yes	1.396	1.308 – 1.491
No	Ref	–
Statin intensity		
No statin	Ref	–
Low	1.268	1.134 – 1.417
Moderate	1.393	1.292 – 1.501
Intensive	1.646	1.442 – 1.879

*The estimates presented above are from separate multivariable conditional logistic regression models controlling for the effect of concomitant drugs and medical comorbidities presented in Table 2.

Table 2: Characteristics of cases and controls in the matched sample.

Characteristics, N (%)	Cases (N = 8,655)	Controls (N = 8,655)	Wald chi sq.	p value
Statin use			157.49	<0.0001
Yes	4,006 (46.29)	3,200 (36.97)		
No	4,649 (53.71)	5,455 (63.03)		
Statin intensity			35.58	<0.0001
No statin	4,649 (53.71)	5,455 (63.03)		
Low-dose	811 (9.37)	741 (8.56)		
Moderate-dose	2,508 (28.98)	2,008 (23.20)		
Intensive-dose	687 (7.94)	451 (5.21)		
Concomitant drugs				
Antipsychotics			58.46	<0.0001
Yes	942 (10.88)	650 (7.51)		
No	7,713 (89.12)	8,005 (92.49)		
Beta-blockers			160.56	<0.0001
Yes	4,149 (47.94)	3,324 (38.41)		
No	4,506 (52.06)	5,331 (61.59)		
Diuretics			31.38	<0.0001
Yes	1,564 (18.07)	1,289 (14.89)		
No	7,091 (81.93)	7,366 (85.11)		
Phenytoin			0.87	0.352
Yes	108 (1.25)	112 (1.41)		
No	8,547 (98.75)	8,533 (98.59)		
Corticosteroids			14.78	0.0001
Yes	1,923 (22.22)	1,718 (19.85)		
No	6,732 (77.78)	6,937 (80.15)		
Medical comorbidities				
Hypertension			103.46	<0.0001
Yes	5,673 (65.55)	5,023 (58.04)		
No	2,982 (34.45)	3,632 (41.96)		
CVD*			14.89	0.0001
Yes	1,266 (14.63)	1,093 (12.63)		
No	7,389 (85.37)	7,562 (87.37)		
COPD*			92.74	<0.0001
Yes	1,848 (21.35)	1,350 (15.60)		
No	6,807 (78.65)	7,305 (84.40)		
CHD*			89.48	<0.0001
Yes	2,727 (31.51)	2,177 (25.15)		
No	5,928 (68.49)	6,478 (74.85)		

*CVD = Cerebrovascular disease; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease.
The Wald chi sq. estimates and p values reported above are from separate univariable conditional logistic regression models.

CONCLUSIONS AND IMPLICATIONS

- Statin use is associated with a significant increase in the risk of type-2 diabetes in elderly Medicare beneficiaries.
- The risk of type-2 diabetes increases with an increase in the intensity of statin therapy.
- This study has significant implications for the management of millions of individuals receiving statins worldwide.
- Prescribers should weigh the pros and cons before prescribing statins to elderly patients with borderline dyslipidemia.

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ACKNOWLEDGEMENTS

This study was conducted as part of a project titled "Using Medicare/Medicaid Claims Data to Support Medication Outcomes and Pharmacovigilance Research," which was supported by grant award 1COCMS330731/01 from the Office of Research, Development and Information, CMS. The authors have no actual or potential conflict of interest in relation to this educational activity or presentation.

Poster # 154 presented at the American College of Clinical Pharmacy Annual Meeting, October 13-16, 2013, Albuquerque, New Mexico, USA