



U.S. Department of Veterans Affairs

### Background

Alzheimer's disease (AD) is a chronic, progressive, and irreversible age-related neurodegenerative disorder characterized by cognitive and memory impairment. It is the most common cause of dementia in older adults. Production and aggregation of the amyloid- $\beta$  (A $\beta$ ) peptide leading to neurodegeneration is considered to be a hallmark of Alzheimer's disease.<sup>1</sup> Production of Aß peptide has been shown to be increased by cholesterol. Statins work by inhibiting the enzyme 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase to prevent cholesterol synthesis, which in turn, have been shown to have an inhibiting effect on Aβ peptide.<sup>1</sup>



Persons who used a statin were half as likely to develop dementia as those who did not use statins (HR = 0.52; 95% CI 0.34, 0.80)

It is unclear whether the incidence of AD differs between lipophilic statins, which can easily pass through the blood-brain barrier (BBB), or hydrophilic statins.

Rosuvastatin Pravastatin Atorvastatin

Simvastatin

Hydrophilic

Lipophilic

It is debated whether lowering of serum cholesterol levels by these drugs could affect brain cholesterol homeostasis. Therefore, the purpose of this retrospective chart review was to determine if the use of atorvastatin, pravastatin, rosuvastatin and simvastatin is associated with a lower incidence of AD and if it differs between lipophilic and hydrophilic statins.

## **Primary Objective**

To compare the incidence in the development of AD between the four study statins.

## **Secondary Objective**

To assess the time to AD development from statin initiation and cholesterol levels at the time of AD diagnosis.

# Assessment of Statin Use and Incidence of Alzheimer's Disease

Lydia A. Jalowiec, PharmD, Kristen Backe, PharmD, BCPP, Rick A. Weideman, PharmD, BCPS Veterans Affairs North Texas Health Care System, Dallas, TX

|  | Inclucion Critoria – Evolucion Critoria  |   |                     |  |                    |              |             |                 |   |                            |               |  |   |   |                                      |                                   |
|--|--|---|---------------------|--|--------------------|--------------|-------------|-----------------|---|----------------------------|---------------|--|---|---|--------------------------------------|-----------------------------------|
|  |  | Inclusion Criteria Exclusion Criteria   |                     |  |                    |              |             |                 |   |                            | Re            | sults (c   | ont )   |   |                                      |                                   |
|  | Ivietno  | Total Population  |                     |  |                    |              |             |                 |   |                            |               |  |   |   |                                      |                                   |
| • Retr   | ospective Electro  | Age $\geq$ 50 at statin Use of one of the other initiation and on one of study stating for $\geq$ 00 days |                     |  |                    |              |             |                 | Incidence of Alzheimer's Disease by Patient |                            |               |  |   |   |                                      |                                   |
| Revi   | ew   | the four study stating for >  |                     |  |                    |              |             |                 | Year (Mean ± 95% Binomial CI)               |                            |               |  |   |   |                                      |                                   |
| • Setti  | ing: Veterans Affa   | 360 davs hefore ΔD drug   |                     |  |                    |              |             |                 | -   | 0                          | .7            | 26/6,853 1   | .3/3,559  |   |                                      |                                   |
| Heal   | Ithcare System   | started or otherwise  |                     |  |                    |              |             |                 |   | ہ <u>۲</u>                 | .6            |  |   |   |                                      |                                   |
| • Time   | e Period: October  | (patients without AD)   |                     |  |                    |              |             |                 |   | r's'p                      | .5            |  |   |   |                                      |                                   |
| Sept   | tember 30, 2018  | AD Population   |                     |  |                    |              |             |                 | -   | 0 eime                     | .4            |  |   |   |                                      |                                   |
| Statistical Analysis   |  |   |                     | Received a VA prescription Vascular dementia, Lewy |                    |              |             |                 |   |                            |               | 0 Alzho  | .3 <b>64/27,898</b>   |   |                                      |                                   |
|  |  |   |                     | for either an body dementia, alcohol-              |                    |              |             |                 |   |                            | -             | 0 e  | .2  |   |                                      | 312/213,224                       |
| • Fise   | cher's Exact Test  | acetylcholinesterase related dementia,  |                     |  |                    |              |             |                 |   | denc                       | 1             |  |   | Ŧ   |                                      |                                   |
| • Inc  | idence of AD and   | inhibitor (AChEI) or dementia due to traumatic  |                     |  |                    |              |             |                 |   |                            |               |  |   |   |                                      |                                   |
| Со   | nfidence Interval  | memantine brain injury or   |                     |  |                    |              |             |                 | 1   |                            | Atorvastatin  | Pravastatin Ro   | suvastat  | in Simvastatin  |                                      |                                   |
|  |  | cognitive impairment or   |                     |  |                    |              |             |                 | Lipid levels at time of AD diagnosis        |                            |               |  |   |   |                                      |                                   |
|  |  | Parkinson's Disease   |                     |  |                    |              |             |                 | -   |                            |               | TC (mg/c   | IL) LC  | DL (mg/dL)  |                                      |                                   |
|  |  | Ba  | selir               | he Chara   | ristics            |              |             |                 |   |                            | At            | orvastatin   | 154   |   | 82                                   |                                   |
|  |  |   |                     | Total Population                                   |                    |              |             |                 |   |                            |               | Si   | mvastatin   | 165   |                                      | 91                                |
| Characteristic Ator  |  |   | vastatin Pravastati |  |                    | Rosuvastatin |             | Simvastatin     |   | a financiana<br>generativa | Ro            | suvastatin   | 154   |   | 79                                   |                                   |
| (n=  |  |   | 11,643) (n=2,639    |  | 2,639)             | (n = 1,226)  |             | (n=42,7         | 708)  |                            | Pr            | ravastatin   | 162   |   | 96                                   |                                   |
| Male (%)   |  |   | 94 94               |  | 94                 | 94           |             | 95              | _   | -                          |               | P-value  | e 0.17  | 53  | 0.1183                               |                                   |
| Average Time on statin     2.4   |  |   | years 2.6 years     |  | years              | 2.9 years    |             | 5 years         |   |                            | • 7           | Time from sta  | atin to AD di   | agnosis   | s (years)                            |                                   |
| Average Age at Start of statin     59  |  |   | years 60 years      |  | years              | 61 years     |             | 60 years        |   | -                          | Simv          | astatin  |   | 6.8 \   | vears                                |                                   |
|  |  |   |                     | AD Population                                      |                    |              |             |                 |   |                            | here          | Atorvastatin   |   |   | 5.9 years                            |                                   |
| <b>Characteristic</b> Ato  |  |   | vastatin Pravastat  |  | astatin            | n Rosuvastat |             | Simvast         | tatin                                       | Pravastatin                |               | 4.4 years  |   | vears   |                                      |                                   |
|  |  |   | (                   | (n=26) (n=26)                                      |                    | =26)         | (n=13)      |                 | (n=312)                                     |                            | -             | Rosuvastatin   |   |   | 4 2 years                            |                                   |
| Average Time on statin   |  |   | 9/<br>Avears        | 37 vers  |                    | 28 years     |             | 97<br>8 A vears |   |                            | NOSU          |  | valua   | т. 2 у  |                                      |                                   |
| Average Age at Start of Statin6  |  |   | 6                   | 7 vears  | vears 72 years     |              | 69 years    |                 | 66 years                                    |                            |               |  | - T   |   | •                                    | 0.000282                          |
| Time from Statin Initiation to AD5.  |  |   | years 4.4 years     |  | vears              | 4.2 years    |             | 6.8 ve          | 6.8 years                                   |                            | Conclusion    |  |   |   |                                      |                                   |
|  |  | Doculto   |                     |  |                    |              |             |                 |   | Base                       | ed on this da | ata, simvas <sup>.</sup>   | atin m  | nay be  |                                      |                                   |
|  |  | Atorvact  | Rocus               | actatin  | statin Dravastatin |              |             |                 | AD This doosn't appear to be correlated to  |                            |               |  |   |   |                                      |                                   |
|  |  |   |                     |  |                    |              | 70/         |                 |   |                            |               | Seru   | m linid leve  | ls Howeve   | r mor                                | e research is                     |
|  | D-Value vs   |   | 0.14/0              |  | 0.2570             |              | //0         | 0.50/0          |   |                            |               | needed to confirm these results.                                   |   |   |                                      |                                   |
|  |  |   |                     |  |                    |              | าว*         | <0              | 0001*                                       | -                          |               |  |   | limitati  | ons                                  |                                   |
|  | Simulatin  |   |                     | 0.002  |                    | 0.005        |             | <0.0001 ·       |   |                            |               | Retrospective  |   |   |                                      |                                   |
|  | $P_{a} = \frac{P_{a}}{P_{a}} = \frac{P_{a}}{P_{a}}$  |   | )*                  |  |                    | 0146         |             | $\cap$          | 0 03/                                       |                            |               | <ul> <li>Unable to capture patients who were prescribed</li> </ul> |   |   |                                      |                                   |
|  | Δtorvastatin   |   |                     |  | 0.1                |              | .+0 U.      |                 | .0.5-                                       |                            |               | A  | ChEI outside t  | the VA  |                                      |                                   |
|  | $\mathbf{P}_{\mathbf{N}} = \mathbf{P}_{\mathbf{N}} = $ |   | <b>ξ</b> * Λ 1      |  | 16                 |              |             |                 | 1   |                            |               | • Di   | ffering presci  | ribing patter   | ns due <sup>·</sup>                  | to formulary                      |
| Rosuvastatin   |  | U.1   |                     | +0   |                    |              |             | ⊥               |   |                            | av<br>• Li    | mited genera   | lizability as A   | lzheim  | er's disease is                      |                                   |
| $\frac{\mathbf{D}_{\mathbf{V}_{\mathbf{U}}}}{\mathbf{D}_{\mathbf{V}_{\mathbf{U}}}} = \frac{\mathbf{D}_{\mathbf{U}}}{\mathbf{V}_{\mathbf{U}}} = \frac{1}{2} $ |  |   | )1*                 | 0.021  |                    | 1            | 1           |                 |   |                            |               | m  | ore common  | in females  |                                      |                                   |
| Pravastatin  |  |   |                     | 0.054  |                    |              | T           |                 |   |                            |               | Reference<br>1. Bane   | s:<br>rjee S, Mukherjee S. Cholester  | ol: A Key in the Pathogenesis                                 | of Alzheimer's D                     | Disease. Chemmedchem [serial      |
|  | ridvdStdtifi   |   |                     |  |                    |              | * Indicated | statistica      | l significance                              | 2                          |               | online<br>2. Haag<br>diseas  | e]. July 7, 2018<br>MD, Hofman A, Koudstaal PJ, S<br>se. The Rotterdam Study. J Neu | tricker BH, Breteler MM. Sta<br>Irol Neurosurg Psychiatry. 20 | ins are associate<br>)9;80(1):13–17. | ed with a reduced risk of Alzheir |
|  |  |   |                     |  |                    |              | marcate     |                 |   |                            |               |  |   |   |                                      |                                   |

School of Pharmacy