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Research Article



Cardiovascular Outcomes in Patients Over 75 Years of Age Taking a Statin for Primary Prevention

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Abstract

Background: The elderly population is rapidly growing, and there is limited evidence for the use of statins for primary prevention of Atherosclerotic Cardiovascular Disease (ASCVD) in this population.

Objective: The primary outcome of this study was a composite of the patient's first cardiovascular event, defined as cardiovascular death, non-fatal Myocardial Infarction (MI) or non-fatal stroke (Three Point Major Adverse Cardiovascular Events: 3P-MACE).

Methods: This retrospective study examined the effect of statin therapy for primary prevention of cardiovascular outcomes in patients at least 75 years of age on moderate to high-intensity statin therapy.

Results: A total of 1853 patients were included in this study. Patients were more likely to experience the composite endpoint if they were in the statin group compared to the control group (19.7% versus 13.2%, $p=0.0004$). Patients in the statin group were significantly more likely to have a non-fatal MI or stroke compared to the control group (3.2% versus 0.5%, $p<0.0001$ and 14.1% versus 10.4%, $p=0.0193$). Patients with diabetes were less likely to die from any cause if they received statin therapy when compared to the control group (19.18% vs. 43.58%, $p<0.0001$).

Conclusion: In conclusion, statin therapy appears to be beneficial in elderly patients with diabetes. However, the same therapy was found to have no benefits against the primary composite endpoint in this population of patients.

Keywords

Atherosclerotic Cardiovascular Disease; Cardiovascular Outcome; Elderly; Primary Prevention; Statins

Background

Globally and nationally, Cardiovascular Disease (CVD) is the number one cause of death. Nearly 801,000 deaths in America-or 1 out of 3 deaths-each year can be attributed to CVD [1]. In 2015, approximately 17.7 million people died from CVD, accounting for 31% of all global deaths [2]. This is despite constant efforts to combat Major Adverse Cardiovascular Events (MACE) over the past several decades. Though partially due to modifiable risk factors, such as smoking, physical inactivity, poor diet, and obesity, age is also a robust predictor of CVD. In 2013, approximately 80% of deaths due to coronary heart disease in the United States occurred in people age

65 years and older [3]. The relationship between CVD risk and age is of concern, especially considering the anticipated growth in the elderly population. Projections illustrate that the population of people over 65 years old in the United States is expected to increase from 13.7% to 20.3% between 2012 and 2030. More specifically, those over the age of 75 years are expected to nearly double in percentage in that same timeframe, going from 19.1 million people in 2012 to 34.2 million people in 2030 [4]. As the elderly population grows, diagnoses of CVD and cardiovascular-related deaths are projected to increase. The medications collectively known as “statins” (3-Hydroxy-3-Methyl-Glutaryl Coenzyme A (HMG-CoA) reductase inhibitors) are commonly recommended for the treatment of dyslipidemia and the prevention of CVD. Many studies have been done with this class of medications, demonstrating the efficacy of statins for primary and secondary prevention of Atherosclerotic Cardiovascular Disease (ASCVD) [5]. However, in most of these studies, the elderly population was frequently excluded, thus yielding a lack of basis for how to properly treat elderly patients. Trials that did include, and sometimes focus on, the elderly population and the use of statins, such as the PROSPER and SAGE trials, often only evaluated their use for secondary prevention of ASCVD [6,7]. Fortunately, these trials both showed that statins do reduce cardiovascular risk in elderly individuals with a history of prior ASCVD. However, whether this benefit exists for the primary prevention of ASCVD in elderly individuals without prior ASCVD could not be extrapolated from these studies. Other trials, such as CARDS and JUPITER, examined the use of statins for primary prevention of ASCVD in elderly patients and demonstrated a significant reduction in the incidence of Myocardial Infarction (MI), Coronary Heart Disease (CHD) death, revascularization, and unstable angina [8,9]. Unfortunately, these trials typically evaluated patients with mean ages between 65 and 75 years and rarely evaluated statin use for primary prevention in patients over the age of 75 years [7,8]. The age threshold of 75 years is particularly important when interpreting the various dyslipidemia guidelines that have published and adopted throughout the world. The most recent guideline published for the management of dyslipidemia in the

United States, a collaboration between the American College of Cardiology (ACC) and the American Heart Association (AHA) in 2018, recommends moderate-intensity statin therapy for patients over the age of 75 years with ASCVD [10]. However, for those over 75 years old without prior ASCVD and a 10-year CVD risk greater than 7.5%, no recommendations are provided. The 2017 guidelines published by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), recommends that individuals over 75 years old with ASCVD risk factors be screened for dyslipidemia and treated to goal LDL-C and non-HDL-C [11]. The 2014 US Department of Veteran Affairs/Department of Defense (VA/DOD) guidelines do not provide specific guidance for the elderly population only noting that all patients with greater than 6% risk for CVD in the next ten years receive a moderate-intensity statin [12]. Due to the rapidly growing elderly population in the United States and abroad, as well as the limited evidence for the use of statins for primary prevention of ASCVD in elderly patients, it is apparent that more research is warranted in this area. In this study, we have evaluated the impact of moderate to high-intensity statin therapy for primary CVD prevention in patients over 75 years of age.

Methods

This retrospective study was conducted in a Veterans Affairs Medical Center. The study complied with the Declaration of Helsinki and the International Conference on Harmonization/ Good Clinical Practice Guidelines and was approved by the on-site VAMC Institutional Review Board (IRB).

The study examined the effect of statin therapy for primary prevention of cardiovascular outcomes in patients at least 75 years of age on moderate to high-intensity statin therapy compared to a control group (Table 1). The primary outcome of this study was a composite of the patient’s first cardiovascular event, defined as cardiovascular death, non-fatal MI or non-fatal stroke (3P-MACE). Secondary endpoints included evaluation of each of the composite endpoints individually, as well as, all-cause mortality.

High	Moderate	Low
Atorvastatin 40mg-80mg	Atorvastatin 10mg -20mg	
Rosuvastatin 20mg-40mg	Rosuvastatin 5mg-10mg	
	Simvastatin 10mg -40mg	Simvastatin 10mg
	Pravastatin 40mg -80mg	Pravastatin 10mg-20mg
	Lovastatin 40mg -80mg	Lovastatin 20mg
	Fluvastatin 80mg	Fluvastatin 20mg-40mg

Table 1: Statin Intensity Daily Dose.

Inclusion criteria included: age of at least 75 years and a prescription for moderate to high-intensity statin therapy for three or more consecutive years during the five-year study period (2012-2017) for the treatment group while those in the control group did not have an active prescription for a moderate or high-intensity therapy during the study period. Also, all patients had to have diagnosis of at least one ASCVD risk factor in addition to age, such as hypertension, diabetes mellitus, dyslipidemia, or current smoking status. Patients were excluded from the study if they had a diagnosis of unstable angina or prior ASCVD, as defined by the ACC/AHA, at the beginning of the study period [10].

A five-year study period was chosen to allow adequate time to analyze the rate of cardiovascular outcomes in each group given trials evaluating the cardiovascular benefit of statin therapy illustrated cardiovascular outcomes in similar follow-up time.

In order to provide a statistical power of 80% to detect a 35% difference (a small effect size of 0.27) in the 3P-MACE occurrence between statin-treated patients and patients not receiving statin therapy with a two-sided significance level and an alpha of 0.05, 226 cardiovascular events were necessary (nQuery Advisor, Statistical Solutions Ltd, Boston, MA).

Patients were further sub-grouped based on their status of diabetes (Control = 296 with diabetes and 998 without diabetes;

Discovery Software (SAS Institute, Cary, NC) was used for the statistical analysis.

Results

A total of 1853 patients were included in this study; this included every eligible patient identified in the electronic health record. Patients were either on moderate or high-intensity statin therapy (n=559) or not receiving a moderate or high-intensity statin (n=1294). Baseline characteristics are noted in table 2. There were fewer patients with diabetes in the control group compared to the statin group (p<0.0001). About 39% of the patients in the control group had a diagnosis of dyslipidemia, while approximately 72% of those in the statin group had dyslipidemia diagnoses (p<0.0001). The patients in the statin group had a higher Body Mass Index (BMI) (25.6 vs. 26.8) (p<0.0001). Moreover, age was statistically greater in the control group (80.8 vs. 79.4 years) (p<0.0001).

Patients were more likely to experience the composite endpoint (CV death, non-fatal stroke or non-fatal MI) if they were in the statin group compared to the control group (19.7% versus 13.2%, p=0.0004) as illustrated in table 3. Further, patients in the statin group were significantly more likely to have a non-fatal MI or stroke compared to the control group (3.2% versus 0.5% p<0.0001 and 14.1% versus 10.4% p=0.0193), respectively. All-cause mortality in the control group was

Characteristic	Control Group (1294)	Statin Group (559)
Age mean (SD)	80.81 (4.04)	79.42 (3.55) †
Male gender n (%)	1265 (97.8)	546 (97.7)
Caucasian race (n) (%)	1230 (95.1)	543 (97.1)
Diagnosis of dyslipidemia n (%)	507 (39.2)	401 (71.7) †
Diagnosis of hypertension n (%)	1112 (86)	476 (85.1)
Diagnosis of diabetes n (%)	296 (22.9)	219 (39.2) †
Diagnosis of current smoking n (%)	136 (10.5)	46 (8.1)
BMI mean (SD)	25.64 (4.75)	26.82 (4.49) †

Table 2: Baseline Characteristics of Statin and Control Groups.

†Statistically significant difference between control and statin group
BMI: Body Mass Index; n: Number; SD: Standard Deviation

statin = 219 with diabetes and 340 without diabetes). A nominal logistic regression analysis was applied to the data with Group (i.e., treatment vs. control) and Diabetes Status being the regressors. The model also contained an interaction term between the two regressors. A p-value < 0.05 was considered significant. The data were further analyzed using a Chi-square test to examine the difference (in the % of patients experiencing the end-point) in the end-points between the two groups concerning patients with diabetes only. JMP Statistical

observed at a rate more than double of that in the statin group (35.6% vs. 17.5%, p<0.0001).

The sub-group analysis detailed in table 4 revealed patients diagnosed with diabetes had a higher all-cause mortality compared to patients without diabetes regardless of the treatment. However, there was a higher percentage of patients with diabetes experiencing death in the control group versus patients without diabetes in the same group (43.58% vs.

33.27%, p=0.0011). This difference between patients with and without diagnoses of diabetes with respect to death was not observed in the statin group (19.18% vs. 16.47%, p=0.4112).

of patients experienced MI in the statin group as opposed to that in the control group (3.65% vs. 1.01%, p=0.0405). Statin therapy was not protective concerning the primary composite endpoint (p=0.0839).

	Control Group (n=1294)	Statin Group (n=559)	p value
Composite CV death, non-fatal stroke, non-fatal MI n (%)	171 (13.2)	110 (19.7)	0.0004
CV death n (%)	43 (3.4)	23 (4.1)	0.3988
Non-fatal MI n (%)	7 (0.5)	18 (3.2)	<0.0001
Non-fatal stroke n (%)	134 (10.4)	79 (14.1)	0.0193
All-cause mortality n (%)	461 (35.6)	98 (17.5)	<0.0001

Table 3: ASCVD Outcomes and All-Cause Mortality.
ASCVD: Atherosclerotic Cardiovascular Disease; CV: Cardiovascular; MI: Myocardial Infarction; n: Number

Composite CV death, non-fatal stroke, non-fatal MI (%)							
Control Group (n=1294)		p value	Statin Group (n=559)		p value	p value overall ^a	p value diabetes ^b
DM	Non-DM	0.0534	DM	Non-DM	0.5266	0.0047	0.0839
0.1655	0.1222		0.21	0.1882			
CV death (%)							
Control Group		p value	Statin Group		p value	p value overall ^a	p value diabetes ^b
DM	Non-DM	0.1242	DM	Non-DM	0.3855	0.6254	0.1059
0.0473	0.0291		0.0502	0.0353			
Non-fatal MI (%)							
Control Group		p value	Statin Group		p value	p value overall ^a	p value diabetes ^b
DM	Non-DM	0.2069	DM	Non-DM	0.6417	0.0002	0.2011
0.0101	0.004		0.0365	0.0294			
Non-fatal stroke (%)							
Control Group		p value	Statin Group		p value	p value overall ^a	p value diabetes ^b
DM	Non-DM	0.1679	DM	Non-DM	0.6101	0.0659	0.2033
0.125	0.0972		0.1507	0.1353			
All-Cause Mortality in Sub-Group Analysis							
Control Group		p value	Statin Group		p value	p value overall ^a	p value diabetes ^b
DM	Non-DM	0.0011	DM	Non-DM	0.4112	<0.0001	0.0178
0.4358	0.3327		0.1918	0.1647			

Table 4: ASCVD Outcomes and All-Cause Mortality in Sub-Group Analysis.
DM: Diabetes Mellitus
^aControl versus statins overall, regardless of diabetes diagnosis
^bDiabetes versus non-diabetes overall, regardless of control or statin

Further, the data analysis found that statin therapy was beneficial in preventing death in patients with diabetes. Patients with diabetes were less likely to die from any cause if they received statin therapy when compared to the control group (19.18% vs. 43.58%, p<0.0001), however, a slightly higher percentage

Discussion

The benefits of statin therapy in middle-aged patients at risk for cardiovascular disease or with a history of cardiovascular disease is well-established. However, utilizing statins for

primary prevention in elderly patients remains a topic of debate. This study showed that in older patients, specifically at least 75 years of age there is potentially an all-cause mortality benefit for patients taking moderate or high intensity statins for at least three years. However, in the absence of diabetes, moderate to high-intensity statin therapy may not be beneficial in reducing the first occurrence of cardiovascular disease or death. In patients diagnosed with diabetes, statin therapy remained a beneficial pharmacological therapy in preventing all cause-mortality, however, did not provide a significant reduction in the primary outcome. Given the higher risk of mortality in diabetes, the benefits of statin therapy as it relates to mortality may be worth exploring further. In the absence of diabetes and a history of the established cardiovascular disease, however, this study remains to offer up any benefit for pharmacological intervention as a means to prevent CV death, non-fatal MI or non-fatal stroke. Potential limitations of the study include its retrospective nature and subsequent reliance on appropriate electronic health record coding. There were noted statistically significant differences in baseline characteristics. However, not all are presumed to be clinically significant (i.e., an age difference of 1.4 years and BMI difference of 1.2kg/m²). It was not surprising to see significantly more patients diagnosed with diabetes and dyslipidemia on statin therapy as that follows recommendations from numerous clinical practice guidelines owing to higher atherosclerotic risks related to the pathophysiology of those diseases. Finally, patients in the control group could have been taking a low intensity statin or a moderate or high intensity statin with less than 80% adherence.

Safety was not evaluated in this trial but is another important aspect of future studies, specifically prospective designed trials, and warrants thorough discussion with patients falling in this age group at risk of cardiovascular disease.

The recently published guidelines by ACC/AHA for the management of dyslipidemia provide some insight into statin use in the elderly; however, only a few of the cited articles specifically address the population of 65 years and older [10]. A sub-analysis in ALLHAT-LTT of patients at least 75 years of age revealed no significant difference in coronary heart disease events, stroke or all-cause mortality between patients prescribed pravastatin 40mg daily versus usual care [13]. In contrast, a meta-analysis of the JUPITER and HOPE-3 trials showed that in patients at least 70 years of age taking rosuvastatin 10 or 20mg the composite endpoint of non-fatal MI, non-fatal stroke and cardiovascular death was significantly reduced compared to placebo [14]. Age limitations are not explicitly stated in the VA DoD Clinical Practice Guidelines that note, “for primary prevention, we recommend a moderate dose statin as the agent

of choice” with strong strength of recommendation. Evidenced by this trial and others, the favoring for or against statin therapy in elderly patients is not answered simply and requires a more in-depth analysis of reason to trial and potential risks.

In conclusion, statin therapy appears to be beneficial in elderly patients with diabetes. However, the same therapy was found to have no benefits against the primary composite endpoint in this population of patients (i.e., primary CVD prevention in patients over 75 years of age).

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