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Statins for primary prevention in physically active individuals: Do the risks outweigh the benefits?☆

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ABSTRACT

Objectives: There are little data on the potential benefits and adverse events of statins among physically fit individuals. Our objective was to examine the associations of statin use with beneficial cardiovascular outcomes and adverse events in active duty military (a surrogate for high level of physical fitness).
Design: This is a retrospective propensity score-matched cohort study of healthy active duty military (fiscal years [FY] 2002–2011).
Methods: Statin-users received statins during FY 2005 as their only prescription medication. FY 2002–2004 was used to describe baseline characteristics; and FY 2006–2011were used to capture outcomes. Study outcomes included major acute cardiovascular events (MACE), diabetes mellitus and its complications, kidney diseases, musculoskeletal diseases, obesity, and malignancy.
Results: We propensity score matched 837 statin-users to 2488 nonusers. During follow-up, 1.6% statin-users and 1.5% nonusers were diagnosed with MACE (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.55–1.98), 12.5% of statin-users and 5.8% of nonusers were diagnosed with diabetes (OR 2.34, 95% CI 1.79–3.04), and 1.7% statin- users and 0.7% nonusers were diagnosed with diabetes with complication (OR 2.47, 95% CI 1.21–5.04). There were no differences in rates of other adverse events.
Conclusions: Among healthy physically active individuals, statin use was associated with doubled the odds of diabetes and diabetic complications without countervailing cardiovascular benefits.
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1. Introduction

Physical activity and cardiorespiratory fitness (CRF) have strong inverse relationships to cardiovascular (CV) morbidity and mortality.[1] Regardless of the anatomical extent of coronary artery disease, patients with good functional capacity (>10 Metabolic Equivalents [METS]) had lower CV mortality.[2] However, physical activity is not included in CV risk calculators that are utilized in estimating the necessity of statin therapy for primary prevention of CV disease.[3]

Statins effectively lower CV morbidity and mortality but are not without adverse events; specifically, statins are associated with increased risk of diabetes,[4] diabetic complications,[5] obesity,[6–8] and musculoskeletal diseases,[9,10] which may inversely affect physical activity. Hence, the overall impact of prescribing statin therapy for primary prevention for individuals who regularly perform intense physical activity can be different from those who live a sedentary lifestyle.[1] There is no statin primary prevention clinical trial that examined the overall effects of statins in physically active individuals who would be expected to benefit less from use of statins for primary prevention.

In a previous study including enrollees of Tricare (The US Military Healthcare System), which included active duty military, Veterans, and their families, our group has reported that short-term statin therapy was not associated with reduction in cardiovascular morbidity but was associated with increased risk of adverse events.[11] Scarce data exist that exclusively examined the effects of statins in healthy physically active individuals. The objective of this study is to examine the associations of statin use with short- and long-term beneficial CV outcomes and adverse effects in a cohort of active duty military. We considered active duty status as a strong proxy for physical activity with good CRF because of the mandatory biannual military physical fitness test. The military physical fitness

☆ This study was not posted or presented previously.
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Table 1
Short-term outcomes of statin-users in comparison to similar nonusers during FY2006 (1st year of follow-up period).

	Statin-users N (%) 837	Nonusers N (%) 2488	OR (95% CI)	*p*-value
Major acute cardiovascular events	2 (0.2)	4 (0.2)	1.49 (0.27–8.14)	0.65
Acute myocardial infarction	1 (0.1)	1 (0.0)	n/a	–
Cardiac arrest and ventricular fibrillation	1 (0.1)	0 (0.0)	n/a	–
Acute cerebrovascular disease	0 (0.0)	3 (0.1)	n/a	–
Peripheral and visceral atherosclerosis	0 (0.0)	1 (0.0)	n/a	–
Diabetes mellitus	8 (1.0)	5 (0.2)	4.79 (1.56–14.69)	0.006
Diabetes mellitus with complications	0 (0.0)	2 (0.1)	n/a	–
Acute and unspecified renal failure	1 (0.1)	0 (0.0)	n/a	–
Chronic kidney disease	0 (0.0)	3 (0.1)	n/a	–
Osteoarthritis and arthropathies	65 (7.8)	166 (6.7)	1.18 (0.87–1.59)	0.28
Dislocation/strain/sprain	38 (4.5)	122 (4.9)	0.92 (0.64–1.34)	0.67
Malignancy	6 (0.7)	10 (0.4)	1.79 (0.65–4.94)	0.26

n/a = due to the small number of events in treatment arms calculation of OR was not meaningful.

test includes measured push-ups, sit-ups, and a timed run; hence, it is a good marker of CRF.[12]

2. Methods

The Institutional Review Boards at Brooke Army Medical Center and the VA North Texas Health System approved this study. We extracted national TRICARE data from the Military Health System (MHS) Data Repository (MDR), as detailed in a previous publication.[11] The MDR includes patient demographic information, outpatient and inpatient medical encounters within MHS and outside of MHS, laboratory data performed within MHS, and the Pharmacy Data Transaction Service (PDTS). PDTS tracks medication utilization regardless of dispensing pharmacy location or affiliation. According to our agreement with TRICARE, all data were de-identified, to include rounding dates of medical encounters to the nearest quarter of the year.

The study period comprised the fiscal years (FY) 2002–FY2011 (10/1/2001–9/30/2011). The period from FY 2002 to 2004 was used to describe baseline characteristics (Baseline period); FY 2005 was used to identify patients as statin-users or nonusers (exposure period); and the period from FY 2006 to 2011 was used to capture outcomes (follow-up period).

We included all active duty military at age 35 years or older, who had at least one medical encounter at baseline and were still enrolled in the system at FY 2011. To form a healthy cohort, we: (1) included patients who had a medical encounter in FY 2005 but were not prescribed any medication during the exposure period (FY 2005) except for potentially a statin; (2) excluded patients with pre-existing CV diseases at baseline according to the Agency for Health Research and Quality Clinical Classifications Software (AHRQ-CCS): coronary artery diseases, cerebrovascular diseases, and peripheral vascular diseases.

Statin-users initiated statins during FY 2005 and continued to use statins for a cumulative duration ≥60 days during FY 2005, but not thereafter. We restricted statin use to FY 2005 only to minimize confounding by indication (as detailed later). Statin-users were considered new users if they did not receive statins in FY 2002–2004. We required that statin-users did not receive other prescription medications in FY 2005 to ensure that no other drugs may have contributed to the outcomes nor caused drug interactions as shown in previous studies.[13]

Statin nonusers never received a statin throughout the study. We limited nonusers to those who had medical encounters in the first 6 months of FY 2005 because the number of these patients was very large.

An outcome event was defined as the occurrence of International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes during the follow-up period. The outcomes were *a priori* diagnosis groups as defined by AHRQ-CCS categories[14]: (1) major acute CV events (MACE), which comprised acute myocardial infarction, cardiac arrest and ventricular fibrillation, acute cerebrovascular disease, and peripheral and visceral atherosclerosis; (2) diabetes mellitus; (3) diabetes mellitus with complication; (4) acute and unspecified renal failure; (5) chronic kidney disease; (6) osteoarthritis and arthropathies; (7) dislocation, strain, sprain; and (8) malignancy (Appendix A).[15]

Patients' comorbidities were identified using ICD-9-CM codes and their Charlson Comorbidity Index was calculated using Deyo's method.[15] Baseline characteristics of groups were compared using χ^2 for categorical variables and Student's t-test for continuous variables. We created a propensity score to match statin-users and nonusers at a ratio of 1:3 using 50 variables comprising: demographics, personal history, comorbidities, occurrence of outcomes of interest at baseline, undergoing procedures,[14] and healthcare utilization (Supplementary Table S1 in the online version at DOI: 10.1016/j.jsams.2016.12.075). We used logistic regression to create the propensity score and perform nearest number matching with a caliper of 0.01 as previously described.[11]

We captured outcomes at three different intervals: (1) short-term outcomes: FY 2006 only (Table 1); (2) intermediate-term outcomes: FY 2006–2009 (Supplementary Table S2 in the online version at DOI: 10.1016/j.jsams.2016.12.075); and long-term outcomes: FY 2006–2011 (Table 2). To increase specificity of chronic diseases diagnoses, we required that they had been diagnosed in ≥2 separate encounters as previously published[11]; however, we accepted 1 encounter in defining acute diseases such as cardiac arrest or in conditions known to have low sensitivity in identification using ICD-9-CM codes such as obesity (Appendix B).

To minimize confounding by indication in determining MACE, we adopted several measures. First, we included healthy population who received statins as the only prescription medication. Patients with CV disease are likely to receive anti-platelet agents, beta-blockers, and other medications. Second, we included statin-users who used statins in FY 2005 only since studies have shown that patients who adhered to statins for shorter periods only were less likely to have diseases that compel long-term statin prescription.[16] Third, we did not include the exposure period (FY2005) in our outcomes; excluding a time period equivalent to the expected period for a drug to attain efficacy can mitigate the effects of confounding by indication.[17] Fourth, we counted the incidence of undergoing invasive cardiac procedures during baseline to serve as a measure for our success in minimizing confounding by indication. If confounding by indication is present, statin-users were expected to have more invasive procedures.

For primary analysis, we used conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (95% CI) in the propensity score- matched cohort in each of short-term, intermediate-term, and long-term follow-up.

For Secondary analyses, we performed several analyses adjusting for variables such as vital signs and laboratory values measured

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