Statin Therapy in Low-Risk Air Force Aviators with Isolated Hypercholesterolemia

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INTRODUCTION: This study evaluated the use of statin therapy in U.S. Air Force (USAF) aviators with isolated hypercholesterolemia in terms of compliance with clinical practice guidelines (CPGs) and effectiveness in reducing low-density lipoprotein cholesterol (LDL-C) and coronary heart disease (CHD) risk.

METHODS: This was a mixed design, 8-yr retrospective study that included 8185 participants with isolated hypercholesterolemia, of which 1458 (17.81%) were prescribed statin monotherapy.

RESULTS: Overall agreement between CPG recommendations and patient-clinician decision makers was 0.920 (95% confidence interval: 0.955, 0.959) and 0.891 (95% confidence interval: 0.843, 0.851) per 2002 and 2013 CPGs, respectively. Overall agreement was primarily driven by the negative proportion of specific agreement; positive agreement was moderate for the 2002 CPG and poor for the 2013 CPG. LDL-C levels marginally decreased for all participants except non-CPG-recommended statin users per the 2002 CPG. CHD risk was minimally reduced for all participants per the 2002 CPG with the exception of CPG-recommended statin users, for whom risk increased; CHD risk decreased for CPG-recommended statin users, but increased for non-CPG-recommended statin users per the 2013 CPG. No one statin medication was found to be more clinically effective in reducing LDL-C or CHD risk, regardless of dose intensity.

CONCLUSIONS: Aerospace medicine practitioners are following CPG recommendations for statin therapy. Statins provided minimal benefit, however, and CPG recommendations proved irrelevant in reducing LDL-C and CHD risk in this population of Air Force aviators. This result is attributable, in part, to the young age of the study cohort and the short follow-up period.

KEYWORDS: 3-hydroxy-methylglutaryl coenzyme A reductase inhibitor, coronary heart disease, low-density lipoprotein, risk, effectiveness, military.

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A 40-yr-old male U.S. Air Force (USAF) aviator presents to a flight medicine clinic for a periodic health assessment. The aviator is a nonsmoker without significant past medical history other than hypercholesterolemia. The aviator's systolic blood pressure is 128 mmHg without antihypertensive medication, total cholesterol is 240 mg · dL^{-1}, high-density lipoprotein cholesterol (HDL-C) is 45 mg · dL^{-1}, triglycerides are 183 mg · dL^{-1}, calculated low-density lipoprotein cholesterol (LDL-C) is 158 mg · dL^{-1}, and fasting glucose is 99 mg · dL^{-1}. The aviator inquires whether he should be taking a "statin," but is concurrently concerned about recent media attention on the potential adverse effects of statins. Do the benefits outweigh the risks for this aviator to initiate statin therapy?

Extensive epidemiological data demonstrate that elevated cholesterol levels are associated with an increased risk for atherosclerotic coronary heart disease (CHD).[14,22] "Statins," or 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, are a widely used group of drugs that are effective in reducing CHD events, largely by reducing LDL-C.[2,11,20] However, there is debate among physicians over cholesterol therapy, particularly

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in terms of the primary prevention of CHD in individuals with isolated hypercholesterolemia who are otherwise healthy.[6,7,16] The opinion of expert physicians is to not treat elevated cholesterol levels in isolation, but rather direct risk-reducing therapies to those at the highest risk who are most likely to benefit, achieving therapy goals in the safest and most cost-effective manner.[13,15] In occupations with high physical demands (e.g., fighter/attack pilots), it is important for both aviators and aerospace medicine practitioners to understand whether treatment of elevated cholesterol levels with statins in otherwise healthy aviators significantly decreases risk for CHD.

Therefore, the purposes of this study of USAF aviators with isolated hypercholesterolemia were to determine: 1) whether statins were prescribed according to the 2002 National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III[13] and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines,[19] henceforth referred to as the clinical practice guidelines, or CPGs; 2) whether patients treated with statin therapy per CPG recommendations selectively benefited in terms of reduction in LDL-C and calculated 10-yr CHD risk; and 3) which statin was most clinically effective at reducing LDL-C and CHD risk.

Based on the preceding study questions, the following research hypotheses (H) were adopted for this study:

H1: The proportion of overall agreement between the CPG recommendation and patient-clinician decision makers will be good (i.e., $p_o = 0.61–0.80$) for USAF aviators with isolated hypercholesterolemia.

H2: There will be a significant reduction in LDL-C over time for USAF aviators with isolated hypercholesterolemia treated with statins when indicated by the CPG (+statin/+CPG group), but not in aviators treated with statins when not indicated by the CPG (+statin/∅CPG group) or not prescribed statins (i.e., ∅statin/+CPG and ∅statin/∅CPG groups).

H3: There will be a significant reduction in calculated 10-yr CHD risk over time for USAF aviators with isolated hypercholesterolemia treated with statins when indicated by the CPG (+statin/+CPG group), but not in aviators treated with statins when not indicated by the CPG (+statin/∅CPG group) or not prescribed statins (i.e., ∅statin/+CPG and ∅statin/∅CPG groups).

H4: There will be differences between statins in clinical effectiveness in reducing LDL-C risk in USAF aviators with isolated hypercholesterolemia.

H5: There will be differences between statins in clinical effectiveness in reducing calculated 10-yr CHD risk in USAF aviators with isolated hypercholesterolemia.

There were two premises underlying H2 and H3. First, the purpose of the CPGs is to identify individuals who are likely to benefit from statin therapy. Thus, statin therapy in an individual in whom therapy is not indicated by the CPG will fail to exhibit a benefit of treatment in terms of a significant change in LDL-C or 10-yr CHD risk. Second, if statin therapy is not prescribed for an individual, regardless of CPG recommendation, then there will be no observed pharmaceutical treatment effect.

METHODS

Study Population

The study was conducted under a human-use protocol approved by the 711th Human Performance Wing Institutional Review Board and in accordance with federal and USAF regulations on the protection of human participants in biomedical and behavioral research. The study used a retrospectively defined cohort of USAF aviators with isolated hypercholesterolemia from which subgroups were drawn to test the abovementioned hypotheses. The study enrolled participants who were on active duty in the USAF from 2004–2013. The inclusion criteria for participants were as follows: 1) Air Force Specialty Code (AFSC) of 11–13, 18, 43A, 46F, 48, 1A, 1C, 1T, 1U, 1W, or 4M, or an AFSC of 4N with a qualifying Aviation Service Code; and 2) a total cholesterol ≥ 200 mg $\cdot$ dL^{-1} at baseline. Participants were excluded from the study if they had 1) total cholesterol $<$ 200 mg $\cdot$ dL^{-1} at baseline; 2) comorbid diabetes, hypertension [systolic blood pressure (SBP) $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg], or tobacco use; 3) a prescription for a nonstatin lipid lowering medication (e.g., resins/bile acid sequestrants, fibrates, niacin, etc.); 4) a prescription for a hypertension medication; or 5) insufficient data to calculate a baseline CHD risk score.

Archival data (January 1, 2004, to December 31, 2013) were extracted from three databases: Air Force Personnel Center, Cardiovascular Risk Assessment and Management (CRAM), and the Pharmacy Data Transaction Service (PDTS). The Air Force Personnel Center provided data on participants' gender, self-reported race, and AFSC. CRAM, which is a system used to ensure all active duty Air Force personnel undergo mandatory cardiac risk assessment during their periodic health assessments, furnished data on participants' age, SBP and DBP, presence of diabetes, smoking status, total cholesterol, LDL-C, and HDL-C; 10-yr CHD risk was calculated from these data using the Total Framingham Risk Score[13] (2002 CPG) and the Pooled Cohort Equations[19] (2013 CPG). PDTS contributed data on medications prescribed, dates dispensed, and the days supplied of medication(s) dispensed. All three databases contained Social Security number and date of birth, which were used to link participants' data across databases and to calculate age; Social Security numbers and dates of birth were then removed from the study dataset.

Design and Procedure

Fig. 1 outlines the study design and procedures. PDTS data were used to identify participants who received prescriptions in the therapy class of 3-hydroxy-methylglutaryl coenzyme A reductase inhibitor (statin) and the dates of the prescriptions. Participants with prescriptions in this therapy class were assigned to the statin (+statin) group, and the remaining participants were by default assigned to the nonstatin (∅statin) group. For participants in the +statin group, T_0 was established as the start date of the first statin prescription. The CRAM data from between $T_{-12\text{months}}$ and T_0 and closest to T_0 were used to define the pretest assessment. T_0 for participants in the ∅statin

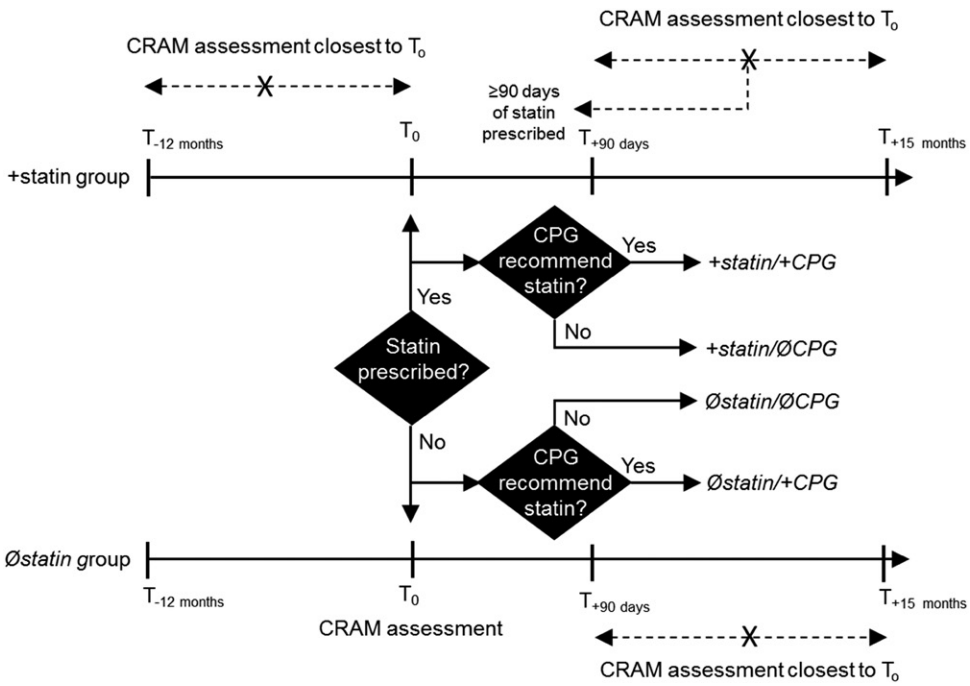

Fig. 1. Study design and procedure.

group was established as the date of the first available CRAM data meeting the study inclusion criteria.

Using pretest CRAM data, participants were classified into one of two categories based on the 2002 CPG: drug therapy indicated by CPG (+CPG_{2002}) vs. drug therapy not indicated by CPG (øCPG_{2002}). Since study participants were selected based on the presence of isolated hypercholesterolemia, the relevant factors used in the CPG were age, gender, HDL-C, LDL-C, and calculated 10-yr CHD risk. Information on family history of premature CHD was not available in the archival data used in this study and thus could not be assessed; all participants were assumed to have no family history of premature CHD. Participants were classified as +CPG_{2002} using the following NCEP ATP III criteria:

- LDL-C $\geq$ 190 mg · dL^{-1}, or
- LDL-C $\geq$ 160 mg · dL^{-1}, $\geq$ 2 risk factors (e.g., men $\geq$ 45 yr or women $\geq$ 55 yr, HDL-C $<$ 40 mg · dL^{-1}), and 10-yr CHD risk $<$ 10%, or
- LDL $\geq$ 130 mg · dL^{-1}, $\geq$ 2 risk factors (e.g., men $\geq$ 45 yr or women $\geq$ 55 yr, HDL $<$ 40 mg · dL^{-1}), and 10-yr CHD risk 10–20%.

Per NCEP ATP III criteria, initiation of drug therapy was optional when LDL-C levels were 160–189 mg · dL^{-1} and 0–1 risk factors were present. For participants meeting these criteria, participants placed on statin therapy were categorized as +CPG_{2002} and those not placed on therapy were categorized as øCPG_{2002}.

Similarly, pretest CRAM data were used to classify participants into one of two categories based on the newer 2013 CPG: drug therapy indicated by CPG (+CPG_{2013}) vs. drug therapy not indicated by CPG (øCPG_{2013}). Participants were categorized as +CPG_{2013} using the following ACC/AHA criteria:

- LDL-C $\geq$ 190 mg · dL^{-1}, or
- 10-yr atherosclerotic cardiovascular disease risk $\geq$ 7.5% and age 40–75 yr.

Participants with CRAM data available between $T_{+90\ d}$ and $T_{+15\ mo}$ were deemed to have a post-test assessment. For participants in the +statin group, PDTS data were used to confirm participants were prescribed statin monotherapy for $\geq$ 90 d immediately prior to the time the post-test CRAM data were collected; otherwise, the CRAM data were not considered a valid post-test assessment. Additionally, PDTS data were used to identify the specific statin prescribed during the 90 d preceding the post-test CRAM assessment.

Based on CPG categorization, participants in the +statin and østatin groups were assigned into one of the following (sub)-groups: +statin/+CPG_{yr}, +statin/øCPG_{yr}, østatin/+CPG_{yr}, østatin/øCPG_{yr}. Hypothesis 1 was tested using a cross-sectional study design based on simple contingency table analysis of the abovementioned subgroups. Hypotheses 2–5 were tested using a pre/post-test study design. Hypotheses 2 and 3 testing included all participants with valid post-test data, while Hypotheses 4 and 5 testing was limited to participants in the +statin group with valid post-test data. All analyses were conducted using SAS versions 9.2 and 9.4 (SAS Institute, Cary, NC) and SPSS version 20.0 software (IBM Corp., Armonk, NY), and the level of significance was set a priori to 0.05.

RESULTS

Descriptive statistics were computed for all study variables and groups for both pre-test and post-test observations based on the 2002 NCEP ATP III CPG (**Table I**) and 2013 ACC/AHA CPG (**Table II**). Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using mean and SD.

Hypothesis 1 predicted that the proportion of overall agreement between the CPG recommendation and patient-clinician decision makers would be good. Agreement was evaluated using the proportion of overall agreement (p_o) and the positive and negative proportions of specific agreement; significance testing of p_o was accomplished using the Pearson Chi-squared (χ^2) test. Applying the 2002 CPG, the proportion of overall agreement was 0.920 [95% confidence interval (CI): 0.918, 0.922; $\chi^2 = 8152.24$, $P < 0.001$]; positive agreement was 0.475

Table I. Baseline and Follow-Up Data Applying 2002 NCEP ATP III CPGs.

VARIABLE	⊘STATIN/⊘CPG	+STATIN/⊘CPG	⊘STATIN/+CPG	+STATIN/+CPG
N	6601	35	126	1423
Baseline Characteristics:				
Male, no. (%)	6081 (92.10)	35 (100.00)	120 (95.20)	1398 (98.20)
Age, yr, mean (SD)	33.61 (6.72)	47.51 (3.30)	35.12 (8.26)	39.04 (6.42)
Total cholesterol, mg · dL^{-1}, mean, (SD)	220.04 (16.19)	185.46 (24.59)	268.59 (21.11)	220.52 (35.20)
HDL, mg · dL^{-1}, mean (SD)	52.00 (14.14)	34.51 (4.29)	47.78 (11.93)	46.07 (11.36)
SBP, mmHg, mean (SD)	122.02 (9.89)	125.06 (11.54)	122.33 (9.62)	125.32 (10.71)
DBP, mmHg, mean (SD)	74.46 (7.72)	77.94 (8.04)	75.43 (8.44)	77.83 (8.48)
Baseline Outcomes:				
LDL-C, mg · dL^{-1}, mean (SD)	142.70 (17.98)	107.73 (16.55)	194.85 (13.77)	145.07 (32.83)
10-yr CHD risk, mean (SD)	0.014 (0.010)	0.053 (0.025)	0.029 (0.027)	0.017 (0.014)
Follow-up Outcomes:				
LDL-C, mg · dL^{-1}, mean (SD)	143.38 (16.57)	107.77 (28.81)	161.12 (19.20)	134.05 (32.98)
10-yr CHD risk, mean (SD)	0.017 (0.013)	0.049 (0.022)	0.027 (0.025)	0.019 (0.017)

Observed mean (SD); ⊘statin = not prescribed statin, +statin = prescribed statin, ⊘CPG = statin not recommended based on CPG, +CPG = statin recommended based on CPG.

(95% CI: 0.461, 0.489) and negative agreement was 0.957 (95% CI: 0.956, 0.958). When applying the more recent 2013 CPG, the proportion of overall agreement was 0.891 (95% CI: 0.889, 0.892; $\chi^2 = 829.86$, $P < 0.001$); positive agreement was 0.187 (95% CI: 0.174, 0.200) and negative agreement was 0.941 (95% CI: 0.940, 0.942). Accordingly, Hypothesis 1 was accepted. In both cases, there was very good agreement between CPG recommendations and patient-clinician decision makers, which was primarily driven by the negative proportion of specific agreement (i.e., when both the CPG and the patient-clinician decision makers were in agreement that statin therapy was not indicated). Positive agreement was moderate for the 2002 CPG and poor for the 2013 CPG. Of note, there was a significant difference in the number of participants for whom the CPG recommended statin therapy when comparing the 2002 CPG ($N = 2803$) vs. the 2013 CPG ($N = 2044$) ($\chi^2 = 18{,}970.27$, $P < 0.001$).

Hypothesis 2 predicted that there would be a significant reduction in LDL-C over time for participants in the +statin/+CPG group, but not in the other groups (i.e., +statin/⊘CPG, ⊘statin/+CPG, ⊘statin/⊘CPG). This hypothesis was tested using linear mixed model analyses. The fixed effects included the covariates of sex, age, total cholesterol, HDL-C, SBP, and DBP and the independent variables of time (pre/post), group (4 levels), and the time by group interaction; random effects controlled for the interpersonal variability of subjects. When applying the 2002 CPG, there was a significant time by group interaction effect [$F(3, 8441.72) = 24.50$, $P < 0.001$]. A significant reduction in LDL-C over time was observed for the +statin/+CPG group (mean difference = 2.06, $P < 0.001$), the ⊘statin/+CPG group (mean difference = 0.585, $P < 0.001$), and the ⊘statin/⊘CPG group (mean difference = 9.55, $P < 0.001$), but not the +statin/⊘CPG group (mean difference = −1.45, $P = 0.578$). Repeating the analysis using the 2013 CPG, there was again a significant time by group interaction effect [$F(3, 8298.26) = 37.31$, $P < 0.001$]. A significant reduction in LDL-C over time was observed for the +statin/+CPG group (mean difference = 9.27, $P < 0.001$) as well as the ⊘statin/+CPG group (mean difference = 9.26, $P < 0.001$), the ⊘statin/⊘CPG group (mean difference = 0.587, $P < 0.001$), and this time the +statin/⊘CPG group (mean difference = 1.32, $P < 0.001$). Accordingly, we reject Hypothesis 2 that significant reductions in LDL-C over time would only be observed when statin therapy was provided when recommended by the CPG. Of note, although statistically

Table II. Baseline and Follow-Up Data Applying 2013 ACC/AHA CPGs.

VARIABLE	⊘STATIN/⊘CPG	+STATIN/⊘CPG	⊘STATIN/+CPG	+STATIN/+CPG
N	6606	1313	121	145
Baseline Characteristics:				
Male, no. (%)	6096 (92.30)	1291 (98.30)	105 (86.80)	142 (97.90)
Age, yr, mean (SD)	33.62 (6.73)	39.23 (6.45)	34.43 (8.00)	39.37 (6.86)
Total cholesterol, mg · dL^{-1}, mean, (SD)	220.07 (16.20)	213.43 (30.25)	268.74 (22.86)	276.28 (27.43)
HDL, mg · dL^{-1}, mean (SD)	51.94 (14.12)	45.74 (11.30)	50.89 (14.00)	46.28 (12.11)
SBP, mmHg, mean (SD)	122.02 (9.89)	125.38 (10.75)	122.17 (9.76)	124.80 (10.50)
DBP, mmHg, mean (SD)	74.48 (7.72)	77.87 (8.55)	74.73 (8.50)	77.52 (7.74)
Baseline Outcomes:				
LDL-C, mg · dL^{-1}, mean (SD)	142.76 (18.02)	137.86 (27.61)	193.32 (19.48)	201.31 (21.05)
10-yr CHD risk, mean (SD)	0.010 (0.017)	0.018 (0.013)	0.029 (0.059)	0.035 (0.056)
Follow-up Outcomes:				
LDL-C, mg · dL^{-1}, mean (SD)	143.40 (19.56)	130.65 (31.34)	161.06 (20.17)	158.55 (37.98)
10-yr CHD risk, mean (SD)	0.013 (0.024)	0.021 (0.031)	0.024 (0.033)	0.028 (0.035)

Observed mean (SD); ⊘statin = not prescribed statin, +statin = prescribed statin, ⊘CPG = statin not recommended based on CPG, +CPG = statin recommended based on CPG.

significant differences were observed, the reductions in LDL-C over time were clinically not significant (defined a priori as reduction in baseline LDL-C < 10%), even for the +statin/+CPG group.

Hypothesis 3 predicted that there would be a significant reduction in calculated 10-yr CHD over time for participants in the +statin/+CPG group, but not in the other groups (i.e., +statin/∅CPG, ∅statin/+CPG, ∅statin/∅CPG). This hypothesis was tested using linear mixed model analyses as per the same procedure used to test Hypothesis 2. When applying the 2002 CPG, there was a significant time by group interaction effect [$F(3, 8162.23) = 15.01$, $P < 0.001$]. A significant increase in CHD risk over time was observed for the +statin/+CPG group (mean difference = −0.0008, $P = 0.001$) as compared to a significant decrease in risk for the +statin/∅CPG group (mean difference = 0.0055, $P = 0.002$), the ∅statin/+CPG group (mean difference = 0.0032, $P < 0.001$), and the ∅statin/∅CPG group (mean difference = 0.0003, $P = 0.012$). Repeating the analysis using the 2013 CPG, there was again a significant time by group interaction effect [$F(3, 8087.59) = 5.50$, $P = 0.001$]. A significant reduction in CHD risk over time was observed for the +statin/+CPG group (mean difference = 0.0049, $P = 0.024$) and a significant increase in risk over time was observed for the +statin/∅CPG group (mean difference = −0.0022, $P = 0.002$). CHD risk did not significantly change over time for the ∅statin/+CPG group (mean difference = 0.0041, $P = 0.064$) or the ∅statin/∅CPG group (mean difference = −0.0004, $P = 0.165$). Accordingly, we should reject Hypothesis 3 based on the 2002 NCEP ATP III model, but accept Hypothesis 3 based on the 2013 ACC/AHA model. However, in both models, the observed differences in CHD risk over time were clinically not significant (defined a priori as reduction in CHD risk < 0.5%), even for the +statin/+CPG group, and so we reject Hypothesis 3.

Hypothesis 4 predicted that there would be differences between statins in clinical effectiveness in terms of reducing LDL-C. The two most frequently prescribed statins in the study sample (i.e., simvastatin and atorvastatin) were examined by the prescribed dose intensity (i.e., low, medium, high) as advised by the 2013 CPG. The following medication groups were formed: low intensity simvastatin, medium intensity simvastatin, medium intensity atorvastatin, and high intensity atorvastatin (**Table III**). This hypothesis was tested using linear mixed model analysis. The fixed effects included the covariates of age, total cholesterol, HDL-C, SBP, and DBP and the independent variables of time (pre/post), statin medication group, and the interaction of time by statin medication group; random effects controlled for the interpersonal variability of participants. The interaction between statin medication group and time on LDL-C was not significant [$F(3, 413.88) = 1.11$, $P = 0.346$]. Accordingly, Hypothesis 4 was rejected as there was no observed difference between statin groups in LDL-C over time.

Hypothesis 5 predicted that there would be differences between statins in clinical effectiveness in terms of reducing calculated 10-yr CHD risk. This hypothesis was tested using linear mixed model analyses as per the same procedure used to test Hypothesis 4. The interaction between statin medication group and time on CHD risk was not significant [$F(3, 441.18) = 0.028$, $P = 0.994$] when risk was calculated per the 2002 CPG. Similarly, the interaction between statin medication group and time was also not significant [$F(3, 449.99) = 0.547$, $P = 0.650$] when risk was calculated used the 2013 CPG. Accordingly, Hypothesis 5 was rejected as there was no observed difference between statin groups in calculated 10-yr CHD risk over time.

DISCUSSION

This 8-yr retrospective cohort study examined the use of statin therapy in USAF aviators with isolated hypercholesterolemia per the 2002 CPG and the updated 2013 CPG for assessing CHD risk. Primary prevention of cardiovascular disease

Table III. Baseline and Follow-Up Means by Statin Medication and Dosage Intensity.

VARIABLE	LOW SIMVASTATIN	MEDIUM SIMVASTATIN	MEDIUM ATORVASTATIN	HIGH ATORVASTATIN
N	90	224	155	30
Baseline Characteristics:				
Male, no. (%)	86 (95.60)	221 (98.70)	154 (99.40)	30 (100.00)
Age, yr, mean (SD)	35.94 (5.75)	35.08 (5.63)	35.44 (6.47)	35.43 (6.04)
Total cholesterol, mg · dL^{-1}, mean, (SD)	242.03 (24.52)	249.01 (29.79)	245.47 (27.38)	252.43 (24.80)
HDL, mg · dL^{-1}, mean (SD)	45.84 (10.79)	45.91 (10.62)	46.02 (11.06)	47.10 (13.10)
SBP, mmHg, mean (SD)	122.27 (9.86)	123.50 (9.34)	121.38 (9.75)	126.34 (8.23)
DBP, mmHg, mean (SD)	76.12 (7.42)	75.85 (7.58)	75.87 (7.34)	76.31 (7.37)
Baseline Outcomes:				
LDL-C, mg · dL^{-1}, mean (SD)	163.29 (21.32)	171.85 (27.84)	165.01 (27.98)	170.69 (25.61)
2002 CPG 10-yr CHD risk, mean (SD)	0.019 (0.016)	0.020 (0.015)	0.021 (0.017)	0.022 (0.021)
2013 CPG 10-yr CHD risk, mean (SD)	0.016 (0.033)	0.014 (0.013)	0.015 (0.018)	0.016 (0.012)
Follow-up Outcomes:				
LDL-C, mg · dL^{-1}, mean (SD)	136.70 (32.87)	141.71 (39.63)	131.81 (41.13)	133.28 (52.39)
2002 CPG 10-yr CHD risk, mean (SD)	0.016 (0.012)	0.016 (0.012)	0.017 (0.013)	0.018 (0.017)
2013 CPG 10-yr CHD risk, mean (SD)	0.013 (0.021)	0.017 (0.072)	0.012 (0.014)	0.014 (0.013)

Observed mean (SD).

remains a major public health challenge.[1,3,21] Given the debate surrounding the use of statin therapy,[16,17] the current findings sought to fill the knowledge gap on statin use in an active duty population of otherwise healthy USAF aviators.

The present findings reveal a high proportion of overall agreement for clinicians to adhere to both the 2002 and 2013 overall CPG recommendations regarding initiation of statin therapy, and a high proportion of clinicians followed CPG recommendations to not initiate statin therapy when it was advised not to. A small proportion of participants (5.4–7.8%) were prescribed statin therapy when such therapy was not recommended, yet only 54.9% and 26.1% of participants were prescribed statin therapy when therapy was advised based upon the 2002 and 2013 CPGs, respectively, suggesting a trend for clinicians to err on the side of caution in the prescription of statins. It should be noted that such decisions are typically made jointly with the patient,[20] so aviators may be less inclined to start drug therapy if they believe the potential exists that it could jeopardize their work performance. Moreover, advising patients to initiate a healthier lifestyle is a first line of action upon detection of high cholesterol prior to initiating statin therapy;[5,18,22] unfortunately, this could not be investigated in the current study.

Contrary to that hypothesized, LDL-C was reduced, albeit very modestly, for all participants regardless of actual statin use or CPG recommendations, with the exception of participants using statins but not recommended statin therapy per the 2002 CPG, who demonstrated no change in LDL-C. However, since the latter observation was not borne out when the 2013 CPG were applied, it is likely a chance difference. The largest LDL-C reductions occurred in those participants for whom therapy was recommended, regardless of actual statin use. Again, clinicians are likely recommending lifestyle changes to all qualified patients, which potentially explains the reduction in LDL-C for all aviators regardless of CPG recommendation for, or actual, statin use.

Based upon the 2002 CPG, CHD risk increased in statin-prescribed aviators for whom statin therapy was recommended yet decreased for all other aviators. However, per the 2013 CPG, only recommended statin users had a small, yet significant, reduction in CHD risk, whereas risk increased for non-CPG-recommended statin users and remained unchanged for those not taking a statin regardless of CPG recommendation. It appears, therefore, that similar to previous research,[15] statin therapy had minimal, if any, benefit, and that recommended CPGs may not be relevant in this low-risk population of USAF aviators. It should be noted that although the observed changes in LDL-C and CHD risk were statistically significant, such changes were not judged to be clinically significant based on effect size.

This study found no significant difference between the top two prescribed statin medications in the clinical effectiveness of lowering LDL-C or CHD risk, regardless of dose intensity. Such results are of significance alone, in that statin dose intensity did not significantly contribute to clinical changes in LDL-C or CHD risk from baseline to follow-up, when it would be expected.[20] These results, however, are consistent with evidence from published statin randomized placebo-controlled trials that suggest that pravastatin, simvastatin, and atorvastatin, when used at their standard dosages, show no statistically significant difference in cardiovascular outcomes.[23] It should be noted that although the study investigators were able to monitor date and medication information for statins prescribed, patient medication compliance could not be assessed.

While the 2002 CPG was based on the 10-yr risk of CHD only, the 2013 CPG expanded outcomes to comprise all hard atherosclerotic cardiovascular disease using the Pooled Cohort Equations. Additionally, the 2013 CPG substantially lowered the risk threshold for statin therapy in asymptomatic individuals from 20% CHD risk in the 2002 CPG to 7.5% CHD risk in the 2013 CPG. Concern has been raised that the 2013 CPG causes too many individuals to be eligible for statin therapy because the guidelines overestimate risk and set the threshold for statin therapy eligibility too low.[4,10,12] This concern was not apparent in the present study, where the number of aviators recommended for statin therapy markedly decreased from 1549 to 266 when applying the 2002 and 2013 CPGs, respectively. This result is likely attributable to the relatively young age of the aviators comprising the study cohort, the mean age of which was 34.64 yr. The 2013 CPG focuses on an eligible age spectrum of 40–79 yr,[19] and a systematic examination of the Pooled Cohort Equations showed that age was a major driver of risk and thus eligibility for statin therapy.[9] Consequently, the 2013 CPG potentially has limited utility in the population of Air Force aviators with isolated hypercholesterolemia. Other risk factors, such as a positive family history of premature CHD, a high-sensitivity C-reactive protein greater than 2 $mg \cdot L^{-1}$, or an elevated coronary artery calcium score may be useful in guiding clinical decision making about statin therapy.

Strengths of the present study were the ability to examine current aerospace medicine practitioner practices regarding prescribing statin therapy and assess the impact of that therapy on a relatively large number of USAF aviators with isolated hypercholesterolemia. A strength and limitation of the current study was that participants prescribed medications other than statins were not included, as well as participants prescribed statin medications concurrently with other cholesterol-lowering medications/supplements. Excluding polypharmacy allowed the examination of the sole effects of statin monotherapy without confounding from other medications, but at the expense of sample size and generalizability. Moreover, information on family history of premature CHD, which is used to identify and recommend individuals for statin therapy based on the 2002 CPG, was not available, potentially resulting in some participants being misclassified in terms of CPG recommendation of statin therapy.

Another important limitation was the general low risk profile of the study cohort, which limited the potentially observable effect of statin therapy. Since this study focused on aviators with isolated hypercholesterolemia, three risk

factors (hypertension, tobacco use, and diabetes) that are used by the CPGs to recommend statin therapy were exclusion criteria, resulting in selection of a study cohort at low risk with no comorbidities. Air Force aviators in general also tend to be a relatively young population, as evidenced by an observed mean age of 34.64 yr in this study cohort, further limiting potential risk. Out of an eligible population of 8185 aviators, only 1458 (17.8%) were prescribed statin therapy and, of these, only 145 (9.9%) met the 2013 CPG recommendation of statin therapy. Thus, the likelihood of observing clinical significance given this cohort size, observation period, and limited risk difference to be detected was very low.

Given that the current study results found minimal, if any, benefit to statin therapy, additional health behavior data should be examined to more fully understand the effects of nonpharmacological and pharmacological interventions in relatively young, otherwise healthy individuals with isolated hypercholesterolemia. For example, Jenkins and colleagues demonstrated that dietary modifications could have similar efficacy to first-generation statins in achieving lipid goals for primary prevention.[8] Additionally, this study should be repeated including aviators with additional risk factors, including hypertension, tobacco use, and/or diabetes, in whom statin therapy may be more efficacious.

Returning to our case presentation of the 40-yr-old male USAF aviator with isolated hypercholesterolemia, his calculated 10-yr risk based on the 2013 CPG Pooled Cohort Equations was 1.9% as compared to a 0.6% risk with optimal risk factors. On the basis of his calculated risk alone, the 2013 CPG does not recommend statin therapy. However, this aviator has a significantly elevated lifetime risk of CHD, calculated at 50.0% as compared to 5.0% with optimal risk factors, which is a potential concern for long-term fitness for flying duty. Given his LDL-C is nearly 160 $mg \cdot dL^{-1}$, if this aviator has additional risk factors, such as a positive family history of premature CHD or an elevated high-sensitivity C-reactive protein and/or coronary artery calcium score, he may benefit from low- to moderate-dose statin therapy. Given the uncertainty of individual risk prediction, additional risk factor data would help refine the calculated prediction and guide the decision on statin therapy. Nonetheless, since this aviator is not at short-term elevated risk, the more prudent approach is a trial of therapeutic lifestyle modification before pursuing additional studies to refine his estimated risk.

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REFERENCES

1. Alla VM, Agrawal V, DeNazareth A, Mohiuddin S, Ravilla S, Rendell M. A reappraisal of the risks and benefits of treating to target with cholesterol lowering drugs. Drugs. 2013; 73(10):1025–1054.
2. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. [Published erratum appears in Lancet. 2005; 366(9494):1358 and Lancet. 2008; 371(9630):2084.] Lancet. 2005; 366(9493):1267–1278.
3. Bruckert E, Ferrières J. Evidence supporting primary prevention of cardiovascular diseases with stains: gaps between updated clinical results and actual practice. Arch Cardiovasc Dis. 2014; 107(3):188–200.
4. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015; 162(4):266–275.
5. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Lee I, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 129(25, Suppl. 2)S76–S99.
6. Goldfine AB. Statins: is it really time to reassess benefits and risks? N Engl J Med. 2012; 366(19):1752–1755.
7. Hu M, Cheung B, Tomlinson B. Safety of statins: an update. Ther Adv Drug Saf. 2012; 3(3):133–144.
8. Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, et al. Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. Am J Clin Nutr. 2005; 81(2):380–387.
9. Karmali KN, Goff DC, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014; 64(10): 959–968.
10. Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, et al. Comparison of application of the ACC/AHA guidelines, adult treatment panel III guidelines, and European society of cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA. 2014; 311(14):1416–1423.
11. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. J Am Coll Cardiol. 2012; 59(6):572–582.
12. Muntner P, Colantonio LD, Cushman M, Goff DC Jr, Howard G, et al. Validation of the atherosclerotic cardiovascular disease pool cohort risk equations. JAMA. 2014; 311(14):1406–1415.
13. National Institutes of Health, National Heart, Lung, and Blood Institute. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III): final report. Bethesda (MD): National Institutes of Health; 2002. NIH Publication No. 02-5215. [Accessed 1 Oct. 2016]. Available from https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/Circulation-2002-ATP-III-Final-Report-PDF-3143.pdf.
14. Newschaffer CJ, Liu L, Sim A. Cardiovascular disease (ICD-10 I20-I25, I-50, I60-I69, I73). In: Remington PL, Brownson RC, Wegner MV, editors. Chronic disease epidemiology and control, 3rd ed. Washington (DC): American Public Health Association; 2010:383–428.
15. Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med. 2010; 170(12):1024–1031.
16. Redberg RF, Katz MH. Healthy men should not take statins. JAMA. 2012; 307(14):1491–1492.
17. Redberg RF, Katz MH. Statins for primary prevention: the debate is intense, but the data are weak. JAMA. 2016; 316(19):1979–1981.
18. Rosenthal RL. Effectiveness of altering serum cholesterol levels without drugs. Proc Bayl Univ Med Cent. 2000; 13(4):351–355.

19. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report on the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. [Erratum published in J Am Coll Cardiol. 2015; 66(24):2812 and J Am Coll Cardiol. 2014; 63(25, Pt. B):3024–3025.] J Am Coll Cardiol. 2014; 63(25, Pt. B):2889–2934.
20. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013; (1):CD004816.
21. Vrecer M, Turk S, Drinovec J, Mrhar A. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke: meta-analysis of randomized trials. Int J Clin Pharmacol Ther. 2003; 41(12):567–577.
22. Wilt TJ, Bloomfield HE, MacDonald R, Nelson D, Rutkis I, et al. Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med. 2004; 164(13):1427–1436.
23. Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. Am Heart J. 2006; 151(2):273–281.