RESEARCH ARTICLE

Statin Efficacy and Safety for Lipid Modification in Apparently Healthy Male Military Aircrew

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Introduction: Military aircrew men represent an elite group of relatively young, fit, and healthy people. The effectiveness of statin treatment in reducing low-density lipoprotein cholesterol (LDL-C) according to the current National Cholesterol Education Program (NCEP) guidelines, its safety, and compliance in this group of people has not yet been determined. ***Methods:*** We prospectively evaluated 84 military aircrew men (mean age 43 ± 7 yr) with LDL-C above the current NCEP guidelines. The patients were divided into two groups according to their coronary risk factors: Group 1, LDL-C goal < 160 mg · dL^{-1}; Group 2, LDL-C goal < 130 mg · dL^{-1}. All patients received statins in addition to therapeutic lifestyle changes and were followed for a mean of 3 ± 1 yr according to a simple flow chart. Lipoprotein levels, liver function tests, creatinine phosphokinase, and subjective adverse reactions were checked periodically. ***Results:*** LDL-C significantly declined by 32% ($p < 0.0001$) within the first month of treatment and 99% of subjects achieved their LDL-C goal within 114 ± 35 d from statin therapy initiation. The Framingham estimated 10-yr coronary risk showed a reduction at an average of 12 mo after statin therapy initiation from a baseline value of 6.54% to 3.95% ($p = 0.003$). No subjects were grounded or disqualified from duty, there were no cardiovascular events during follow-up, and compliance to therapy was high [82/84 (98%)]. ***Discussion:*** Statin treatment in this highly select, relatively young group of aircrew men significantly and safely lowered LDL-C cholesterol levels.

Keywords: statins, lipoproteins, lipids, coronary disease, aircrew.

PRIMARY PREVENTION of arteriosclerosis aims to prevent new onset coronary artery disease (CAD) and reduce its global risk. The treatment of patients with abnormal plasma lipids, particularly those with high low-density lipoprotein cholesterol (LDL-C) levels, has been improved with the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). The use of statins, which has brought about a change in the approach to treatment of patients with CAD, has produced a significant reduction of 20–30% in coronary morbidity and mortality, as well as in total mortality in these patients (6,13).

The ability of statins to act as primary preventers of coronary disease is somewhat less clear. Three large prospective trials have shown beneficial effects of statin use for primary prevention (3,10,11) when treating high-risk patients who suffer from hyperlipidemia (11), or even normolipidemia (10) or low-risk patients with average LDL-C but low high-density lipoprotein cholesterol (HDL-C) (3).

Many young adults with no clinical evidence of cardiovascular disease could have two or more risk factors that increase the likelihood for subsequent clinical events and death (1,2,4,5). Military aircrew personnel (pilots, navigators, and mechanics) represent a highly select group of people whose profession warrants regular and strict medical check-ups in general, and cardiovascular follow-up in particular. Stress and echocardiography tests are routinely performed in order to determine combat readiness, since any slight medical problem could seriously influence performance. The effectiveness of statin treatment in reducing LDL-C, according to the current National Cholesterol Education Program (NCEP) guidelines (2,4–6,8,9,13), its safety, and compliance in this select group has not yet been determined.

The current study aimed to check the efficacy and safety of statin therapy within male, military air-force personnel whose LDL-C levels were above optimal (according to the current NCEP guidelines), and to determine the period of time and to what extent it is possible to reach LDL-C goals in this group of subjects adhering to a simple flow chart (**Fig. 1**) for routine follow-up.

METHODS

This was a prospective, non-blinded study conducted in the Israel Aero-Medical Center, which is the central medical unit of the Israeli Air Force. The 84 subjects designated for the study were all Israeli male Air Force personnel, with ages between 19–55 yr, who undergo regular medical checkups every 6 mo, and whose LDL-C levels were above the current NCEP guidelines (6,13).

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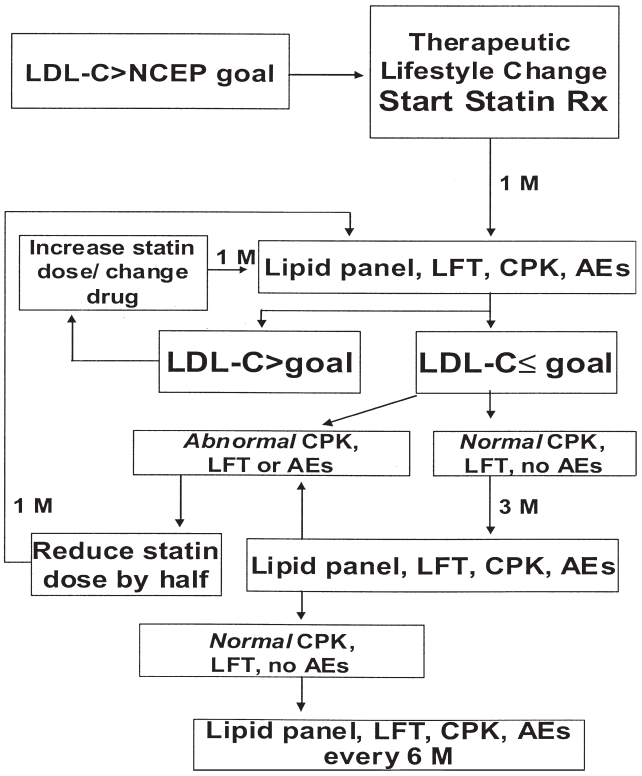

Fig. 1. Flow-chart for treating patients with statins. AEs = adverse events; CPK = creatinine phosphokinase; LDL-C = low-density lipoprotein cholesterol; LFT = liver function tests; M = months; NCEP = National Cholesterol Education Program; Rx = treatment.

A full lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides) after a 12-h or longer overnight fast was attained for each subject and CAD risk factors (diabetes, age, smoking, hypertension, family history, BMI > 25 kg $\cdot$ m^{-2} or HDL-C < 40 mg $\cdot$ dl^{-1}) were registered. Subjects were divided into two groups according to their LDL-C goal (Group 1, n = 34, LDL-C < 160 mg $\cdot$ dL^{-1}; and Group 2, n = 50, LDL-C < 130 mg $\cdot$ dL^{-1}; baseline characteristics for each group are shown in **Table I**). A 10-yr risk estimate for CAD according to the Framingham point scores was also calculated (13).

Subjects were treated and followed up with according to a simple flow-chart which took into account each subject's response to lipid-lowering therapy and reaction to potential adverse events (Fig. 1). Mean follow-up was 3 ± 1 yr. Each subject received instructions regarding therapeutic lifestyle changes based on the NCEP ATP III guidelines (6,13). Treatment with pravastatin 20 mg daily for 1 mo was recommended for each subject and recommendations for lifestyle modifications were made. However, in a few cases the choice of statin and dosing was determined by the treating physician. After 1 mo subjects were summoned for a second medical examination which included a lipid panel (total cholesterol, LDL-C, HDL-C, and triglycerides), creatinine phosphokinase (CPK), and liver function tests (LFT) such as alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. In addition, specific questions were asked regarding potential side effects such as weakness and/or muscle ache.

If the LDL-C goal was reached with no elevation in CPK of > 10 times the upper normal limit (UNL), and/or LFT results of > 3 times the UNL were observed (see Fig. 1), the patient continued therapy with the same medication and dose, and was summoned for a further medical examination in 3 mo. If the LDL-C goal was not met after 1 mo and no elevation in CPK of > 10 times the UNL and/or LFT results of > 3 times the UNL were observed, the patient was advised to continue the same medication but double the dose, and was summoned for another medical examination 1 mo later. If any adverse events were encountered and the LDL-C goal was not met, the generic statin was replaced, and the patient was summoned for another medical examination after 1 mo.

However, if 1 mo later the LDL-C goal was still not reached, the generic statin was replaced with a more potent one, and the patient was summoned for a further medical examination 1 mo later. If during that medical examination the LDL-C goal was achieved and no adverse reactions were encountered, the patient was summoned for another medical examination 3 mo later. If at that

TABLE I: BASELINE CHARACTERISTICS OF STUDY POPULATION.

	All Participants (n = 84)	Group 1 (n = 34)	Group 2 (n = 50)
Age, yr	43 ± 7	40 ± 7	44 ± 7
BMI, kg $\cdot$ m^{-2}	25.8 ± 2.9	24.6 ± 2.2	26.7 ± 2.9
Risk Factors			
Hypertension	13%	3%	20%
BMI > 25 kg $\cdot$ m^{-2}	51%	21%	70%
Smoking	25%	9%	36%
HDL-C < 40 mg $\cdot$ dL^{-1}	35%	9%	52%
Family history of CAD	34%	12%	48%
Age > 45 yr	17%	6%	24%
Lipid Profile			
Total cholesterol, mg $\cdot$ dL^{-1}	252 ± 26	260 ± 22	248 ± 28
LDL-C, mg $\cdot$ dL^{-1}	179 ± 23	187 ± 21	175 ± 23
HDL-C, mg $\cdot$ dL^{-1}	42 ± 9	45 ± 10	41 ± 7
Triglycerides, mg $\cdot$ dL^{-1}	142 ± 62	131 ± 47	148 ± 69
Framingham 10-yr estimate of CAD	6.5%	3.5%	8.6%

Values are expressed as mean ± SD; BMI = body mass index; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

medical examination the LDL-C goal was met, the patient was summoned for regular medical examination every 6 mo, at which time blood tests for lipid panel, CPK, and LFT were performed, and specific questions regarding potential side effects, such as weakness and/or muscle ache were asked (Fig. 1). In the event of any adverse reactions, such as CPK > 10 times the UNL, and/or LFT > 3 times the UNL, and/or muscle pain or weakness were encountered, the medication dose was reduced by half and the patient was scheduled for a further medical examination a month later (Fig. 1).

Group data are expressed as mean ± SD. Differences between clinical characteristics and lipoproteins were evaluated and analyzed between the two study groups at baseline and after 1, 3, and 6 mo by unpaired *t*-tests. The paired Student's *t*-test was used to calculate differences in each group over time. A p-value of < 0.05 was considered significant.

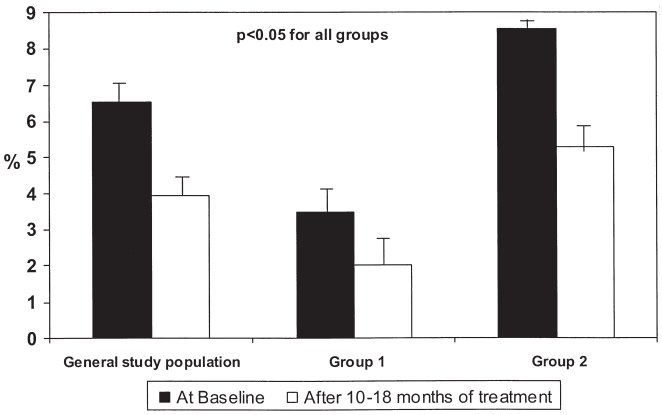

Fig. 3. Bar graphs showing the Framingham 10-yr risk for coronary artery disease calculated at baseline (black bars) and after 10–18 mo of treatment (white bars) for the entire study population (n = 84) and sub-groups (Group 1, n = 34; Group 2, n = 50). For all groups, $p < 0.05$.

RESULTS

At study entry about 60% of patients had > 1 risk factor for CAD: 3 patients (4%) had > 3 risk factors; 20 patients (24%) had 3 risk factors; 27 patients (32%) had 2 risk factors; 21 patients (25%) had 1 risk factor; and 13 patients (16%) had no risk factors for CAD (Table I). The most common risk factors were: BMI > 25 kg · m^{-2}; HDL < 40 mg · dL^{-1}; and a family history for ischemic heart disease. Since diabetes is a disqualifying factor for Israeli military aircrew personnel, none of the patients suffered from this disease. The mean Framingham score (10-yr risk for coronary heart disease estimate) was 6.5% at study entry.

Pravastatin 20 mg daily was the statin and dose of choice since it was the only Food and Drug Administration approved statin for primary prevention of CAD at the beginning of the current study. It should be stated, however, that in several cases, although we recommended treatment with pravastatin, the treating physician preferred using a different statin (e.g., simvastatin or atorvastatin) and/or a different starting dose (e.g., 10 or 40 mg).

Total cholesterol significantly declined by 24% (from 252 ± 26 mg · dL^{-1} at baseline to 192 ± 28 mg · dL^{-1}, $p < 0.0001$) after 1 mo of therapy and was maintained at a steady level thereafter (**Fig. 2**, **Fig. 3**). LDL-C also significantly decreased by 32% (from 179 ± 23 to 123 ± 25 mg · dL^{-1}, $p < 0.0001$) within the first month of treatment. From study onset to their first medical examination, 65 patients (78%) reached LDL-C levels according to their NCEP goal. Of these patients, 45 (54%) had their first medical examination within 1 mo, 13 (15.5%) between 1–2 mo, and 7 patients (8.5%) within a period of longer than 2 mo after initiation of treatment. During the entire follow-up period, 84/84 patients (100%) reached their LDL-C goal. HDL-C and triglyceride levels showed only a slight and non-significant change (Fig. 2). Calculation of the Framingham estimated 10-yr coronary risk showed a reduction at an average of 12 mo after statin therapy initiation from a baseline value of 6.54% to 3.95% ($p = 0.003$; Fig. 3).

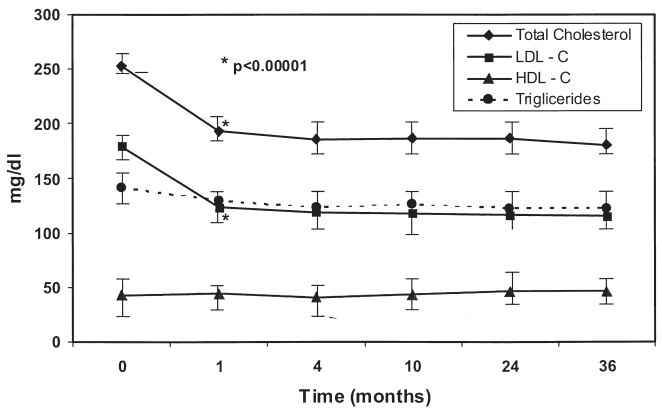

Fig. 2. Line graphs showing the change in lipid values during the study period in the general study population (n = 84). Rhomboid = total cholesterol, square = LDL-C, triangle = HDL-C, circle = triglycerides. For total cholesterol and LDL-C, $p < 0.00001$ during the first month of treatment.

During the study there was only one episode of muscle pain, which resolved itself spontaneously without any treatment change. There were no significant elevations in CPK or LFT during the follow-up period. None of the aircrew personnel treated with statins were grounded or disqualified from active duty due to therapy. There were no cardiovascular events (such as chest pain, myocardial infarction, cerebrovascular events, angina pectoris, heart failure) during follow-up of study participants. At each visit patients were encouraged to continue taking their statin therapy and to contact the treating physician if for any reason they might not have complied with the study regimen. Overall, adherence to statin therapy was high [82/84 (98%)] and no patient was lost from follow-up.

DISCUSSION

Statin treatment in this highly select, relatively young group of military Air Force male personnel significantly, rapidly, and safely lowered LDL-C to the current NCEP ATP III guideline levels. Our study demonstrated that it is both simple and efficient to use a flow-chart (Fig. 1) when managing patients with statin therapy for primary prevention of CAD. To the best of our knowledge, no reports exist in the literature regard-

ing routine follow-up charts for primary prevention of patients receiving statins. The exact time and frequency of medical examination and evaluation of LFT and CPK are usually left to the discretion of the treating physician, resulting in individual rather than across-the-board interpretation of results, and sometimes there may even be discrepancies between results of patients treated by the same doctor. In our current study we showed that a working system dictated by a simple flow-chart is easy to follow and keeps therapy at a uniform level. In addition, this kind of follow-up provides a safer regimen for patients by minimizing the possibility of inappropriate therapy and under-diagnosed side effects, while facilitating user-friendly, computerized access.

Primary prevention of CAD and arteriosclerosis provides important epidemiological and pharmacoeconomic advantages, particularly when bearing in mind the accumulative effects of the arteriosclerotic process, which begins in childhood and continues on into adult life. During the last decade several studies have shown the efficacy of primary prevention of CAD (3,10,11). According to the West of Scotland pravastatin study (6–8,11,12,14), statin treatment for primary prevention was found to be even more economically effective than the treatment of hypertensive patients, as shown by the lower number of needed-to-treat patients in primary prevention with statins compared with hypertension (8,14). When we confront selected populations, such as in our study (relatively young, healthy, intelligent, and highly motivated subjects with a unique occupation), primary prevention of disease is of particular importance in view of the high-risk, demanding tasks they perform.

The study group comprised a relatively small, homogenous, and relatively low-risk population. No method was used to evaluate the direct arteriosclerotic burden, since we assumed that LDL-C reduction would improve the outcome of long-term CAD and arteriosclerosis, even after a relatively short mean follow-up of 3 ± 1 yr. In addition, we did not carry out a double-blind placebo-controlled study since, based on other previous primary prevention studies (1,10), we felt it would be unethical to use this method in such a population. Further studies with larger groups of patients and longer follow-up are needed to assess the impact of our treatment strategy on clinical outcomes.

CONCLUSION

In conclusion, the current study demonstrated that statin therapy improves LDL-C levels [based on the Framingham score 10-yr risk for coronary heart disease estimate (Fig. 3)]. Our study demonstrated that LDL-C goals can be easily, rapidly, and safely achieved in a select group of patients motivated by their treating physician and by routine flow-chart visits. Statin therapy of choice at doses required to achieve NCEP LDL-C targets was very effective and safe with high compliance. Despite comprehensive tests and physical fitness demands on our subjects, none of them were suspended from active duty, grounded, or had any side effects, which further emphasizes the fact that treatment with statins for the primary prevention of arteriosclerosis is safe. While in the near future recommendations for periodic LFTs and CPK could disappear, and statins might be sold over the counter in some places, our straightforward (or user-friendly) statin therapy flow-chart strategy might be a useful and effective diagnostic tool for the physician in primary preventive treatment of CAD.

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REFERENCES

1. American Heart Association. 2002 heart and stroke statistical update. Dallas, TX: American Heart Association; 2001:4–5.
2. Dhawan J. Coronary heart disease in Asian Indians. Curr Opin Lipidol 1996; 7:196–8.
3. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279:1615–22.
4. Executive summary of the 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). JAMA 2001; 287:2486–97.
5. Forrester J, Birey Merz CN, Bush TL, et al. Task Force 4. Efficacy of risk factor management. J Am Coll Cardiol 1996; 27:964–1047.
6. Grundy SM, Cleeman JI, Bairey Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004; 110:227–39.
7. Hsu I, Spinler S, Johnson N. Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. Ann Pharmacother 1995; 29:743–59.
8. Maher V, Sinfugeo J, Chao P, et al. Primary prevention of coronary heart disease: what has WOSCOPS told us and what questions remain? Drugs 1997; 54:1–8.
9. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation 2000; 101:207–13.
10. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7–22.
11. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333:1301–7.
12. Smith S, Greenland P, Grundy S. Beyond secondary prevention: identifying the high risk patient for primary prevention. Circulation 2000; 101:111–6.
13. 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. Circulation 2002; 106:3143–421.
14. Vanuzzo D, Pilotto L, Ambrosio G, et al. on behalf of the EUROSPIRE group. Potential for cholesterol lowering in secondary prevention of coronary heart disease in Europe: findings from EUROSPIRE study. Atherosclerosis 2000; 153:505–17.