Application of the National Cholesterol Education Program and joint European treatment criteria and clinical benefit in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

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Aims The Air Force/Texas Coronary Atherosclerosis Prevention Study reported that diet with lovastatin, 20–40 mg daily, reduced the risk for a first coronary event by 37%. Because only 17% of this cohort would have qualified for drug therapy according to current U.S. guidelines, we assessed clinical benefit by risk categories.

Methods and Results The main outcome measures were event rates of first acute major coronary events stratified by National Cholesterol Education Program and European criteria and target goal. Both those who would and would not be eligible for drug therapy, according to National Cholesterol Education Program guidelines, benefited from intervention. As expected, drug-eligible participants (event rate: lovastatin 1%/year, placebo 1.87%/year [relative risk 0.53, 95% confidence interval: 0.33, 0.84]) were at greater absolute risk for acute major coronary events than non-eligible participants (lovastatin 0.62%/year, placebo 0.93%/year [relative risk 0.67, 95% confidence interval: 0.51, 0.88]). Similar results were found using European guidelines for coronary risk management. Treatment to a target goal suggested a non-significant trend to greater benefit.

Conclusions The consistent relative benefit across risk categories suggests that it may be possible to improve identification of at-risk persons who would benefit from primary prevention, and to recommend appropriate goals of such treatment.


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Key Words: Atherosclerosis, primary prevention, lovastatin, guidelines.

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Intervention with Pravastatin in Ischaemic Disease trials have extended cardiovascular morbidity and mortality benefits to coronary patients with moderate, or average, elevations in low-density lipoprotein cholesterol\[3\]-[5]. In primary prevention, the West of Scotland study demonstrated that lipid modification with pravastatin in high-risk primary prevention could reduce the risk for coronary morbidity and mortality\[3\].

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) is the first primary-prevention trial to investigate the effect of cholesterol reduction in a cohort of individuals with average total cholesterol and low-density lipoprotein cholesterol concentrations\[6\]. Furthermore, AFCAPS/TexCAPS participants had below average high-density lipoprotein cholesterol. These lipid characteristics characterize the study cohort as being at more moderate coronary risk than those of previous primary-prevention trials of coronary heart disease. In general, the risk factor profile of the AFCAPS/TexCAPS cohort was similar to the comparable U.S. reference population from the third National Health and Nutrition Examination Survey (NHANES III) defined as men 45–73 years old and women 55–73 years old without prior history of coronary heart disease.

The results of the study are described in full elsewhere\[6\]. In brief, after a mean follow-up of 5.2 years, lovastatin therapy reduced the risk for a first acute major coronary event, defined as the composite end-point of fatal or non-fatal myocardial infarction, unstable angina, or sudden cardiac death, by 37% (95% confidence interval, 29%–50%; \( P<0.001 \)). The risk for the first heart attack was reduced by 40% (95% confidence interval, 17%–57%; \( P=0.002 \)).

These results, taken in aggregate with other large-scale clinical trials of HMG-CoA reductase inhibitors, demonstrate compellingly the benefit of reducing low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol across a broad range of baseline cholesterol values. Because of considerations such as inter-individual variability in response to dose and the clinical paradigm of treating patients with the lowest effective dose, AFCAPS/TexCAPS, like the Scandinavian Simvastatin Survival Study, was designed to allow individualization of treatment. In this case, treatment was titrated to target a low-density lipoprotein cholesterol goal of \( \leq 2.84 \text{ mmol}.\text{L}^{-1} \) (110 mg . dl\(^{-1} \)), beginning with the usual starting dosage of lovastatin.

Only 17% of the AFCAPS/TexCAPS cohort would be recommended to receive pharmacological therapy to manage their cholesterol concentrations according to National Cholesterol Education Program guidelines. New recommendations for risk assessment and prevention of coronary heart disease have been published (in 1998) by a joint task force including the European Society of Cardiology, the European Atherosclerosis Society, and the European Society of Hypertension. Risk is evaluated based on age, gender, smoking status, total cholesterol and systolic blood pressure\[7\]. In the present analysis, we examined the ability of both sets of guidelines to distinguish higher- and lower-risk individuals in the AFCAPS cohort and to predict clinical benefit in these groups.

**Methods**

The trial design is described in detail elsewhere\[8\]. AFCAPS/TexCAPS is a randomized, double-blind, placebo-controlled primary-prevention trial with 6605 men and women and was conducted at two sites in Texas: Wilford Hall Medical Center at Lackland Air Force Base in San Antonio and the University of North Texas Health Science Center in Fort Worth. All participants provided written informed consent and the study protocol was approved by both Institutional review boards.

**Participant recruitment and follow-up**

Men (45–73 years) and post-menopausal women (55–73 years) who met the lipid entrance criteria and who had no prior history or signs or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident, or transient ischaemic attack, were eligible for participation. Lipid inclusion criteria (total cholesterol, 4.65–6.82 mmol . l\(^{-1} \) \([180–264 \text{ mg . dl}^{-1} \]]; low-density lipoprotein cholesterol, 3.36–4.91 mmol . l\(^{-1} \) \([130–190 \text{ mg . dl}^{-1} \]); high-density lipoprotein cholesterol, \( \geq 1.16 \text{ mmol}.\text{L}^{-1} \) \([45 \text{ mg . dl}^{-1} \]) for men or \( \geq 1.22 \text{ mmol}.\text{L}^{-1} \) \([47 \text{ mg . dl}^{-1} \]) for women, and triglycerides \( \leq 4.52 \text{ mmol}.\text{L}^{-1} \) \([400 \text{ mg . dl}^{-1} \]) to be met at both 4 and 2 weeks prior to randomization, with <15% difference in low-density lipoprotein cholesterol values. In addition, those with low-density lipoprotein cholesterol between 3.23–3.34 mmol . l\(^{-1} \) (125–129 mg . dl\(^{-1} \)) were included when the ratio total cholesterol:high-density lipoprotein cholesterol was >6.0.

Participants who met entrance criteria and completed a 12-week American Heart Association Step 1 diet run-in, including a 2-week placebo baseline run-in, were randomized to once daily treatment with either lovastatin 20 mg or matching placebo. Eighteen weeks after randomization, there was a one-time titration from 20 mg daily to 40 mg daily for lovastatin-treated participants with mean low-density lipoprotein cholesterol >2.84 mmol . l\(^{-1} \) (110 mg . dl\(^{-1} \)) at weeks 6 and 12 after randomization. Fifty percent of study participants (1657/3304) were titrated to 40 mg daily. The blind was maintained by titrating equal numbers of randomly selected placebo group participants to two tablets daily. Throughout the trial, dietary reinforcement and other risk factor modification information were provided. Follow-up for end-point events continued through study termination, even for withdrawn participants.
Stratifying effects of lipid modification with guidelines

**Table 1  Baseline and on-treatment lipid concentrations***

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>Treatment group</th>
<th>n</th>
<th>Baseline value Mean (SD)</th>
<th>Year 1 value Mean (SD)</th>
<th>% Change from baseline at year 1‡ Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mmol . l⁻¹)</td>
<td>Lovastatin</td>
<td>2933</td>
<td>5·86 (0·69)</td>
<td>4·75 (0·62)</td>
<td>-18·4 (11·1)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2885</td>
<td>5·88 (0·69)</td>
<td>5·90 (0·72)</td>
<td>-9·1 (11·4)</td>
</tr>
<tr>
<td>LDL-C (mmol . l⁻¹)</td>
<td>Lovastatin</td>
<td>2874</td>
<td>4·00 (0·60)</td>
<td>2·96 (0·52)</td>
<td>-25·0 (14·4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2807</td>
<td>4·03 (0·59)</td>
<td>4·04 (0·63)</td>
<td>-1·5 (16·2)</td>
</tr>
<tr>
<td>HDL-C (mmol . l⁻¹)</td>
<td>Lovastatin</td>
<td>2934</td>
<td>0·97 (0·20)</td>
<td>1·02 (0·21)</td>
<td>6·0 (15·0)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2884</td>
<td>0·97 (0·19)</td>
<td>0·97 (0·20)</td>
<td>1·2 (14·4)</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>Lovastatin</td>
<td>2874</td>
<td>4·29 (1·04)</td>
<td>3·03 (0·81)</td>
<td>-28·0 (17·2)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2807</td>
<td>4·32 (1·05)</td>
<td>4·32 (1·07)</td>
<td>-1·6 (19·1)</td>
</tr>
<tr>
<td>TG† (mmol . l⁻¹)</td>
<td>Lovastatin</td>
<td>2933</td>
<td>1·87 (0·95)</td>
<td>1·61 (0·82)</td>
<td>-15·0 (34·1)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2885</td>
<td>1·86 (0·93)</td>
<td>1·84 (0·93)</td>
<td>-2·3 (38·2)</td>
</tr>
</tbody>
</table>

TC=total cholesterol; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; SD=standard deviation.
*Based on data from Johns Hopkins Laboratory.
†Median triglyceride values given.
‡All between-group differences significant (P<0·001).

**Measurement of lipid and lipoprotein components**

Blood samples were collected after 12 to 14 h of fasting and left to coagulate for 1–2 h at room temperature. For analysis of changes in lipids, frozen sera (−70 °C) obtained on the date of randomization before active treatment and at the year 1 visit (post-treatment) were assayed at a specialized lipid laboratory at Johns Hopkins University, Baltimore, Maryland. The laboratory was standardized for lipid and lipoprotein measurements through the Centers for Disease Control and Prevention, National Heart, Lung and Blood Institute Lipid Standardization Program[9]. All low-density lipoprotein cholesterol values were calculated based upon the Friedewald estimation[10]. Lipid changes in the study are summarized in Table 1.

**End-point**

AFCAPS/TexCAPS was designed and powered to investigate whether chronic lipid modification with lovastatin will decrease the rate of first acute major coronary events (composite primary end-point defined as fatal or non-fatal myocardial infarction, unstable angina, or sudden cardiac death) compared with placebo during at least 5 years of follow-up in a cohort without clinical evidence of atherosclerotic cardiovascular disease and with average total cholesterol and low-density lipoprotein cholesterol and below average high-density lipoprotein cholesterol. The procedures for end-point adjudication have been described in detail previously[8]. In summary, end-points were adjudicated by the end-point committee, which was blinded to the treatment assignment of the participants. Only the first end-point for an individual patient was included in the analysis.

**Statistical analyses**

**Event reduction in participants who qualify for drug treatment according to guidelines**

Post hoc analyses were performed within certain subgroups of the study population, namely those qualified and not qualified for drug therapy by current National Cholesterol Education Program second Adult Treatment Panel guidelines and by recent joint European guidelines. Those who qualified for drug treatment, according to the second Adult Treatment Panel guidelines, were those participants with either a low-density lipoprotein cholesterol of 4·91 mmol . l⁻¹ (190 mg . dl⁻¹) or greater with fewer than two other coronary risk factors, or low-density lipoprotein cholesterol 4·14 mmol . l⁻¹ (160 mg . dl⁻¹) or greater with two or more other coronary risk factors. The first Adult Treatment Panel guidelines were in effect during study recruitment[11]. According to joint European criteria, participants would receive drug therapy if they had an absolute coronary risk of at least 2%/year.

Treatment groups were compared using the log rank statistic in a model stratified by study site and sex, the randomization strata. Estimates of relative risk with 95% confidence intervals were from a Cox regression model stratified by study site and sex. The interaction between treatment and the subgroup factor (qualified or not for drug therapy based upon both sets of guidelines) was evaluated in a Cox regression model stratified by study site and sex and found not significant (P=0·384). In such cases, the best estimate of effects within subgroups is the overall cohort effect. However, the subgroup results are presented for information.

**Event rates by target goals**

An exploratory, hypothesis-generating analysis was conducted to examine the effect of treatment with
Lovastatin on risk for an acute major coronary event according to whether participants achieved the following low-density lipoprotein cholesterol goals at year 1: ≤2.84 mmol. l⁻¹ (110 mg . dl⁻¹), >2.84–3.36 mmol. l⁻¹ (110–130 mg . dl⁻¹), and >3.36 mmol. l⁻¹ (130 mg . dl⁻¹). Within the lovastatin treatment group, the number of participants with an acute major coronary event was tabulated by subgroups composed of participants who, after 1 year of treatment, reached the above low-density lipoprotein cholesterol targets. Trend across the subgroups was evaluated using the Mantel–Haenszel procedure[23]. This analysis was not pre-specified.

Results

Event rates in participants according to whether they qualify at baseline for drug treatment according to National Cholesterol Education Program guidelines

Table 2. Event rates in AFCAPS/TexCAPS participants according to whether they qualify at baseline for drug treatment according to National Cholesterol Education Program guidelines

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Treatment</th>
<th>n</th>
<th>Cases</th>
<th>Rate*</th>
<th>Relative risk (95% CI)†</th>
<th>Group P-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualify</td>
<td>Lovastatin</td>
<td>530</td>
<td>27</td>
<td>1.00</td>
<td>0.53</td>
<td>(0.33, 0.84)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>566</td>
<td>53</td>
<td>1.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not qualify</td>
<td>Lovastatin</td>
<td>2774</td>
<td>89</td>
<td>0.62</td>
<td>0.67</td>
<td>(0.51, 0.88)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2735</td>
<td>130</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence interval.
*% per year or 100 person-years at risk.
†Cox proportional hazard model, stratified by study centre and gender.
‡Between treatment group log rank statistic, stratified by study centre and gender.

Adapted from: National Cholesterol Education Program ATPII JAMA 1993; 269: 3015

Based on current second Adult Treatment Panel guidelines[1], only 17% (1096 participants) of the AFCAPS/TexCAPS cohort would have been recommended to receive lipid-modifying medication. In these participants, lovastatin reduced the relative risk for developing an acute major coronary event by 47% (P=0.006) (Table 2). While lovastatin reduced the risk of acute major coronary events in the remaining 5509 participants (83%) by 33% (P=0.003), this subgroup would not have been recommended to receive pharmacological therapy based on the current National Cholesterol Education Program guidelines. Of note, for most of these latter participants, their on-treatment low-density lipoprotein cholesterol was below 3.36 mmol. l⁻¹ (130 mg . dl⁻¹), much lower than the current National Cholesterol Education Program goal of low-density lipoprotein cholesterol <4.14 mmol. l⁻¹ (160 mg . dl⁻¹) for this type of cohort.

Event rates by target goals

The differences between the event rates according to the cutpoints we used, while not statistically significant, suggest a trend towards greater benefit with treatment when the lower target low-density lipoprotein cholesterol was achieved (Table 5). Of the 1216 participants in the lovastatin group with low-density

Table 3. AFCAPS/TexCAPS participants categorized by coronary risk according to new European guidelines

<table>
<thead>
<tr>
<th>Group</th>
<th>Low and mild</th>
<th>Moderate</th>
<th>High</th>
<th>Very high</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lovastatin</td>
<td>3 (0.09)</td>
<td>2605 (79.76)</td>
<td>655 (20.06)</td>
<td>3 (0.09)</td>
<td>3266</td>
</tr>
<tr>
<td>placebo</td>
<td>2 (0.06)</td>
<td>2590 (79.84)</td>
<td>652 (20.10)</td>
<td>0 (0.00)</td>
<td>3244</td>
</tr>
<tr>
<td>total</td>
<td>5</td>
<td>5195</td>
<td>1307</td>
<td>3</td>
<td>6510</td>
</tr>
</tbody>
</table>

Frequency missing=95 did not have systolic blood pressure measurements taken and were excluded.
lipoprotein cholesterol at or below the study goal, 31 (2.55%) had a primary end-point. Of the 1113 participants who did not achieve the study goal but did reach an on-treatment low-density lipoprotein cholesterol of 2.84–3.36 mmol. l\(^{-1}\) [110–130 mg. dl\(^{-1}\)], 33 (2.96%) had a primary end-point. Eighteen (3.33%) of the 540 participants with low-density lipoprotein cholesterol >3.36 mmol. l\(^{-1}\) (130 mg. dl\(^{-1}\)) had a primary end-point. Participants achieving the study goal of 2.84 mmol. l\(^{-1}\) (110 mg. dl\(^{-1}\)) were 24% less likely to have an acute major coronary event than participants not reaching the National Cholesterol Education Program goal of <3.36 mmol. l\(^{-1}\) (130 mg. dl\(^{-1}\)). Participants who reached a low-density lipoprotein cholesterol <2.84 mmol. l\(^{-1}\) (110 mg. dl\(^{-1}\)) were 11% less likely to have an acute major coronary event than participants who reached the National Cholesterol Education Program goal.

### Discussion

Most individuals with characteristics similar to the AFCAPS/TexCAPS cohort (83%) would not be recommended for drug treatment to modify their lipids and would be considered to be ‘at goal’ with a low-density lipoprotein cholesterol <4.14 mmol. l\(^{-1}\) (160 mg. dl\(^{-1}\)). Furthermore, 2137 (32%) of the AFCAPS/TexCAPS cohort with total cholesterol <6.21 mmol. l\(^{-1}\) (240 mg. dl\(^{-1}\)) would not have been recommended to have a fasting lipid profile. In terms of risk factor distribution, all AFCAPS/TexCAPS participants had age as a risk factor, because of the entry criteria. Sixty-three percent of the cohort had age plus one other risk factor recognized by the U.S. guidelines. Fifteen to 16% of the AFCAPS/TexCAPS cohort had family history of coronary disease as a risk factor, although the use of family history in risk evaluation has created debate. While U.S. guidelines consider family history to be an important non-modifiable risk factor, European calculations do not adjust for family history and only note that a positive family history increases the predicted risk.

In AFCAPS/TexCAPS, one year of lovastatin, 20–40 mg daily, resulted in mean on-treatment levels of low-density lipoprotein cholesterol of 2.96 mmol. l\(^{-1}\) (114.6 mg. dl\(^{-1}\), a 25% reduction from baseline) and of high-density lipoprotein cholesterol of 1.02 mmol. l\(^{-1}\) (39.3 mg. dl\(^{-1}\), a 6% increase from baseline). As previously reported, these lipid changes were associated with a 37% decrease in acute major coronary events[6]. Among those treated with lovastatin, differences in rates of acute major coronary events were not significantly different across the following exploratory subgroups of on-treatment low-density lipoprotein cholesterol goals: ≤2.84 mmol. l\(^{-1}\) (110 mg. dl\(^{-1}\)), >2.84–3.36 mmol. l\(^{-1}\) (>110–130 mg. dl\(^{-1}\)), and >3.36 mmol. l\(^{-1}\) (>130 mg. dl\(^{-1}\)). However, the number of events reported for those with an on-treatment low-density lipoprotein cholesterol >3.36 mmol. l\(^{-1}\) was numerically higher than that reported for the other two subgroups. Since the majority (82%) of the cohort treated with lovastatin achieved the low-density lipoprotein-cholesterol goal of <3.36 mmol. l\(^{-1}\) (130 mg. dl\(^{-1}\)), the current National Cholesterol Education Program low-density lipoprotein-cholesterol target of <4.14 mmol. l\(^{-1}\) (160 mg. dl\(^{-1}\))
may be too conservative in terms of a feasible goal in primary prevention. Candidates for primary prevention similar to those studied in AFCAPS/TexCAPS may benefit from a low-density lipoprotein cholesterol goal <3.36 mmol·l⁻¹ (130 mg·dl⁻¹). Such a goal would complement the recommendation that drug therapy be considered in secondary prevention at an initiation level of low-density lipoprotein cholesterol ≥ 3.36 mmol·l⁻¹ (130 mg·dl⁻¹), with a goal of low-density lipoprotein cholesterol ≤ 2.59 mmol·l⁻¹ (100 mg·dl⁻¹).

Like the NIH Post-CABG trial and 4S, the design of AFCAPS/TexCAPS specifically considered the importance of individualizing treatment so as to reach a low-density lipoprotein cholesterol goal. To address these implications in terms of current National Cholesterol Education Program guidelines, our analysis stratified participants according to whether or not they would qualify for drug treatment. Of note, significant benefit with lovastatin therapy was observed regardless of such status, although those who qualified for drug treatment were at greater absolute risk for a coronary event than those who did not.

As reported previously, approximately 80 million Americans would meet the major AFCAPS/TexCAPS entry criteria. Based upon the risk profile of this reference population and assuming that a similar proportion of these people (83%) would not be treated with medication to lower cholesterol under second Adult Treatment Panel guidelines, approximately 6.6 million additional persons in the United States could potentially benefit from pharmacological treatment to lower cholesterol. In this subgroup of 6.6 million individuals who do not qualify for drug treatment, lovastatin treatment could prevent 20,460 individuals from having a first acute major coronary event, if one assumes that the event rate is 0.31%/year greater for those untreated, compared with those on lovastatin (Table 2). Similarly, if one assumes that the event rate in the approximately 1.4 million individuals who would be treated according to current guidelines is 0.87%/year greater for untreated persons than for lovastatin-treated persons (Table 2), then, treatment may prevent approximately 12,180 persons from having a first acute major coronary event. When projections for both categories are added, more than 30,000 acute major coronary events and their associated hospitalizations could be prevented each year in the U.S. alone by treating persons with risk profiles similar to those of the AFCAPS/TexCAPS study cohort.

Recent joint European guidelines endorse a multifactorial strategy that attempts to quantify the contributions of various coronary risk factors along a continuum of risk. Pharmacological treatment is generally deferred unless a patient has an estimated coronary risk of 2%/year or higher (20% or higher over 10 years). Using this global-risk paradigm, approximately 1,310 AFCAPS/TexCAPS participants would have been shown as having high or very-high short-term risk for coronary disease, compared with 1,096 participants who would qualify for drug therapy according to the National Cholesterol Education Program. Thus, a methodology that quantifies global risk identified a greater number of participants who may be recommended for drug intervention. Nevertheless, as we observed with the National Cholesterol Education Program guidelines, the relative risk reduction in the two subgroups was comparable with the benefit in the overall cohort, although the absolute risk for an acute major coronary event was greater in the higher risk subgroup. For the purposes of risk calculation, the European guidelines assume high-density lipoprotein cholesterol values of 1.0 mmol·l⁻¹ (39 mg·dl⁻¹) in men and 1.1 mmol·l⁻¹ (43 mg·dl⁻¹) in women, and note that the predicted risk is greater for individuals with lower high-density lipoprotein cholesterol concentrations. Therefore, the low baseline high-density lipoprotein cholesterol observed in the AFCAPS/TexCAPS cohort may represent an important additional consideration in the decision to intervene.

AFCAPS/TexCAPS has important implications for the optimal identification of relatively moderate-risk persons who may best benefit from statin treatment. Although the study was not designed to address the effect of treatment on total mortality, no significant increase in total mortality was observed with lovastatin treatment. The study’s results suggest that pharmacological therapy can reduce the risk for the first acute major coronary event, regardless of baseline risk, perhaps promoting healthy, coronary-event free years of life. These results confirm the importance of a treatment strategy that allows for individualization of dose in order to target a low-density lipoprotein cholesterol goal of at least <3.36 mmol·l⁻¹ (130 mg·dl⁻¹). Titration enabled less responsive persons to achieve clinically meaningful low-density lipoprotein cholesterol reduction, while exposing those who did not require titration to the lowest clinically effective dose, and resulted in an overall relative benefit that is similar to what has been observed in studies of cohorts at much greater absolute risk. These findings suggest that it may be possible to refine primary-prevention guidelines by broadening goals of treatment.

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