Sex Bias and Underutilization of Lipid-Lowering Therapy in Patients With Coronary Artery Disease at Academic Medical Centers in the United States and Canada

Michael Miller, MD; Robert Byington, PhD; Donald Hunninghake, MD; Bertram Pitt, MD; Curt D. Furberg, MD, PhD; for the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) Investigators

**Background:** The efficacy of lipid-lowering therapy (LLT) has been well established for patients with pre-existing coronary artery disease (CAD). However, limited information is available assessing the extent to which these medications are prescribed in academic medical centers.

**Methods:** The use of LLT for patients with CAD was prospectively evaluated in 825 men and women who were recruited from 16 academic medical centers in the United States and Canada to participate in the Prospective Evaluation of the Vascular Events of Norvasc Trial (PREVENT). The assessment of LLT use during the 3-year trial was evaluated in patients receiving amlodipine therapy and placebo; levels of low-density lipoprotein cholesterol (LDL-C) were used to assess the impact of LLT.

**Results:** Despite a baseline prevalence of LLT in 42% of men (38% in 1994), half of the patients had high levels of LDL-C (>3.36 mmol [>130 mg/dL]). During the subsequent 3 years, the prevalence of elevated LDL-C levels dropped in men (29%) but remained stagnant in women (48%). These changes were associated with increased LLT in men (55%) but not in women (35%) (P = .04). In 1994, the LDL-C target goal (<2.59 mmol/L [<100 mg/dL]) was attained in 17% of men and 6% of women (P = .006). At study completion in 1997, the LDL-C target goal was achieved in 31% of men and only 12% of women (P = .001).

**Conclusions:** This study highlights the relatively low treatment rates of hyperlipidemia among patients with CAD overall and women in particular who were participating in a clinical trial at academic medical centers in the United States and Canada. Because LLT has been proven to reduce future cardiovascular events, these results suggest that more intensive efforts should be promoted in order to maximize CAD reduction.

Arch Intern Med. 2000;160:343-347

**RESULTS**

During the past 5 years, randomized clinical trials have provided unequivocal evidence that cholesterol-lowering therapies reduce initial and recurrent cardiovascular events.1-3 These studies are consistent with the National Cholesterol Education Program’s (NCEP’s) recommendations for dietary and pharmacological therapy in subjects at highest risk of coronary artery disease (CAD). While previous reports evaluating the use of hypolipidemic therapy have generally reported low treatment rates by cardiologists4 and primary care physicians,5 there have been limited prospective data evaluating the use of lipid-lowering therapy (LLT) in men and women with CAD. We hypothesized that treatment rates for elevated cholesterol would be considerably higher in academic medical centers, which are heavily employed in clinical research protocols for the secondary prevention of cardiovascular disease. Therefore, we collected data from the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) to further examine this issue.

The mean lipid and lipoprotein levels in PREVENT participants by calendar year are shown in Table 1. Overall improvement in lipid levels was observed from 1994 to 1997, with significant reductions in total cholesterol (TC), LDL-C, and triglyceride (TG) levels (P<.001 for testing the time trend). The fewer numbers of patients in 1997 (n = 443) reflect the remaining subjects in the study. There were no changes in high-density lipoprotein cholesterol (HDL-C) levels during the course of the study.

**Figure 1** illustrates the LDL-C distribution in all subjects participating in PREVENT. During the course of the study,
SUBJECTS AND METHODS

The PREVENT study was a multicenter, randomized, double-blind, placebo-controlled trial of 825 patients (80% men; 89% white) with predefined arteriographic evidence of CAD. Sixteen centers in the United States and Canada participated in the study; these centers are listed in the acknowledgments section. The design and baseline characteristics of PREVENT have been previously reported. Briefly, the primary objective of PREVENT was to determine whether amiodipine therapy reduced the progression of coronary atherosclerosis over a 3-year period. Eligibility criteria included age 30 to 80 years, diastolic blood pressure less than 95 mm Hg, fasting total cholesterol level less than 8.40 mmol/L (<325 mg/dL), fasting blood glucose level less than 11.1 mmol/L (<200 mg/dL), and no anticipated recanalization during the subsequent 3 years. Eligible patients were randomized between November 1992 and September 1994. Prior to randomization, baseline measurements included complete blood cell count, serum electrolyte levels, glycosylated hemoglobin levels, and fasting lipid and lipoprotein analysis. Following randomization, fasting lipid profiles were repeated yearly and at the final examination (month 35), approximately 2 weeks prior to the repeated coronary arteriography. All laboratory measurements were performed by SmithKline Beecham Laboratory, Van Nuys, Calif. Statistical analysis included t tests and maximum likelihood analyses of covariates. It is recognized that many P values are presented in this descriptive article, increasing the likelihood of type I errors. Accordingly, as a crude means of judging significance, the designated level for statistical significance is set at P <.01, although the possibility for type I error is not eliminated.

From the outset of the study, patients were instructed to maintain a phase I American Heart Association (AHA) diet. If their plasma low-density lipoprotein cholesterol (LDL-C) level exceeded 3.36 mmol/L (130 mg/dL), they were instructed to follow a phase II AHA diet. When the results of the Scandinavian Simvastatin Survival Study (4S) were published in November 1994, 1 a letter was distributed to all investigators recommending institution of LLT to a target LDL-C goal below 2.59 mmol/L (100 mg/dL), as outlined by the expert panel of the NCEP. 10 The study was completed in September 1997. This report highlights the use of LLT throughout the trial.

The mean LDL-C level in men and women receiving or not receiving LLT during the course of PREVENT is shown in Table 3. In 1994, lower mean LDL-C levels were observed for men compared with women receiving LLT (P = .01); this finding was observed for every year except 1996. As expected, the decline in LDL-C levels was negligible in men who were not receiving LLT. However, the increases in LDL-C levels observed in women who were not receiving LLT coincided with significant differences between the 2 groups during the last 2 years of the study. Table 4 contrasts the percentage of men and women receiving LLT during PREVENT. Compared with women, there was a consistently higher percentage of men with high (>3.36 mmol/L [>130 mg/dL]) or borderline (2.59-3.36 mmol/L [90-130 mg/dL]) LDL-C levels who were not receiving LLT (September 1997), 56% were receiving LLT. The prevalence of elevated LDL-C was also high (66%) in the small number of African American participants at baseline (n = 44) and remained elevated during the course of the study (range, 52%-62%). Moreover, desirable levels were only achieved in a small subset (15% in 1996 and 0% among the final 8 subjects completing the study in 1997).

Figure 2 illustrates the proportion of PREVENT participants receiving LLT (or a lipid-lowering agent [LLA]) throughout the study. During the final quarter of 1993, 30% of patients received LLT. Following publication of the 4S the following year, the proportion of patients steadily increased to 39% by study completion (September 1997), 56% were receiving LLT.

Table 1. Mean ± SD Lipid and Lipoprotein Levels by Calendar Year in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT)*

<table>
<thead>
<tr>
<th>Year</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>734 (5.61 ± 1.00)</td>
<td>676 (3.46 ± 0.90)</td>
<td>714 (1.22 ± 0.31)</td>
<td>714 (2.18 ± 1.53)</td>
</tr>
<tr>
<td>1995</td>
<td>740 (5.58 ± 1.03)</td>
<td>702 (3.36 ± 0.85)</td>
<td>738 (1.27 ± 0.34)</td>
<td>738 (2.13 ± 1.40)</td>
</tr>
<tr>
<td>1996</td>
<td>704 (5.40 ± 1.01)</td>
<td>671 (3.31 ± 0.85)</td>
<td>704 (1.16 ± 0.31)</td>
<td>704 (2.09 ± 1.42)</td>
</tr>
<tr>
<td>1997</td>
<td>443 (5.22 ± 1.06)</td>
<td>422 (3.13 ± 0.90)</td>
<td>441 (1.22 ± 0.34)</td>
<td>442 (2.04 ± 1.39)</td>
</tr>
</tbody>
</table>

* TC indicates total cholesterol level; LDL-C, low-density lipoprotein cholesterol level; HDL-C, high-density lipoprotein cholesterol level; and TG, triglyceride level.

† P <.001 (testing the time trend).
...achieved in men and women (75% and 70%, respectively) who had higher baseline LDL-C levels. It is likely that the lack of statistical significance in women reflects the small number (n = 10) receiving LLT in combination with a desirable LDL-C level.

The mean LDL-C level in women receiving hormone replacement therapy (HRT) with or without concomitant LLT is outlined in Table 5. Despite the exclusion of premenopausal women (unless they underwent oophorectomy), a small percentage (24%-29%) of women received HRT (primarily estrogen alone) during the course of the study. There were correspondingly fewer women (10%-15%) receiving combination HRT and LLT in PREVENT. Women receiving HRT evidenced mean reductions in LDL-C levels of 0.26 mmol/L (10 mg/dL) compared with those receiving no HRT (maximum likelihood on repeated-measures analysis of variance, P = .001). Reductions in LDL-C levels among the women receiving LLT became evident during the final 2 years of the study. Similarly, combined LLA use and HRT resulted in the most favorable LDL-C levels during the last 2 years.

The LLTs employed included hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, which accounted for 63% of LLTs in 1994, increasing to 79% by 1997. There were corresponding decreases in the other LLTs used during the study, including fibrates (from 17% to 10%), niacin (from 14% to 6%), and bile acid sequestrants (from 6% to 4%). Specific agents and dosages recorded were atorvastatin (10...
The most important finding of this study was the relative paucity of LLT used in patients with CAD who participated in a randomized clinical trial at US and Canadian academic medical centers. In addition to the randomized, double-blind, placebo-controlled design, all patients entering the study evidenced arteriographically demonstrated CAD, and there were similar baseline characteristics between men and women. Moreover, all principal investigators received instructions that LLTs should be employed following the publication of the 4S.1 Limitations of the study included the small percentage (20%) of women in the cohort, the nature of the analyses (post hoc), and the fact that the protocol was evaluated in 2 countries (the United States and Canada). While the use of LLT was 20% higher in Canada, only 15% of the study group was Canadian, and no a priori hypothesis had been formulated to test whether differences in LLT use existed between the countries.

These findings were particularly egregious because letters had been distributed to physicians recommending initiation of LLT following the publication of the 4S. However, nearly one third of patients remained hyperlipidemic through 1997, and only a minority of subjects achieved an LDL-C target of 2.59 mmol/L (100 mg/dL), as recommended by the NCEP.

Equally surprising was the relatively more frequent use of LLT among patients with CAD and desirable LDL-C levels compared with those patients with borderline or elevated LDL-C levels. It is likely that a small proportion of the 70% of patients achieved a desirable LDL-C level following therapy. Nevertheless, considerably fewer patients with high LDL-C levels (>3.36 mmol/L (>130 mg/dL)) were receiving LLT, suggesting an overall misappropriated use of these agents in PREVENT.

The overall reduced rates of therapy were particularly noteworthy in women. Although women represented only 20% of the study cohort, the extent of arteriographic disease and the prevalence of elevated LDL-C levels (Table 3) were similar to those for men at baseline.9 However, during the course of the study, the proportion of patients with LDL-C levels greater than 3.36 mmol/L (>130 mg/dL) was reduced by 42% in men compared with only a 6% reduction in women. Both men and women evidenced similar proportional increases toward attaining the target LDL-C level (2.59 mmol/L [<100 mg/dL]). Nonetheless, treatment in accordance with NCEP-defined LDL-C goals for women with CAD in 1997 (12%) still lagged considerably behind that for men, approximating the proportion of men with CAD who were treated in accordance with NCEP-defined LDL-C level goals in 1994 (17%). Under-treatment to target LDL-C levels was previously observed in women with CAD participating in the Heart and Estrogen/Progestin Replacement Study (HERS) at baseline.11 This effect persisted because LLT was subsequently initiated in approximately 20% of women, yielding modest reductions in LDL-C levels (14% in HRT group vs 3% in controls) after the first year of treatment.12 The relatively infrequent use of LLT in women with CAD in the HERS predated the results of the major lipid-lowering secondary prevention trials that have been subsequently published.13,15 PREVENT extends the finding of undertreatment to target NCEP LDL-C goals in women with preexisting CAD. Furthermore, these results provide evidence of considerable sex bias at academic medical centers in the United States and Canada.

Sex bias has previously been reported for cardiovascular diagnostic procedures and therapies.13,14 The delay

### Table 4. Men and Women Receiving Lipid-Lowering Therapy (LLT) by Low-Density Lipoprotein Cholesterol (LDL-C) Levels and Calendar Year in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT)

<table>
<thead>
<tr>
<th>LDL-C Distribution, No. (%) Receiving LLT</th>
<th>Year</th>
<th>Men</th>
<th>Women</th>
<th>LLT Only</th>
<th>HRT Only</th>
<th>LLT and HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.59 mmol/L (≤100 mg/dL)</td>
<td>1994</td>
<td>92</td>
<td>44</td>
<td>36 (36%</td>
<td>278 (42%</td>
<td>271 (33%)</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>99 (59)</td>
<td>16 (44)</td>
<td>221 (55)</td>
<td>256 (52)</td>
<td>63 (43)</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>113 (67)</td>
<td>19 (58)</td>
<td>294 (57)</td>
<td>23 (32)</td>
<td>61 (33)</td>
</tr>
<tr>
<td>&gt;2.59-3.36 mmol/L (100-130 mg/dL)</td>
<td>1994</td>
<td>69 (35%</td>
<td>7 (12%)</td>
<td>138 (36%</td>
<td>58 (28)</td>
<td>192 (36%)</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>97 (59)</td>
<td>16 (44)</td>
<td>216 (55)</td>
<td>48 (38)</td>
<td>159 (55)</td>
</tr>
<tr>
<td>&gt;3.36 mmol/L (&gt;130 mg/dL)</td>
<td>1994</td>
<td>54 (36%</td>
<td>5 (12%)</td>
<td>147 (36%</td>
<td>30 (12)</td>
<td>192 (35%)</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>68 (41)</td>
<td>16 (44)</td>
<td>283 (55)</td>
<td>41 (32)</td>
<td>242 (42)</td>
</tr>
</tbody>
</table>

*P < .05 for the difference in the rate of LLT use vs women with LDL-C levels less than 2.59 mmol/L (≤100 mg/dL).

**P < .05 for the difference in the rate of LLT use vs men with LDL-C levels less than 2.59 mmol/L (≤100 mg/dL).

### Table 5. Mean ± SE Low-Density Lipoprotein Cholesterol (LDL-C) Levels in Women Receiving Hormone Replacement Therapy (HRT) With or Without Lipid-Lowering Therapy (LLT) in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) by Calendar Year

<table>
<thead>
<tr>
<th>No. of Subjects (mmol/L) (mg/dL)</th>
<th>No Therapy</th>
<th>LLT Only</th>
<th>HRT Only</th>
<th>LLT and HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>69 (3.57 ± 0.10) [138 ± 3.7]</td>
<td>30 (3.85 ± 0.14) [149 ± 5.3]</td>
<td>22 (3.57 ± 0.16) [138 ± 6.2]</td>
<td>13 (3.54 ± 0.21) [137 ± 8.0]</td>
</tr>
<tr>
<td>1995</td>
<td>54 (3.67 ± 0.12) [142 ± 4.6]</td>
<td>37 (3.54 ± 0.14) [137 ± 5.3]</td>
<td>21 (3.54 ± 0.18) [137 ± 7.0]</td>
<td>15 (3.46 ± 0.21) [134 ± 8.0]</td>
</tr>
<tr>
<td>1996</td>
<td>54 (3.80 ± 0.11) [147 ± 4.1]</td>
<td>31 (3.28 ± 0.13) [127 ± 5.0]</td>
<td>19 (3.52 ± 0.16) [136 ± 6.5]</td>
<td>21 (2.95 ± 0.16) [114 ± 6.2]</td>
</tr>
<tr>
<td>1997</td>
<td>36 (4.06 ± 0.15) [157 ± 5.8]</td>
<td>29 (3.31 ± 0.16) [128 ± 6.4]</td>
<td>9 (4.03 ± 0.28) [156 ± 7.7]</td>
<td>11 (2.97 ± 0.25) [115 ± 9.5]</td>
</tr>
</tbody>
</table>

*The interaction of year × therapy (no therapy, LLT, HRT, and LLT and HRT) was significant (P < .001), implying that the therapeutic effects on mean LDL-C levels differed across time as follows: in 1994, no significant differences; in 1995, no significant differences; in 1996, HRT only > LLT and HRT (P = .01), no therapy > LLT and HRT (P < .001), and no therapy > LLT (P < .001); in 1997, HRT only > LLT and HRT (P < .001) and no therapy > LLT only (P < .001).
in identifying women who are at increased risk of CAD events may be an important determinant of the height-
ened morbidity and mortality rates that are observed com-
pared with men.13 When intervention takes place in an expeditious manner, however, the outcome in women is at least comparable with that observed for men.16,17 In PREVENT, specific preselected arteriographic criteria were required for all subjects who were enrolled. Moreover, baseline characteristics were remarkably similar be-
tween men and women. However, despite these similari-
ties, treatment rates were significantly reduced in women. Heightened awareness of this marked discrepancy should facilitate the identification of women who may benefit from closer monitoring of cardiac risk factors. In view of the accumulating data supporting LLT in both men and women,18 more intensive efforts should be initiated at academic medical centers to ensure that all patients with dyslipidemia and CAD are appropri-
ately treated.

Accepted for publication August 19, 1999.

This study was supported by Pfizer Pharmaceuticals Inc, New York, NY.

The PREVENT Investigators include David C. Booth, MD, University of Kentucky, Lexington; Anthony T. Chap-
ekis, MD, Ohio State University, Columbus; Vivian Clark, MD, Wayne State University, Detroit, Mich; Gilles Cote, MD, Montreal Heart Institute, Montreal, Quebec; Robert Feld-
man, MD, Ocala Heart Institute, Ocala, Fla; David M. Herrin-
gton, MD, Wake Forest School of Medicine, Winston-
Salem, NC; Lyall A. J. Higginson, MD, University of Ottawa, Ottawa, Ontario; Craig Hjemdahl-Monsen, MD, New York Medical College, Valhalla; Donald B. Humminghake, MD, University of Minnesota, Minneapolis; Glen J. Kovalchuk, MD, University of North Carolina, Charlotte; Stephen M. Mallon, MD, University of Miami, Miami, Fla; Michael Miller, MD, University of Maryland, Baltimore; K. B. Ra-
amanathan, MD, University of Tennessee, Memphis; Don-
ald Ricci, MD, University of Vancouver, Vancouver, British Columbia; David D. Waters, MD, University of Connecticut, Hartford; Steven W. Werns, MD, University of Michigan, Ann Arbor.

Corresponding author: Michael Miller, MD, Division of Cardiology, SSB06, University of Maryland Hospital, 22 S Greene St, Baltimore, MD 21201 (e-mail: mmiller@heart.umaryland.edu).

REFERENCES

1. Scandinavian Simvastatin Survival Study Group. Randomised trial of choles-

2. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Preven-


4. Downs JR, Cleftfield M, Weis S, et al, for the Air Force/Texas Coronary Athero-
sclerosis Prevention Study (AFCAPS/TexCAPS) Research Group. Primary pre-
vention of acute coronary events with lovastatin in men and women with aver-

5. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in pa-


7. McBride P, Schrott HG, Plane MB, Underbakke G, Brown RL. Primary care prac-
tice adherence to National Cholesterol Education Program guidelines for pa-

8. Harnick DJ, Cohen JL, Schechter CB, Fuster V, Smith DA. Effects of practice set-
ting on quality of lipid-lowering management in patients with coronary artery dis-

9. Byington R, Miller ME, Herrington D, et al, for the PREVENT Investigators. Ra-
tionale, design, and baseline characteristics of the Prospective Randomized Evalua-
tion of the Vascular Effects of Norvasc Trial (PREVENT). Am J Cardiol. 1997;
80:1087-1090.


11. Schrott HG, Bittner V, Vittinghoff E, Herrington DM, Hulley S, for the HERS Re-
search Group. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease: the Heart and Estrogen/ Progestin Replacement Study (HERS) JAMA. 1997;277:1261-1268.

12. Hulsey S, Grady D, Bush T, et al, for the Heart and Estrogen/Progestin Replace-
ment Study (HERS) Research Group. Randomized trial of estrogen plus proges-


ment Investigators. Sex differences in the management of coronary artery dis-

15. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mor-

16. Woodfield SL, Lundercan OF, Reiner JS, et al. Gender and acute myocardial in-
farction: is there a different response to thrombolyis? J Am Coll Cardiol. 1997;
29:35-42.
