Background: The statin treatment of dyslipidemia is associated with a reduced risk of development of Alzheimer disease (AD). The effect may be mediated by a reduction in cholesterol biosynthesis in the brain, by lowering levels of apolipoprotein E (apo E)–containing lipoproteins, or by pleitropic effects such as reduction in \( \beta \)-amyloid production. In the brain, cholesterol from damaged or dying neurons is converted to 24S-hydroxycholesterol by cholesterol 24-hydroxylase (CYP46). The oxysterol is subsequently transferred across the blood-brain barrier, transported to the liver by low-density lipoproteins (LDLs), and excreted as bile acids. Most of plasma 24S-hydroxycholesterol is derived from brain cholesterol; consequently, plasma levels of the oxysterol reflect brain cholesterol catabolism.

Objective: To examine the effect of 3 statins and a non–statin hypolipidemic agent on plasma levels of 24S-hydroxycholesterol and apo E in patients with AD.

Study Design: The study had a sequential parallel design. It was open-labeled and involved lipoprotein and 24S-hydroxycholesterol evaluations at baseline and at 6 weeks of treatment with 40 mg of lovastatin, simvastatin, or pravastatin sodium per day, or 1 g of extended-release niacin per day. Blood samples were drawn after a 12-hour fast for measurement of plasma sterols, oxysterols, lipoprotein cholesterol, and levels of apo E, plasma transaminases, and glucose. Measurements were made at baseline and during treatment.

Results: Statin treatment reduced levels of plasma lathosterol by 49.5%, 24S-hydroxycholesterol by 21.4%, LDL cholesterol by 34.9%, and total cholesterol by 25%. The ratios of lathosterol-campesterol and 24S-hydroxycholesterol–LDL cholesterol were reduced significantly, but the ratio of 24S-hydroxycholesterol–total cholesterol was unchanged. Extended-release niacin also significantly reduced levels of 24S-hydroxycholesterol by 10% and LDL cholesterol by 18.1%. None of the agents lowered plasma concentration of apo E.

Conclusions: Statins lowered levels of plasma 24S-hydroxycholesterol without affecting levels of apo E. The LDL lowering was more pronounced than 24S-hydroxycholesterol reductions. The effect of statins on LDL partially explains the reduction of plasma oxysterol level.

Arch Neurol. 2003;60:510-515

Alzheimer disease (AD) is the most common late-life dementing illness. A central event in the development of AD is thought to be abnormal processing of the cell membrane–associated amyloid precursor protein followed by deposition of toxic \( \beta \)-amyloid protein in the form of amyloid plaques in the extracellular space of the neocortex. It has been demonstrated that amyloid plaques contain apolipoprotein E (apo E), a lipid transporter. It has also been shown that there is a higher frequency of the apo E allele named \( \epsilon 4 \) in patients with AD than in the general population (allele frequency of 40% vs 15%). However, the mechanism of this association is still poorly understood at the molecular level. Another emerging lipid candidate for AD risk is the level of 24S-hydroxycholesterol in plasma. A recent report indicated that levels of plasma 24S-hydroxycholesterol are elevated in patients with AD. The levels of this sterol could be an indication of neuronal cell death, since neuronal degeneration should result in increased release of cholesterol from membranes. In addition, it has been shown that levels of 24S-hydroxycholesterol are higher in subjects with the \( \epsilon 4 \) allele for apo E. However, the prevalence of apo E4 does not explain the higher levels of the sterol in AD. The level of 24S-hydroxycholesterol is high in AD regardless of apo E genotype.

24S-hydroxycholesterol is a product of brain cholesterol metabolism.
enzyme that catalyzes the conversion of cholesterol to 24S-hydroxycholesterol is CYP46. Once the sterol is formed, it traverses the blood-brain barrier and is transported in plasma by low-density lipoprotein (LDL). A small fraction also is transported by high-density lipoprotein. The adult brain synthesizes small amounts of cholesterol; the reaction involves 3-hydroxy-3-methylglutaryl coenzyme A reductase. This enzyme can be inhibited competitively by a class of drugs known as statins. It is therefore of interest to determine whether levels of 24S-hydroxycholesterol can be reduced in subjects with AD during treatment with statins.

METHODS

Subjects were included in the study who met criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Associations for probable AD. None had a history of cardiovascular disease, and none was taking hypolipidemic agents. Patients were excluded if they had a plasma total cholesterol level of less than 160 mg/dL (4.14 mmol/L) or if they had a history of sensitivity to any of the drugs tested in this study. Of those recruited, 6 failed screening (5 had cholesterol levels of greater than 150 mg/dL [1.69 mmol/L] on recruitment into the study (Table 1). They had similar demographic and baseline lipid characteristics among the groups (Table 1) except for body mass index. Levels of LDL cholesterol, lathosterol, 24S-hydroxycholesterol, lactic acid, and very-low-density lipoprotein cholesterol were carried out by repeated-measures analysis of variance. Baseline characteristics among the study groups were compared by 1-way analysis of variance. A P value of .05 was regarded as statistically significant. An SAS statistical software (Statview; SAS Institute Inc, Cary, NC) was used for data analysis.

Patients had baseline levels of plasma total cholesterol of 200 mg/dL (5.17 mmol/L) or more and triglycerides of greater than 150 mg/dL (1.69 mmol/L) on recruitment into the study (Table 1). They had similar demographic and baseline lipid characteristics among the groups (Table 1) except for body mass index. Levels of LDL cholesterol, lathosterol, 24S-hydroxycholesterol, and very-low-density lipoprotein cholesterol were estimated by the Friedewald equation. Levels of apo E were quantified immunochemically by electroimmunoassay as detailed elsewhere.

24S-hydroxycholesterol was quantified by isotope dilution with mass spectrometry. Briefly, tert-butylated hydroxytoluene was mixed with deuterated 24S-hydroxycholesterol and added to a small aliquot of plasma (500 μL). The sample was hydrolyzed with alcoholic potassium hydroxide and sterols were extracted with 2 volumes of chloroform. The lipid extract was dried under nitrogen and the residue was dissolved in tolulene. The sterol mixture was passed through a silica cartridge. Sterols were separated from oxysterols by means of 2 organic solvent mixtures. The oxysterol fraction was derivatized and a small aliquot was injected into a mass spectrometer–gas-liquid chromatography unit (HP 5890; Agilent Technologies, Böblingen, Germany). Oxysterols were separated on a dimethylsilicone column (Ultra-1; Agilent Technologies). 24S-hydroxycholesterol was quantified by selected ion monitoring on a mass selective detector. Ions were monitored at m/z (mass-charge ratio) 413 and m/z 416. The coefficient of variation for the assay is 4%. Quantitation was carried out by area ratios.

Levels of plasma lathosterol, campesterol, and sitosterol were significantly lower than all other subgroups. Levels of apo E were significantly lower than subgroup randomized to lovastatin or extended-release nicotinic acid; P=.04 by unpaired t test.

Table 1. Clinical Characteristics of Patients at Baseline

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Lovastatin (40 mg/d)</th>
<th>Simvastatin (40 mg/d)</th>
<th>Pravastatin Sodium (40 mg/d)</th>
<th>Extended-Release Niacin (1 g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. F/M</td>
<td>4/6</td>
<td>7/3</td>
<td>7/4</td>
<td>6/4</td>
</tr>
<tr>
<td>Age, y</td>
<td>66 ± 8</td>
<td>70 ± 8</td>
<td>74 ± 9†</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>BMI</td>
<td>28.8 ± 5.4</td>
<td>25.4 ± 3.4</td>
<td>23.5 ± 2.5†</td>
<td>27.5 ± 3.4</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>62 ± 7</td>
<td>66 ± 9</td>
<td>68 ± 9</td>
<td>64 ± 8</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>199 ± 21</td>
<td>200 ± 27</td>
<td>210 ± 41</td>
<td>227 ± 27‡</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>163 ± 121</td>
<td>120 ± 72</td>
<td>122 ± 62</td>
<td>194 ± 101</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49 ± 11</td>
<td>55 ± 20</td>
<td>56 ± 17</td>
<td>57 ± 23</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HDL, high-density lipoprotein.

Data are given as mean ± SD, unless otherwise indicated.

*Significantly higher than subgroup randomized to lovastatin or extended-release nicotinic acid; P=.04 by unpaired t test.

†Significantly higher than all other subgroups; P=.05 by 1-way analysis of variance.

‡Significantly lower than all other subgroups; P=.05 by 1-way analysis of variance.

STATISTICAL ANALYSES

Data are summarized as descriptive statistics with mean and SD. Comparisons of baseline with treatment levels of plasma sterols and lipoprotein cholesterol were carried out by repeated-measures analysis of variance. Baseline characteristics among the study groups were compared by 1-way analysis of variance. A P value of .05 was regarded as statistically significant. An SAS statistical software (Statview; SAS Institute Inc, Cary, NC) was used for data analysis.
Table 2. Effect of Treatment on Levels of Plasma LDL Cholesterol and Sterols

<table>
<thead>
<tr>
<th></th>
<th>Lovastatin (40 mg/d)</th>
<th>Simvastatin (40 mg/d)</th>
<th>Pravastatin Sodium (40 mg/d)</th>
<th>Extended-Release Nicotinic Acid (1 g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>126 ± 23</td>
<td>132 ± 21</td>
<td>134 ± 31</td>
<td>138 ± 20</td>
</tr>
<tr>
<td>Lathosterol, mg/dL</td>
<td>0.24 ± 0.08</td>
<td>0.20 ± 0.12</td>
<td>0.23 ± 0.07</td>
<td>0.33 ± 0.12</td>
</tr>
<tr>
<td>Campesterol, mg/dL</td>
<td>58 ± 9</td>
<td>60 ± 14</td>
<td>64 ± 28</td>
<td>60 ± 11</td>
</tr>
<tr>
<td>Sitosterol, mg/dL</td>
<td>0.18 ± 0.09</td>
<td>0.19 ± 0.08</td>
<td>0.26 ± 0.13</td>
<td>0.27 ± 0.14</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>88 ± 18†</td>
<td>80 ± 19†</td>
<td>87 ± 17†</td>
<td>113 ± 26†</td>
</tr>
<tr>
<td>Lathosterol, mg/dL</td>
<td>0.13 ± 0.05†</td>
<td>0.09 ± 0.07†</td>
<td>0.12 ± 0.07†</td>
<td>0.27 ± 0.12†</td>
</tr>
<tr>
<td>Campesterol, mg/dL</td>
<td>46 ± 9†</td>
<td>46 ± 10†</td>
<td>51 ± 24†</td>
<td>54 ± 13†</td>
</tr>
<tr>
<td>Sitosterol, mg/dL</td>
<td>0.13 ± 0.11</td>
<td>0.19 ± 0.10</td>
<td>0.24 ± 0.12</td>
<td>0.21 ± 0.09†</td>
</tr>
</tbody>
</table>

Abbreviation: LDL, low-density lipoprotein.
*Data are given as mean ± SD.
†Significantly different between baseline and treatment by repeated-measures analysis of variance; P < .001.
‡Significantly different between baseline and treatment by repeated-measures analysis of variance; P < .003.

Table 3. Effect of Treatment on Plasma Sterol Ratios

<table>
<thead>
<tr>
<th></th>
<th>All Statins</th>
<th>Extended-Release Nicotinic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
</tr>
<tr>
<td>Lathosterol-campesterol ratio</td>
<td>1.17 ± 0.82</td>
<td>0.63 ± 0.49†</td>
</tr>
<tr>
<td>24S-hydroxycholesterol-total cholesterol ratio</td>
<td>0.29 ± 0.06</td>
<td>0.30 ± 0.07</td>
</tr>
<tr>
<td>24S-hydroxycholesterol-LDL cholesterol ratio</td>
<td>0.46 ± 0.10</td>
<td>0.57 ± 0.16†</td>
</tr>
</tbody>
</table>

Abbreviation: LDL, low-density lipoprotein.
*Data are given as mean ± SD.
†Significantly different between baseline and treatment by repeated-measures analysis of variance; P < .001.

Lovastatin, simvastatin, and pravastatin significantly reduced levels of 24S-hydroxycholesterol, LDL cholesterol, and lathosterol. Extended-release niacin also reduced the levels of 24S-hydroxycholesterol, LDL cholesterol, lathosterol, and phytosterols, but to a lesser extent than the statins (Table 2). The ratios of lathosterol-campesterol, 24S-hydroxycholesterol-total cholesterol, and 24S-hydroxycholesterol-LDL cholesterol remained unchanged (Table 3). Extended-release niacin had no significant effect on the ratios of the sterols.

Levels of plasma apo E were not significantly affected by treatment with statins or extended-release niacin. Average baseline level of apo E for all patients was 5.1 ± 2.7 mg/dL and statin treatment mean was 5.1 ± 3.1 (P = .39); the mean baseline apo E level for the extended-release niacin group was 5.7 ± 3.3 mg/dL and the treatment mean was 5.3 ± 2.2 mg/dL (P = .52).

The results of liver function tests at baseline were as follows: aspartate aminotransferase (AST), 19.3 ± 5.4 IU/L, and alanine aminotransferase (ALT), 16.4 ± 5.1 IU/L. Statin treatment did not change the transaminase levels significantly (AST, 20.6 ± 5.4 IU/L, P = .13; and ALT, 16.8 ± 8.4 IU/L, P = .77). Patients treated with extended-release niacin had no significant changes in the liver aminotransferases (baseline vs treatment AST, 18.0 ± 3.0 IU/L vs 26 ± 23 IU/L, P = .32; baseline vs treatment ALT, 14.5 ± 7.1 IU/L vs 16.6 ± 10.1 IU/L, P = .61). One patient had an increase in AST from a baseline level of 18 IU/L to 92 IU/L during treatment. Plasma glucose levels averaged 80 ± 23 mg/dL (4.4 ± 1.3 mmol/L) during baseline for niacin and during treatment the levels increased to 97 ± 20 mg/dL (5.4 ± 1.1 mmol/L), but the average increment was not statistically significant (P = .06).

Recent studies indicate that the level of 24S-hydroxycholesterol, a major product of brain cholesterol metabolism, is elevated in plasma of patients with AD. In contrast, patients with advanced AD seem to have low levels of 24S-hydroxycholesterol. The sterol is produced from the own lipoprotein system, since cholesterol is not very little from plasma, it must recycle its cholesterol within the CNS. To do so effectively, it must have evolved its own lipoprotein system, since cholesterol is not very

**COMMENT**

Cholesterol composes 22% of the gray matter, 27.5% of the white matter, and 27.7% of myelin in the central nervous system (CNS). However, the synthetic rate of brain cholesterol in adults is very low. Also, in vitro studies have shown that 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis, can be regulated by plasma lipoproteins in primary glial cell cultures. If the brain does not synthesize large amounts of cholesterol and acquires very little from plasma, it must recycle its cholesterol within the CNS. To do so effectively, it must have evolved its own lipoprotein system, since cholesterol is not very
soluble in aqueous media. In recent years, it has been demonstrated that CNS lipoproteins contain apo E, a cholesterol transporter also found in plasma. It also has been shown that brain cholesterol is converted to 24S-hydroxycholesterol in preparation for removal from the CNS.6-7

About 80% of the 24S-hydroxycholesterol present in the body is found in the brain.6-7 In turn, the sterol is excreted from the body by the liver. The sterol must be transferred from the CNS to the plasma compartment. The detailed mechanism of this transfer is poorly understood. However, it has been established that there are 2 major pathways for cholesterol biosynthesis in the brain.20 One pathway involves the conversion of lanosterol to 7-dehydrocholesterol and another involves the conversion of lanosterol to desmosterol and then to cholesterol. In the CNS, oligodendrocytes seem to use the 7-dehydrodesmo-sterol pathway preferentially. The rate of cholesterol synthesis via this pathway correlates with the rate of myelination, and this has been suggested to be the ratelimiting step in brain cholesterol biosynthesis.

Three epidemiologic studies provide evidence that patients treated with statins have a lower prevalence and incidence of AD and of vascular dementia.21-23 It has also been shown that very high doses of simvastatin reduce levels of 24S-hydroxycholesterol in patients with hypercholesterolemia24 and AD.25 However, epidemiologic studies have used standard doses of statins that seemed beneficial to patients with AD. Accordingly, in this study, we used standard doses of statins.

Treatment of AD with statins may require consideration of apo E gene polymorphisms. It has been reported that the prevalence of the apo E4 allele is high in the AD population.3 This may be of importance in the interindividual variation of LDL-sterol response to atorvastatin therapy. Some statin trials26-28 have shown that subjects with at least 1 e4 allele do not respond as well as those with e2 or e3 alleles. However, other studies did not find significant differences in the cholesterol-lowering effects of statins in subjects with different apo E genotypes.30-34 In the current study, apo E genotype was not determined because studies on statin-genotype interactions may require a large AD population to assess the impact of candidate gene polymorphisms on the response to statins.

Statins reduce hepatic synthesis of cholesterol by inhibiting competitively the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase that converts 3-hydroxybutyrate to mevalonic acid. About 90% of the statins are cleared by the liver in the first pass; consequently, levels of the drug are relatively low systemically. Statins also can traverse the blood-brain barrier in varying degrees. For example, lovastatin and simvastatin are more likely to cross the barrier than pravastatin.35,36 It also has been shown that statins have a number of pleiotropic effects. For example, simvastatin and lovastatin reduce levels of intracellular and extracellular Aβ42 and Aβ40 in primary cultures of hippocampal neurons and mixed cortical neurons;37 also, guinea pigs treated with high doses of simvastatin had a reduction in cerebral Aβ42 and Aβ40 levels in the cerebrospinal fluid and in brain homog-enate.37 It has been suggested that the reduced dementia seen in statin-treated patients may be an effect of the drug on Aβ-amyloid protein. Controlled-release lovastatin also decreases Aβ-amyloid peptide in patients with hypercholesterolemia.38,39 Therefore, statins hold promise for intervention in both AD and vascular dementia.

In the current study, 3 statins were used to determine their effect on plasma levels of 24S-hydroxycholesterol. Lovastatin was the first statin used in clinical trials. Simvastatin is more potent than lovastatin. It was used in the Scandinavian Simvastatin Survival trial, the first major clinical trial conducted during a 5-year period that showed efficacy, safety, and long-term reduction in rates of morbidity and mortality from cardiovascular disease.39 Unlike lovastatin and simvastatin, pravastatin does not traverse the blood-brain barrier readily. In the current study, the 3 statins lowered levels of LDL cholesterol effectively. Plasma lathosterol levels also were markedly reduced. Lathosterol is an indicator of de novo cholesterol biosynthesis. Each of the statins significantly reduced the levels of the sterol, demonstrating a marked effect on cholesterol biosynthesis. The effect was also noted with pravastatin, which was unexpected.

The ratios of lathosterol-campesterol were calculated because campesterol is an exogenous phytosterol that was not expected to change as a result of statin treatment, since these drugs do not decrease sterol absorption. Therefore, the ratio of lathosterol-campesterol demonstrates the preferential reduction of lathosterol relative to campesterol, and the ratio is used by some investigators as an index of cholesterol biosynthesis. Since the ratio was reduced by all the statins, it is clear that cholesterol synthesis was reduced. It is also very likely that the ratio reflects a reduction in hepatic cholesterol synthesis, not brain cholesterol synthesis.

Inhibition of hepatic cholesterol biosynthesis results in enhanced expression of LDL receptors on the surface of hepatocytes. This increase in receptor expression likely accounts for the majority of LDL reduction. In the current study, all the statins decreased LDL cholesterol levels. Similarly, the levels of 24S-hydroxycholesterol were reduced. However, the ratio of 24S-hydroxycholesterol/LDL cholesterol was markedly increased, suggesting that the levels of LDL cholesterol were reduced much more than those of 24S-hydroxycholesterol. In contrast, the ratio of 24S-hydroxycholesterol–total cholesterol remained unchanged. The data suggest that part of the oxysterol reduction is mediated by LDL clearance from circulation. However, further work is required to determine the mechanism of 24S-hydroxycholesterol reduction by statins.

This study shows that standard doses of statins reduce 24S-hydroxycholesterol in plasma of patients with AD. Therefore, it would be of interest to determine whether long-term statin therapy would slow AD progression. It would also be of great interest to determine whether the sterol levels are biochemical markers for AD or for AD progression.

Other hypolipidemic agents such as niacin have been shown to have vasodilatory effects. Niacin has a different mechanism of action from statins. The drug reduces hepatic secretion of lipoproteins and raises HDL cholesterol levels. In the current study, extended-release niacin reduced LDL and total cholesterol levels signifi-
cantly; it also reduced levels of 24S-hydroxycholesterol and lathosterol, albeit not as much as the statins. Interestingly, the drug also reduced levels of plasma phytosterols, and this explains the lack of change in lathosterol-campesterol ratios.

In conclusion, the current study shows that statins lower 24S-hydroxycholesterol level by about 20%. This class of drugs may be potentially beneficial in treatment of AD through a direct effect on brain cholesterol metabolism or a pleiotropic effect. Interestingly, extended-release niacin also reduced the oxysterol levels by about 10%. It would be of interest to determine whether a combination of a statin and extended-release niacin has an additive effect on levels of 24S-hydroxycholesterol. If so, the combination would be very useful in therapeutic trials that examine the association of hypolipidemic agents with cognitive function in patients with AD. Additional work remains to be carried out regarding the mechanism involved in reduction of the oxysterol level. This will likely involve tracer studies to determine whether the reduction of 24S-hydroxycholesterol level can be explained by a reduction in the synthesis of the oxysterol. It is also important to confirm previous observations on the effects of statins on β-amyloid protein and emerging markers for AD diagnosis.

Accepted for publication November 11, 2002.

Author contributions: Study concept and design (Drs Vega, Weiner, and Lipton and Ms Svetlik); acquisition of data (Drs Vega, Weiner, Lipton, von Bergmann, and Lütjohann and Ms Moore); analysis and interpretation of data (Drs Vega and von Bergmann); drafting of the manuscript (Drs Vega and Weiner and Mss Moore and Svetlik); critical revision of the manuscript for important intellectual content (Drs Vega, Weiner, Lipton, von Bergmann, and Lütjohann); statistical expertise (Dr Vega); obtained funding (Drs Vega, Weiner, von Bergmann, and Lütjohann); administrative, technical, or material support (Drs Vega, Weiner, and Lipton and Ms Svetlik); study supervision (Drs Vega, Weiner, and Lipton and Mss Moore and Svetlik).

This study was supported in part by a grant from the Wallace, Barbara, and Kelly King Charitable Foundation Trust, the Merit Review Grant of the Veterans Affairs Medical Center, and the Moss Heart Foundation, Dallas, and grant P-30-AG12300 from the National Institute on Aging, Bethesda, Md. Grant BMFT 01EC9402 from the Bundesministerium für Forschung und Technologie in Germany supported the sterol measurements, and General Clinical Research Center grant M01-RR0633 from the National Institutes of Health, Bethesda, Md, supported the statistical consultation.

We express our appreciation for the excellent technical work of Anh Nguyen, Biman Pramanik, MS, and Kevin Vo of the Nutrition and Metabolism Laboratory of the Center for Human Nutrition, and to the clinical staff of the AD Center in Dallas. Anja Kerkisch and Silvia Winnen from Bonn, Germany, measured plasma sterols. Beverley Huett-Adams, MS, biostatistician of the General Clinical Research Center, was a consultant for the statistical analysis of the data.

CORRESPONDING AUTHOR AND REPRINTS: Gloria Lena Vega, PhD, Center for Human Nutrition, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390 (e-mail: Gloria.Vega@utsouthwestern.edu).

REFERENCES

23. Rockwood K, Kirkland S, Hogan DB, et al. Use of lipid-lowering agents, indica-


