Apoprotein E (apoE) plays a central role in the clearance of atherogenic lipoprotein particles from the circulation.1 The APOE gene in humans is polymorphic with 3 common alleles, APOE*2, APOE*3, and APOE*4, which code for apoE2, apoE3, and apoE4. These isoforms differ by the amino acids at positions 112 and 158, where apoE2 has Cys at both sites, apoE4 has Arg at both sites, and apoE3 has Cys-112 and Arg-158. There is a well-established association between the APOE polymorphism and the risk for vascular diseases; individuals with APOE*4 allele have increased plasma cholesterol and an increased risk of atherosclerosis.2,3 Although these increases are modest, they have a large impact on the overall human population, because 25% carry 1 or 2 APOE*4 alleles. However, this association is paradoxical when one considers that apoE4 binds to the LDL receptor (LDLR) with equal or a slightly greater affinity than apoE3, the most common isoform.4–6 Additionally, individuals homozygous for apoE4, which binds to the LDLR with much less affinity than either apoE3 or apoE4, have low plasma cholesterol and are generally protected from atherogenesis, except for the 5% to 10% of apoE2 homozygotes who develop type III hyperlipoproteinemia.1 The present explanation of this paradox is that the high affinity of apoE4 for the receptor leads to increased apoE-mediated cholesterol uptake followed subsequently by downregulation of the LDLR gene. This then leads to reduced apoB100-mediated uptake of LDL, accumulation of LDL cholesterol, and the vascular problems.2,7,8 Conversely, the low affinity of apoE2 is thought to lead to upregulation of LDLR. Although this explanation seems reasonable given that the loss of function of even one LDLR allele leads to markedly elevated plasma LDL and premature atherosclerosis,9,10 it has not been proven.

In the present study, we find that, contrary to the expectations of this hypothesis, increased Ldlr expression in mice with human APOE*4 causes severe atherosclerosis with marked elevation of plasma cholesterol when they are fed a Western-type diet. Mice with APOE*3, on the other hand, are not harmed by the increase in Ldlr expression. Based on these studies, we propose an alternative mechanism that the increased amount of LDLR can trap apoE and deplete the pool of apoE transferable to nascent lipoproteins.

Objective—Increased expression of the low-density lipoprotein receptor (LDLR) is generally considered beneficial for reducing plasma cholesterol and atherosclerosis, and its downregulation has been thought to explain the association between apolipoprotein (apo) E4 and increased risk of coronary heart disease in humans.

Methods and Results—Contrary to this hypothesis, doubling Ldlr expression caused severe atherosclerosis with marked accumulation of cholesterol-rich, apoE-poor remnants in mice with human apoE4, but not apoE3, when the animals were fed a Western-type diet. The increased Ldlr expression enhanced in vivo clearance of exogenously introduced remnants in mice with apoE4 only when the remnants were already enriched with apoE4. The rates of nascent lipoprotein production were the same. The adverse effects of increased LDLR suggest a possibility that the receptor can trap apoE4, reducing its availability for the transfer to nascent lipoproteins needed for their rapid clearance, thereby increasing the production of apoE-poor remnants that are slowly cleared. The lower affinity for the LDLR of apoE3 compared with apoE4 could then explain why increased receptor expression had no adverse effects with apoE3.

Conclusions—Our results emphasize the occurrence of important and unexpected interactions between APOE genotype, LDLR expression, and diet. (Arterioscler Thromb Vasc Biol. 2004;24:91-97.)

Key Words: apolipoprotein E isoforms • atherosclerosis • genetic interaction • lipid metabolism • postprandial hypercholesterolemia

Received July 2, 2003; revision accepted August 27, 2003.
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Arterioscler Thromb Vasc Biol is available at http://www.atvbaha.org DOI: 10.1161/01.ATV.0000094963.07902.FB

91
TABLE 1. Keys to the Shorthand Definition of Mice Described in This Study

<table>
<thead>
<tr>
<th>Mice</th>
<th>Genotype</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3m</td>
<td>Apoe&lt;sup&gt;3&lt;/sup&gt;Ldlr&lt;sup&gt;+/+&lt;/sup&gt;</td>
<td>Mice with human apoE3</td>
</tr>
<tr>
<td>3h</td>
<td>Apoe&lt;sup&gt;3&lt;/sup&gt;Ldlr&lt;sup&gt;h/&lt;/sup&gt;</td>
<td>Mice with human apoE3 and increased LDLR</td>
</tr>
<tr>
<td>4m</td>
<td>Apoe&lt;sup&gt;4&lt;/sup&gt;Ldlr&lt;sup&gt;+/+&lt;/sup&gt;</td>
<td>Mice with human apoE4</td>
</tr>
<tr>
<td>4h</td>
<td>Apoe&lt;sup&gt;4&lt;/sup&gt;Ldlr&lt;sup&gt;h/&lt;/sup&gt;</td>
<td>Mice with human apoE4 and increased LDLR</td>
</tr>
<tr>
<td>4KO</td>
<td>Apoe&lt;sup&gt;4&lt;/sup&gt;Ldlr&lt;sup&gt;h/-&lt;/sup&gt;</td>
<td>Mice with human apoE4 and no LDLR</td>
</tr>
<tr>
<td>2m</td>
<td>Apoe&lt;sup&gt;2&lt;/sup&gt;Ldlr&lt;sup&gt;h/&lt;/sup&gt;</td>
<td>Mice with human apoE2</td>
</tr>
<tr>
<td>2h</td>
<td>Apoe&lt;sup&gt;2&lt;/sup&gt;Ldlr&lt;sup&gt;h/-&lt;/sup&gt;</td>
<td>Mice with human apoE2 and increased LDLR</td>
</tr>
</tbody>
</table>

Methods

Mice heterozygous for targeted replacement of the mouse Ldlr gene with the human LDLR minigene (Apoe<sup>3</sup>/Ldlr<sup>h</sup>)<sup>11</sup> were bred to mice homozygous for replacement of the mouse apoE gene with either the human APOE<sup>3</sup> or APOE<sup>4</sup> allele (Apoe<sup>3</sup>Ldlr<sup>h</sup> and Apoe<sup>3</sup>Ldlr<sup>h</sup>)<sup>11</sup>. The experimental animals were mostly littersmates generated by crossing Apoe<sup>3</sup>Ldlr<sup>h</sup> (3m) with Apoe<sup>3</sup>Ldlr<sup>h</sup> (3h) and Apoe<sup>4</sup>Ldlr<sup>h</sup> (4m) with Apoe<sup>4</sup>Ldlr<sup>h</sup> (4h), respectively. Mice with human APOE<sup>4</sup> and lacking LDLR (4KO) were generated by crossing Apoe<sup>4</sup> and Ldlr<sup>−−</sup> mice (see Table 1 for the definition of the shorthand designation of the mice used in this study). All mice were hybrids between 129 and C57BL/6, having approximately one fourth to one eighth of their genome from 129 and the remaining three fourths to seven eighths from C57BL/6. Twelve- to 36-week-old mice of both sexes were used for experiments that were conducted under protocols approved by the Institutional Animal Care and Use Committees. Littersmates were used in each experiment as much as possible. Mice were fed either normal mouse chow (NC) containing ≈4.5% (wt/wt) fat and 0.022% (wt/wt) cholesterol (Prolab RMH 3000, Agway Inc) or a high-fat Western-type diet (HFW) containing 21% (wt/wt) fat and 0.2% (wt/wt) cholesterol (TD88137; Teklad). Experimental procedures can be found online at http://atvb.ahajournals.org.

Results

Increased Ldlr expression causes hypercholesterolemia in mice with human APOE<sup>4</sup>. We replaced the endogenous mouse Ldlr with a minigene coding for human LDLR (Ldlr<sup>H</sup>) that produces an mRNA with an increased half-life<sup>11</sup> and introduced 1 copy of this Ldlr<sup>H</sup> allele into mice expressing solely apoE3 (Apoe<sup>3</sup>) or apoE4 (Apoe<sup>4</sup>;<sup>6,12</sup>). When mice were fed NC, the increase in Ldlr expression significantly lowered the plasma lipids in both Apoe<sup>3</sup>Ldlr<sup>h</sup> (3h) and Apoe<sup>4</sup>Ldlr<sup>h</sup> (4h) mice, relative to the Apoe<sup>3</sup>Ldlr<sup>−</sup> (3m) or Apoe<sup>4</sup>Ldlr<sup>−</sup> (4m) mice (Table 2). The Ldlr genotype had highly significant effects on total cholesterol (TC), triglyceride (TG), and HDL cholesterol (HDL-C) (P<0.0001). The effects of the Apoe genotype on TC and HDL-C were not significant, but females with apoE4 tended to have higher TG than those with apoE3 whereas males with apoE3 tended to have higher TG than those with apoE4 (P=0.0002 for Apoe, sex interaction). All classes of plasma lipoproteins including HDL were reduced in mice with increased LDLR, as assayed by FPLC analysis (Figure 1A, ○).

Feeding a HFW increased the plasma TC and the HDL-C levels of all of the mice (Table 2). Surprisingly, however, the increase in plasma TC was much greater in the 4h mice than in 4m mice (120±11 versus 32.5±2 mg/dL, P<0.0001). This increase resulted mainly from a dramatic accumulation of non-HDL particles that elute in the VLDL region during fast performance liquid chromatography (FPLC, Figure 1A, ○). In contrast, the 3h mice on HFW showed only a small increase in non-HDL particles, and they had significantly lower cholesterol levels than the 3m mice primarily because of reduced HDL. Thus, the Ldlr genotype has markedly different effects on the response to HFW in mice with apoE4 compared with those with apoE3.

The 4h remnants were mostly in very low to intermediate density fractions (d<1.02 g/mL) by ultracentrifugation and were enriched in TC but poor in TG, with a TC/TG ratio of 4.5 compared with 0.6, 0.6, and 1.2 in 4m, 3m, and 3h remnants, respectively. The apolipoprotein compositions of

TABLE 2. Plasma TC, TG, and HDL-C

<table>
<thead>
<tr>
<th>Mice Genotype (Apoe, Ldlr)</th>
<th>Sex</th>
<th>TC, mg/dL</th>
<th>TG, mg/dL</th>
<th>HDL-C, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NC / HFW</td>
<td>NC / HFW</td>
<td>NC / HFW</td>
</tr>
<tr>
<td>3m (3/3, +/+)</td>
<td>M</td>
<td>95±4(14)</td>
<td>114±12(14)</td>
<td>79±6 (14)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>66±3(18)</td>
<td>106±10 (9)</td>
<td>40±4 (18)</td>
</tr>
<tr>
<td>3h (3/3, h/+)</td>
<td>M</td>
<td>53±4 (22)</td>
<td>72±8 (12)</td>
<td>44±5 (22)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>37±4 (11)</td>
<td>92±9 (7)</td>
<td>27±4 (11)</td>
</tr>
<tr>
<td>4m (4/4, +/+)</td>
<td>M</td>
<td>78±3 (30)</td>
<td>124±8 (34)</td>
<td>54±2 (29)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>63±4 (16)</td>
<td>114±6 (28)</td>
<td>49±5 (16)</td>
</tr>
<tr>
<td>4h (4/4, h/+)</td>
<td>M</td>
<td>52±4 (28)</td>
<td>187±19 (22)</td>
<td>35±2 (29)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>53±4 (29)</td>
<td>199±17 (27)</td>
<td>34±4 (29)</td>
</tr>
</tbody>
</table>

| Sex effects | P=0.005 | NS | P<0.0001 | NS | P=0.001 | NS |
| Apoe effects | P<0.0001 | P=0.04 | NS | NS | NS | NS |
| Ldlr effects | P<0.0001 | P=0.03 | P<0.0001 | P=0.003 | P<0.0001 | P<0.0001 |
| Apoe × Ldlr interaction | P=0.01 | P<0.0001 | NS | NS | NS | NS |

Values are mean±SE. The effects of sex and 2 genotypes were estimated with three-way factorial analysis of pooled data for both sexes. Numbers of animals are in parentheses.
the VLDL fraction also differed significantly (Figure 1B). Densitometric analysis of at least 4 different preparations of the VLDL fractions showed that the 4h remnants had a marked reduction of apoE4 (×0.4) but increased apoB48 (×6.7) and apoAIV (×4.7) compared with 4m remnants. ApoE3 in the 3h remnants was also reduced (×0.5) compared with 3m remnants, but the increase in apoB48 (×3) was less prominent. The 4h remnant fraction contains an average of 4.5 times more apoB proteins than that of the 3h mice and had a smaller apoE/apoB ratio (8±1% relative to that in 4m) compared with 36±4% in 3h fraction (P<0.005). Thus, the remnants of the 4h mice are cholesterol-rich, TG-poor, and apoE-poor compared with those of the 3h mice.

The enrichment of apoAIV in the 4h remnants suggests that they are mainly from intestine-derived chylomicrons. Consistent with this possibility, plasma cholesterol levels declined steadily in fasting 4h mice but not in 4m mice (Figure 2A) and remnant particles were reduced in 4h mice fasted for 18 hours or longer. There were no significant differences in the TC and TG content in the livers of these mice. The relative amounts of apoE protein estimated by Western blot analysis indicate that the elevated LDLR expression increases liver-associated apoE by 30% but reduces plasma apoE by 60% regardless of their apoE genotype.

The level of mouse Ldlr mRNA in the liver of 4h mice with a single copy of the gene was ≈61% of that in 4m mice with 2 copies (100%, Figure 2B). The human Ldlr message was ≈155% (total, 216%). The regulatory machinery of the Ldlr allele is intact, because HFW downregulated the mouse and human Ldlr messages equally to ≈60% of their levels in mice fed NC. The total Ldlr mRNA level in 4h mice fed HFW was

Figure 1. Plasma lipoproteins. A, FPLC of plasma lipoproteins of mice fed NC (○) and HFW (●). Plasma was pooled from at least 6 male mice of each genotype. Fractions containing VLDL, LDL, and HDL are indicated. B, SDS polyacrylamide gel electrophoresis. Plasma was collected from mice fed HFW and separated by ultracentrifugation. Lanes 1 through 7 are density fractions d<1.006, 1.006<d<1.02, 1.02<d<1.04, 1.04<d<1.06, 1.06<d<1.08, 1.08<d<1.10, and 1.10<d<1.21, respectively. Positions of apolipoproteins are indicated on the left.

Figure 2. Effects of increased LDLR expression on mice with human apoE4 on HFW. A, Fasting effects on plasma cholesterol levels in male 4h (●, n=8) and 4m (○, n=8) mice on HFW. Error bars are SEM. *P<0.001 by MANOVA. †P<0.001 and ‡P<0.05 between genotypes by 2-tailed Student’s t test. B, Liver mRNA levels for the mouse Ldlr (black bars) and for the human Ldlr (white bars) expressed as percent of the Ldlr gene expression in 4m mice on NC. Numbers of animals (all males) are shown in the bottom of the bars. Error bars are SEM. *P<0.0001 for diet effect, †P<0.0005 for Ldlr genotype effect by 2-way ANOVA. The effect of Apoe genotype is not significant.
**Severe Atherosclerosis in 4h But Not 3h Mice on HFW Diet**

Accumulation of remnant particles and reduction of HDL-cholesterol in HFW-fed 4h mice is a high-risk profile for atherosclerosis, even though the average plasma total cholesterol of these mice is only marginally elevated (≈200 mg/dL). We therefore evaluated the development of atherosclerosis in mice fed HFW containing 21% fat and 0.5% cholesterol for 3 months. No plaques were found in any of the 3m mice (5 females) or 4m mice (8 females and 5 males) on HFW. Similarly, none of the 7 female 3h mice on HFW developed plaques (Figure 4A). In contrast, all of the 15 female and 7 male 4h mice on HFW developed significant plaques at the aortic sinus area (Figures 4B through 4D) with average plaque sizes of 59±15×10^4 μm^2 in females and 22±7×10^4 μm^2 in males. Although the numbers and sizes of plaques varied in individual animals, most of the mice had mature complex plaques with fibrous caps, necrotic lipid cores, cholesterol clefts, and calcifications (Figures 4C and 4D). Thus, mice having human APOE*4 and a moderately increased amount of LDLR develop significant atherosclerosis when fed a diet similar in composition to that of Western societies.

### Discussion

Our clear demonstration of hypercholesterolemia and atherosclerosis in mice that have human apoE4, but not apoE3, replicates in mice fed a Western diet the paradoxical association between APOE polymorphisms and the risk of atherosclerosis in humans. However, contrary to the currently accepted hypothesis that downregulation of LDLR in individuals with an APOE*4 allele is the cause of their high plasma...
cholesterol levels, we find that these isoform-specific effects are only present when LDLR is increased. How can increased LDLR expression ever be harmful? We suggest that this is because the LDLR, under some circumstances, traps sufficient apoE and the supply becomes inadequate to process a high dietary intake of lipids. Exchange of apoE onto nascent triglyceride-rich lipoproteins is a necessary prerequisite for their internalization via LDLR. The overall process that we envision is illustrated in Figure 5.

Figure 4. Representative atherosclerotic plaques in the aortic sinus of mice fed HFW for 3 months. A, 3h female; B, 4h female; C, 4h male; and D, 4h female. Frozen sections were stained with Sudan IVB for lipids and counterstained with hematoxylin. Black arrowheads indicate fibrous caps. Yellow and blue arrows designate calcification and cholesterol clefts, respectively. L indicates lumen; M, media; and A, adventitia. Scale bars=500 μm in a and b and 100 μm in c and d.

Figure 5. ApoE trapping by the LDLR. Triglyceride-rich chylomicrons (yellow) secreted by the intestine into lymph are remodeled to transient particles (orange) mainly in capillaries and in the space of Disse in the liver. This initial capturing phase is very rapid and does not depend on the LDLR; it probably involves heparan sulfate proteoglycans that facilitate lipolysis and apolipoprotein exchange. Enrichment with apoE is a requirement for the fast internalization of the transient particles primarily via LDLR-mediated endocytosis. Otherwise, the particles are additionally processed to cholesterol-enriched remnants (red) that are slowly cleared from the plasma. The lipid composition of the remnants in plasma depends on both Apoe genotype and the amount of LDLR. The processing of liver-derived VLDL particles is likely to be similar to that illustrated for chylomicrons.

ApoE4 may be particularly susceptible to this trapping because of its strong affinity for the LDLR. Transient particles that fail to acquire apoE4 are excellent substrates for lipases, and the resulting enhanced lipolysis will increase cholesterol-rich apoE-poor remnant particles in plasma. We suggest that apoE3 is less susceptible to trapping than apoE4, perhaps because of its somewhat lower affinity for the LDLR. Consequently, the 3h mice have sufficient apoE3 to
process nascent lipoproteins for rapid internalization. This differential transfer of apoE3 and apoE4 to lipoproteins can also explain our previous observation that in vivo clearance of exogenously introduced remnants is significantly faster in 3m mice than in 4m mice.6

Previously we reported that mice expressing solely apoE2 (2m) show features typical of type III hyperlipoproteinemia in humans18 but that increased LDLR expression in these mice (2h) completely ameliorates their hyperlipoproteinemia.11 According to our hypothesis, apoE2 with its very low affinity for the LDLR should be virtually free from trapping and should therefore be efficiently transferred to transient TG-rich particles. Although such an apoE2 enrichment of TG-rich particles is likely to increase their LDLR-mediated internalization, it will also severely inhibit lipolysis1 and could account for the prominent accumulation of TG-rich remnants seen in the circulation of the 2m mice.18 In the 2h mice, however, high LDLR expression tips the balance toward more internalization and lowers their plasma cholesterol.11

Clearly, additional studies are necessary to refine and test our proposed apoE trapping by the LDLR. For example, we do not know whether it occurs on the cell surface, as illustrated in Figure 5, or during intracellular trafficking.19,20 The word trapping should not be taken too literally; difference in the interaction between apoE and LDLR or their subsequent processing may result not only from differences in binding affinities but also from other properties influenced by the specific amino acids that differ among 3 isoforms. Interactions of apoE with other molecules, such as proteoglycans and hepatic lipase, that are also expressed on the basolateral microvilli of hepatocytes may also influence the apoE interaction with LDLR in an isoform-specific fashion. Published studies have shown that newly synthesized apoE is incompletely secreted and partially degraded in HepG2 cells in culture21 and a significant portion of apoE synthesized by macrophages undergoes rapid cellular degradation in a nonlysosomal compartment in a sterol-regulated manner.22 Although the role of LDLR in these processes has not been addressed, LDLR is known to bind to newly synthesized apoE in macrophages and limits its secretion.23 LDLR expression in macrophages could also contribute to atherosclerosis in an apoE isoform–specific fashion. For example, a differential effect on cholesterol homeostasis in macrophages by apoE isoforms with apoE4 being least effective in promoting cholesterol efflux from macrophage has been reported.24 Additionally, Linton et al25 have shown that C57BL/6 mice receiving Ldlr–/– marrow developed 63% smaller lesions than mice receiving Ldlr+/– marrow after dietary atherogenic stimuli, demonstrating that macrophage LDLR affects the rate of foam cell formation under conditions of dietary stress.

Some comments are required on the relevance of our findings in mice to the effects of different APOE genotypes in humans. We note that 4h mice preferentially accumulate apoB48-containing lipoproteins of an intermediate density, whereas humans with the APOE*4 allele mainly have elevated levels of apoB100-containing LDL.2 This is not incompatible with our hypothesis, which predicts that trapping of apoE4 by the LDLR will hinder enrichment of VLDL remnants with apoE4, thereby leading to an increase in their conversion to LDL. Because the clearance of LDL particles mediated by binding apoB100 to the receptor is much slower than apoE-mediated VLDL clearance,1,15 we expect that the plasma cholesterol levels in individuals with apoE4 will be increased. Supporting this explanation, an increased conversion of VLDL to smaller remnants and a relative decrease in direct removal of VLDL in APOE*4 homozygotes compared with APOE*3 subjects have been demonstrated.26

Our finding that hypercholesterolemia is seen only when the 4h mice are fed HFW diet is also consistent with observations that human subjects carrying the APOE*4 allele are more responsive than others to LDL cholesterol–lowering by diet.27,28 In addition, some though not all studies have found prolonged postprandial lipemia in normalolipemic subjects that carry APOE*4.29–32 Bergeron and Havel29 have proposed that prolonged residence times of chylomicron and VLDL remnants in persons with APOE*4 raise the concentration of LDL by increasing the amount of VLDL converted to LDL. We additionally note that an apoE5 variant with lysine in place of glutamic acid at position 3 is also associated with hyperlipidemia and atherosclerosis and it has a twice-normal LDLR binding activity.33 Finally, some although not all studies have shown that the cholesterol-lowering effects of statins, thought to be primarily mediated by increased LDLR, are apoE isoform–dependent. In these studies, individuals with the APOE*3/4 and APOE*4/4 genotypes had significantly smaller LDL cholesterol reductions in response to statin treatment than those with the APOE*3/3 genotype.34,35 Clinical studies clearly indicate that statin therapies reduce the risk of cardiovascular disease in humans, including those with apoE4, and no serious adverse effects on plasma lipids have been reported.35,36 Nevertheless, our observations suggest the need for additional studies of the interaction between the cholesterol-lowering effect of statins and genetic variations.

In conclusion, our studies demonstrate that, contrary to the presently accepted downregulation of LDLR hypothesis, increased LDLR has harmful effects in Western diet–fed mice expressing human apoE4 and causes marked accumulation of apoE-poor lipoprotein remnants in plasma and severe atherosclerosis. The alternative mechanism of apoE-trapping by LDLR explains our observations and offers a plausible explanation why apoE4, which has a greater affinity for the LDLR than apoE3, is associated with higher plasma cholesterol and a greater risk of atherosclerosis in humans. Our unexpected findings in mice predict important interactions between APOE genotype, LDLR expression, and diet.

Acknowledgments
This work was supported by grants from NIH (HL42360 to N.M., HL54176 and HL49373 to J.S.P., and HL07115 to L.L.F.). The authors thank Dr Tom Smith for the jugular vein injection during the lipoprotein clearance experiments, Drs Greg Shelness, Leighton James, and Oliver Smithies for discussion, and Jennifer Altenburg and Ellen Young for technical assistance.

References


Harmful Effects of Increased LDLR Expression in Mice With Human APOE*4 But Not APOE*3
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Arterioscler Thromb Vasc Biol. 2004;24:91-97; originally published online September 11, 2003;
doi: 10.1161/01.ATV.0000094963.07902.FB
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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