Diet-Induced Occlusive Coronary Atherosclerosis, Myocardial Infarction, Cardiac Dysfunction, and Premature Death in Scavenger Receptor Class B Type I–Deficient, Hypomorphic Apolipoprotein ER61 Mice

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Background—Normal chow (low fat)–fed mice deficient in both the HDL receptor SR-BI and apolipoprotein E (SR-BI/apoE dKO) provide a distinctive model of coronary heart disease (CHD). They exhibit early-onset hypercholesterolemia characterized by unesterified cholesterol–rich abnormal lipoproteins (lamellar/vesicular and stacked discoidal particles), occlusive coronary atherosclerosis, spontaneous myocardial infarction, cardiac dysfunction, and premature death (≈6 weeks of age). Mice in which similar features of CHD could be induced with a lipid-rich diet would represent a powerful tool to study CHD.

Methods and Results—To generate a diet-inducible model of CHD, we bred SR-BI–deficient (SR-BI KO) mice with hypomorphic apolipoprotein E mice (ApoeR61h/h) that express reduced levels of an apoE4-like murine apoE isoform and exhibit diet-induced hypercholesterolemia. When fed a normal chow diet, SR-BI KO/ApoeR61h/h mice did not exhibit early-onset atherosclerosis or CHD; the low expression level of the apoE4-like murine apoE was atheroprotective and cardioprotective. However, when fed an atherogenic diet rich in fat, cholesterol, and cholate, they rapidly developed hypercholesterolemia, atherosclerosis, and CHD, a response strikingly similar to that of SR-BI/apoE dKO mice fed a chow diet, and they died 32±6 days (50% mortality) after initiation of the high-fat feeding.

Conclusions—The SR-BI KO/ApoeR61h/h mouse is a new model of diet-induced occlusive coronary atherosclerosis and CHD (myocardial infarction, cardiac dysfunction and premature death), allowing control of the age of onset, duration, severity, and possibly regression of disease. Thus, SR-BI KO/ApoeR61h/h mice have the potential to contribute to our understanding of CHD and its prevention and treatment. (Circulation. 2005;111:3457-3464.)

Key Words: apolipoproteins ▪ atherosclerosis ▪ diet ▪ myocardial infarction ▪ receptors
apoE and the HDL receptor scavenger receptor class B, type I (SR-BI).8–10 the SR-BI/apoE double-KO, or dKO, mouse. SR-BI mediates cellular selective uptake of cholesteryl esters, cholesteryl, and other lipids from HDL and promotes efflux of unesterified cholesterol from cells to HDL.11–18 SR-BI KO mice fed a normal chow diet are hypercholesterolemic and exhibit reduced biliary cholesterol secretion, but they have not been observed to develop atherosclerosis or CHD.8,9,19 These single-KO mice do, however, exhibit significantly greater atherosclerosis in the aortic root compared with that in wild-type (WT) controls when fed a high-fat/high-cholesterol Western-type diet (15% [wt/wt] fat and 0.25% [wt/wt] cholesterol) for 5 months.20 SR-BI/apoE dKO mice fed a normal chow diet (low fat) exhibit hypercholesterolemia (∼1000 mg/dL), as well as extensive atherosclerotic plaque (plaques with fibrous caps, fibrin deposition, cholesterol clefts), severe CHD (heart enlargement, MI, cardiac dysfunction such as reduced systolic function and ejection fraction, ECG abnormalities), and very early spontaneous death at 6 weeks of age (range, 5 to 8 weeks).8–10

In the present study, we have generated a murine model in which the many features of human CHD exhibited by SR-BI/apoE dKO mice could be induced by feeding a high-fat, high-cholesterol, and cholic acid–containing (HFC) diet. We constructed this model by breeding SR-BI KO mice with hypomorphic apolipoprotein E (ApoeR61h/h) mice21,22 to generate SR-BI KO/ApoeR61h/h mice. ApoeR61h/h mice express a mutant form of murine apoE, Thr61→Arg61 (Arg-61 apoE), in place of WT apoE at substantially lower plasma concentrations (2% to 5%) than apoE in control WT mice.22 Arg-61 apoE has structural and lipoprotein binding characteristics similar to those of the apoE4 isoform of human apoE.21 Despite the low plasma concentration of Arg-61 apoE in ApoeR61h/h mice, they display a nearly normal lipoprotein cholesterol profile when fed a chow diet.21,22 However, when fed the HFC diet, ApoeR61h/h mice develop severe hyperlipidemia and a lipoprotein profile reminiscent of that of apoE KO mice.21,22 When SR-BI KO/ApoeR61h/h mice were fed a normal chow diet, they were active and healthy and exhibited no evidence of CHD or early death. However, when challenged with the HFC diet, they developed severe hypercholesterolemia and oclusive atherosclerotic CHD (hypertrophy, MI, cardiac dysfunction) and died 32±6 days (50% mortality) after initiation of the HFC feeding. Their cardiovascular pathology was strikingly similar to that of SR-BI/apoE dKO mice fed a chow diet. Thus, SR-BI KO/ApoeR61h/h mice represent a new and powerful murine model to study CHD and MI.

Methods

Animals and Diets

All mice were on mixed C57BL/6j129 backgrounds (either 50/50: WT, SR-BI KO, ApoeR61h/h, SR-BI KO/ApoeR61h/h; or 75/25: apoE KO, SR-BI/apoE dKO) and housed as previously described.8,9,19 Genotypes were determined by polymerase chain reaction.19,22 As anticipated from previous studies of SR-BI KO mice, female, but not male, SR-BI KO/ApoeR61h/h mice are infertile. Thus, female ApoeR61h/h mice with heterozygous null mutations in SR-BI were mated to generate the SR-BI KO/ApoeR61h/h mice. Mice were fed a normal chow (low fat) diet (4.5% fat, 0.022% cholesterol, Prolab 3000, PMI Feeds) or an HFC diet (7.5% cocoa butter, 15.8% fat, 1.25% cholesterol, 0.5% sodium cholate, TD 88051, Harlan-Teklad) as indicated. Unless otherwise noted, animals were fed either the normal diet or the HFC diet for 4 weeks immediately before analysis at 3 months of age. Experiments were performed in accordance with the guidelines of the Committee on Animal Care at the Massachusetts Institute of Technology.

Morphological, Biochemical, and Cardiac Functional Analyses

Histology was performed as previously described with frozen sections (10 μm) using Masson’s trichrome (Sigma) or oil red O and hematoxylin.8–10 Atherosclerosis lesion sizes were calculated as the sum of the cross-sectional areas of oil red O–staining atherosclerotic plaque in a section using image measure/SPOT software (Diagnostic Instruments).8 Plasma cholesterol, phospholipid, and triglyceride (TG) determinations were measured with kits (Wako Chemical USA Inc.).10 Two-dimensional and M-mode echocardiograms were performed under very light sedation.23 ECGs were recorded and analyzed at the Massachusetts Institute of Technology. All other methods were as previously described, including gravimetry, fast protein liquid chromatography plasma fractionation,10 immunoblot analyses of the apolipoproteins,8,19,22 and electron microscopy of phosphotungstic acid–negatively stained lipoproteins from fast protein liquid chromatography fractions.24 No substantial differences were observed between males and females. A value of P<0.05 for differences was considered significant (2-tailed, unpaired Student t test or ANOVA test for groups calculated with Microsoft Excel or StatView).

Results

An Atherogenic Diet Induces Premature Death in SR-BI KO/ApoeR61h/h Mice

The SR-BI KO/ApoeR61h/h mice were healthy and active when fed a chow diet (low fat), with body weights similar to those of controls at both weaning, 3.5 weeks (WT, 13.0±0.7 g, n=8; SR-BI KO, 13.3±1.0 g, n=5; ApoeR61h/h, 13.0±0.6 g, n=6; SR-BI KO/ApoeR61h/h, 13.2±1.4 g, n=7), and 2 months of age (WT, 21.9±2.4 g, n=6; SR-BI KO, 21.4±3.5 g, n=6; ApoeR61h/h, 22.3±3.8 g, n=9; SR-BI KO/ApoeR61h/h, 23.0±4.1 g, n=10). When chow-fed 2-month-old mice were fed an atherogenic HFC diet rich in fat and cholesterol (7.5% cocoa butter, 15.8% fat, 1.25% cholesterol, 0.5% sodium cholate) for 4 additional weeks, all control mice gained weight (13% to 18%), whereas SR-BI KO/ApoeR61h/h mice lost 14% of their 2-month weight (WT, 24.7±1.0 g, n=6; SR-BI KO, 27.5±3.8 g, n=6; ApoeR61h/h, 26.3±5.0 g, n=9; SR-BI KO/ApoeR61h/h, 19.8±3.4 g, n=10; P<0.0001, ANOVA). When challenged with the HFC diet starting at 25, 60, or 172 days of age, all SR-BI KO/ApoeR61h/h mice but none of the controls died within 7 weeks (Figure 1). The durations of dietary challenge that resulted in 50% mortality were as follows: 31±6.5 days (range, 25 to 43 days, initiated at 25 days); 33±4.9 days (range, 25 to 38 days, initiated at 60 days); 33±7.5 days (range, 24 to 48 days, initiated at 172 days; P=0.693; Figure 1). Thus, the developmental status/age of the mice when HFC feeding began (puberty, younger, and older adult) did not significantly alter the time course of disease progression (combined data: mean, 32±6.1 days; range, 24 to 48 days; n=39). One or 2 days before death, the mice exhibited huddling, shivering, shaking, ruffled fur, and reduced activity that we have
previously observed just before death in SR-BI/apoE dKO mice fed a normal chow diet.9

Plasma Lipids and Lipoproteins

To determine the effects of HFC feeding on the plasma lipoproteins of SR-BI KO/ApoeR61/h/h and control mice, we measured plasma lipids and lipoprotein cholesterol profiles. Figure 2A shows the lipoprotein cholesterol profiles and plasma apoE levels (determined by immunoblotting) in chow-fed SR-BI KO, SR-BI KO/ApoeR61/h/h and SR-BI/apoE dKO mice. The profile for SR-BI KO/ApoeR61/h/h mice was similar to that of SR-BI KO mice (slightly larger size, lower elution volume, HDL-like particles in SR-BI KO/ApoeR61/h/h mice) and substantially different from that of SR-BI/apoE dKO mice that have very high levels of large VLDL-sized lipoprotein particles.8–10,19 Thus, relative to SR-BI/apoE dKO mice that express no apoE, the low expression levels of Arg-61 apoE (Figure 2A, inset) in the context of total SR-BI deficiency in SR-BI KO/ApoeR61/h/h mice reduced the total cholesterol levels by 71% to 282 mg/dL (see Table 1), generating a lipoprotein profile similar to that of SR-BI KO mice (also see online Data Supplement Figure for additional profiles of chow-fed controls). Figure 2B through 2F and Table 1 show the results for 3-month-old mice fed the HFC diet for 4 weeks. The relative levels of plasma total cholesterol (Table 1) were as follows: WT, 1.0; SR-BI KO, 3.2; ApoeR61/h/h, 5.7; apoE KO, 12.8; and SR-BI KO/ApoeR61/h/h, 7.0. The lipoprotein profile of SR-BI KO/ApoeR61/h/h/HFC mice (Figure 2B through F) is similar to the profile previously reported for SR-BI/apoE dKO mice fed a chow diet (Figure 2F), although the total cholesterol levels in the chow-fed SR-BI/apoE dKO mice were lower (see Table 1, Data Supplement Figure, and Reference 8). Most of the increased plasma cholesterol in the SR-BI KO/ApoeR61/h/h/HFC mice relative to the WT/HFC, SR-BI KO/HFC, and ApoeR61/h/h/HFC controls was due to an increase in large, VLDL-sized particles. The difference in plasma total cholesterol levels between SR-BI KO/ApoeR61/h/h/HFC and apoE KO/HFC mice primarily arose from a substantially higher level of 

cholesterol in intermediate-density lipoprotein (IDL)/LDL- to VLDL-sized particles in the apoE KO/HFC mice (Figure 2E). The most striking differences between the plasma lipids in SR-BI KO/ApoeR61/h/h/HFC mice and control mice that did not exhibit rapid, diet-induced death (Table 1) were higher TG levels (1.8- to 5.2-fold), a greater ratio of unesterified to total cholesterol (0.8 versus 0.23 to 0.65), and a greater ratio of surface (phospholipids, unesterified cholesterol) to core (TG, cholesteryl esters) lipid (6 versus 1 to 3). These controls included mice (WT, SR-BI KO, ApoeR61/h/h, apoE KO) fed the HFC diet and controls fed a chow diet. The significance of the relatively high TG is unclear. The high ratio of
unesterified to total cholesterol and associated high ratio of surface to core lipid result in the formation of numerous abnormal lamellar/vesicular and stacked discoidal lipoprotein particles in the V LDL-size range in SR-BI KO/ApoeR61\textsuperscript{h/h}h/h mice and scarring. These myocardial lesions were widely distributed in the AV groove, LV wall, RV wall, and apex. 

Effects of HFC Feeding on Atherosclerosis in SR-BI KO/ApoeR61\textsuperscript{h/h}h/h Mice

Atherosclerosis was quantitatively assessed by measuring plaque areas in aortic roots (Figure 4A through 4D and 4I). After 4 weeks of HFC feeding, the average lesion area in the SR-BI KO/ApoeR61\textsuperscript{h/h}h/h mice was \( \approx 25 \) times larger than those in SR-BI KO and ApoeR61\textsuperscript{h/h}h/h mice and \( \approx 300 \) times larger than those in WT mice (Figure 4I; note the log scale). The profound aortic root atherosclerosis in SR-BI KO/ApoeR61\textsuperscript{h/h}h/h mice was accompanied by occlusive coronary atherosclerosis (Figure 4H and 4J) similar to that previously described for 6-week-old chow-fed SR-BI/ApoE dKO mice.\textsuperscript{9} Complex occlusions were found in the major arterial branches of the left ventricular (LV) walls (6 of 6 mice analyzed), the septa (5 of 6), and the right ventricular (RV) walls (6 of 6). No arterial occlusions were seen in HFC-fed and age-matched controls (Figure 4E through 4G). In all 6 HFC-fed SR-BI KO/ApoeR61\textsuperscript{h/h}h/h mice examined in detail, Masson’s trichrome staining suggested that intraplaque hemorrhage was common (Figure 4J). We observed no arterial occlusions in age-matched chow-fed SR-BI KO/ApoeR61\textsuperscript{h/h}h/h mice. Thus, the HFC diet induced extensive, occlusive atherosclerosis in SR-BI KO/ApoeR61\textsuperscript{h/h}h/h but not in control mice.

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Effects of HFC Feeding on Plasma Lipids</th>
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<tr>
<td>Diet</td>
<td>TC, mg/dL</td>
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<tr>
<td>WT</td>
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<tr>
<td>Control (n=5)</td>
<td>81±31</td>
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<tr>
<td>HFC (n=10)</td>
<td>214±43</td>
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<td>SR-BI KO</td>
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<td>Control (n=6)</td>
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<td>HFC (n=5)</td>
<td>693±120</td>
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<td>ApoeR61\textsuperscript{h/h}</td>
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<tr>
<td>Control (n=5)</td>
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<tr>
<td>HFC (n=8)</td>
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<td>Apoe KO</td>
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<tr>
<td>Control (n=8)</td>
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<tr>
<td>HFC (n=9)</td>
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<td>SR-BI KO/ApoeR61\textsuperscript{h/h}</td>
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<tr>
<td>Control (n=9)</td>
<td>282±25†</td>
</tr>
<tr>
<td>HFC (n=17)</td>
<td>1497±316†</td>
</tr>
</tbody>
</table>

TC indicates total cholesterol; PL, phospholipids; and UC, unesterified cholesterol. Ratio of surface to core lipids=(PL+UC)/ (esterified cholesterol+TG), where esterified cholesterol=TC–UC.

*Values are represented as mean±SD.

Statistical significance; statistical test (comparison group): †P<0.0001, ANOVA (WT/HFC, SR-BI KO/ApoeR61\textsuperscript{h/h}h/h, and SR-BI KO/ApoeR61\textsuperscript{h/h}h/h/HFC for HFC diet; ‡P<0.001, §P=0.03, †P=0.71, t test, 2 tailed (apoE KO/HFC and SR-BI KO/ApoeR61\textsuperscript{h/h}h/h/HFC for HFC diet; †P<0.0001, ‡P<0.01, **P=0.35, ANOVA (WT, SR-BI KO, ApoeR61\textsuperscript{h/h}, SR-BI KO/ApoeR61\textsuperscript{h/h}) for normal chow diet (control).
Cardiac function in SR-BI KO/ApoeR61h/h and control mice was assessed with ECG (Figure 6) and echocardiography (Table 2). Normal ECG patterns were seen in all control mice (eg, HFC-fed ApoeR61h/h in Figure 6A and SR-BI KO/HFC and chow-fed SR-BI KO/ApoeR61h/h mice [not shown]), whereas ST depression (Figure 6B) and ST elevation (Figure 6C) were often observed in SR-BI KO/ApoeR61h/h mice after 3 weeks of high-fat feeding. Echocardiographic analysis confirmed severe cardiac dysfunction and LV hypertrophy. The hearts of SR-BI KO/ApoeR61h/h mice fed the HFC diet for 4 weeks displayed substantially increased wall thickness, increased LV internal dimension at end systole, and consequently significantly reduced fractional shortening (P<0.0001), indicating contractile dysfunction (Table 2). The ECG and echocardiography demonstrated impaired heart function in HFC-fed SR-BI KO/ApoeR61h/h mice. Combined with the histological analysis of the cardiac structural defects, these functional studies suggested that profound occlusive coronary atherosclerosis and CHD in the HFC-fed SR-BI KO/ApoeR61h/h mice were probably responsible for their premature death.

**Discussion**

In this study, we report the development of a new murine model of diet-induced MI and CHD. In place of normal murine apoE, SR-BI KO/ApoeR61h/h mice express reduced levels of Arg-61 apoE, a mutant murine apoE with properties similar to those of the human apoE4 isoform. Compared with SR-BI/apoE dKO mice, the SR-BI KO/ApoeR61h/h mice are protected from CHD when fed a normal chow diet (low fat). However, when fed a diet rich in fat and cholesterol, SR-BI KO/ApoeR61h/h mice rapidly become severely hypercholesterolemic. They develop occlusive coronary atherosclerosis, MIs, heart dysfunction and failure, and premature death, thus recapitulating the phenotypes seen in SR-BI/apoE dKO mice.9,10

The low plasma levels of Arg-61 apoE in chow-fed SR-BI KO/ApoeR61h/h mice were sufficient to prevent the occlusive...
atherosclerosis and cardiovascular pathologies seen in normal chow–fed SR-BI/apoE dKO mice. On a chow diet, SR-BI KO/ApoE61/h/h mice had plasma lipid levels (eg, total cholesterol, 282 mg/dL) similar to those in SR-BI single-KO mice19 (Table 1). However, when fed an HFC diet rich in fat and cholesterol for 4 weeks, SR-BI KO/ApoE61/h/h mice developed hypercholesterolemia (total cholesterol, 1497 mg/dL) characterized by the appearance of abnormal lamellar/vesicular and stacked discoidal and unesterified cholesterol–rich lipoprotein particles in the VLDL-size range that were similar to those seen in the plasma of SR-BI/apoE dKO mice10. These unesterified cholesterol–rich particles probably contributed to the rapid formation of occlusive coronary atherosclerosis, resulting in MI, cardiac dysfunction, and the premature death that occurred 32±6.1 days (range, 24 to 48 days) after initiation of HFC feeding.

Of the 3 common human apoE isoforms (E2, E3, E4), apoE3 is the most prevalent and appears to be the functional equivalent of WT murine apoE. Both human apoE4 and apoE3 have an arginine at position 61; however, human apoE4 differs from apoE3 by a single amino acid substitution of arginine at position 112. ApoE4 is associated with elevated plasma LDL cholesterol and predisposes individuals to cardiovascular and neurological diseases.25,26 WT murine apoE has an arginine at position 61 (human equivalent position numbering system); however, it has a threonine at position 61 and exhibits properties similar to those of human apoE3. The substitution of an arginine for the threonine at position 61 in murine apoE (Arg-61 apoE) leads to its exhibiting characteristics of the human apoE4 isoform in plasma lipoprotein metabolism21 (eg, differential distribution among lipoprotein species). Thus, SR-BI KO/ApoE61/h/h mice express a human apoE4-like form of murine apoE.

Figure 5. Anatomic, histological, and gravimetric analyses of hearts from HFC-fed SR-BI KO/ApoE61/h/h and control mice. Hearts from 3-month-old animals of the indicated genotypes fed either the HFC diet initiated at 60 days of age (30-day HFC feeding, A–K) or a normal chow diet only (H, rightmost bar) were harvested. Photographs of intact hearts were taken (A–C); hearts were weighed (H; values represent mean±SD of heart to body weight ratios; n=7 for each group; P<0.0001, ANOVA) and processed for longitudinal sectioning (10 μm), Masson’s trichrome staining, and microscopy (D–G, I–K) as previously described.10 Arrows in A through G indicate right atria; arrowheads in J and K indicate myocytes (enlarged in J) (bars: A–G, 1 mm; I–K, 40 μm).

Figure 6. ECG analysis of cardiac function in HFC-fed SR-BI KO/ApoE61/h/h and control mice. Representative ECGs from unanesthetized mice fed the HFC diet for 3 weeks. A, ApoE61/h/h/HFC mice (n=6), normal ECG; B, SR-BI KO/ApoE61/h/h/HFC mice (n=10), ST depression; C, SR-BI KO/ApoE61/h/h/HFC mice (n=10), ST elevation.
There are some reports that apoE4 may sensitize human lipoprotein metabolism to dietary fat and cholesterol, perhaps because of its influence on chylomicron metabolism. In transgenic mice with a 2-fold-increased LDLR expression, a high-fat/high-cholesterol diet induced a substantial increase in VLDL-sized particles and significant expression, a high-fat/high-cholesterol diet induced a sub-

| Table 2: Echocardiographic Analysis |
|------------------------------|------------------|------------------|------------------|------------------|
|                  | SR-BI KO/ApoeR61/ | ApoeR61/HFC      | SR-BI KO/ApoeR61/ | P, ANOVA         |
|                  | (n=6)            | (n=6)            | (n=9)            |                  |
| Heart rate, bpm  | 550±23           | 539±47           | 425±27           | 0.019            |
| LVMI, cm         | 0.31±0.02        | 0.32±0.01        | 0.32±0.01        | 0.92             |
| FS, %            | 51±2.3           | 59±4.4           | 36±2.3           | <0.0001          |
| PWT, cm          | 0.103±0.005      | 0.102±0.006      | 0.129±0.009      | 0.027            |
| LV mass D3, g    | 0.115±0.008      | 0.115±0.011      | 0.161±0.017      | 0.04             |  

LVMI indicates LV internal dimension (end diastole); LVMI, LV internal dimension (end systole); FS, fraction shortening; and PWT, posterior wall thickness. *Values are mean±SE.

The rapid onset of atherosclerosis, CHD, and early death in hypercholesterolemic SR-BI/apoE dKO mice fed a normal HFC diet (relatively low in fat) offer many advantages for studying atherosclerotic CHD (eg, speed and no need for dietary, surgical, or other interventions). However, rapid and otherwise uncontrollable disease progression limits the usefulness of this model in studying important features of CHD and potential therapies, including collateral vessel formation (therapeutic angiogenesis), the effects of slowly developing cardiac remodeling on heart failure, preconditioning, and certain dietary, gene, and drug therapies to arrest or reverse disease progression. We have developed 2 approaches to address these features of CHD that permit alteration of the kinetics of disease progression. The first involves varying the timing of administration and/or withdrawal of probucol, a hypolipidemic and antioxidant drug that inhibits CHD in these mice. However, uncertainty about the mechanism of action of probucol and limitations in its ability to control CHD restrict its effectiveness. Second, we have shown here that the hypercholesterolemia and CHD in SR-BI KO/ApoeR61/HFC mice induced at different ages (25, 60, or 172 days) with an atherogenic HFC diet are remarkably similar to those in Chow-fed SR-BI/apoE dKO mice. There was no sign of CHD in the Chow-fed controls. Thus, the SR-BI KO/ApoeR61/HFC mouse is a diet-regulated model for CHD. Variations in the timing of the administration and withdrawal of the atherogenic diet, along with alterations in the lipid composition of the diet, will allow investigators to control the age of onset, duration, severity, and possible regression of disease in this model. Thus, SR-BI KO/ApoeR61/HFC mice represent a new and powerful murine model for the analysis of CHD and MI.

Acknowledgments
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Disclosure
Some of the reagents used for the studies reported here have been licensed by MIT to Cardium Pharmaceuticals, Inc., of which Dr Krieger is a founder. The majority of the work presented here was planned, performed, and interpreted before the recent founding of this company.

References


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