Liver X Receptor Signaling Pathways and Atherosclerosis

Anna C. Calkin, Peter Tontonoz

Abstract—First discovered as orphan receptors, liver X receptors (LXRs) were subsequently identified as the nuclear receptor target of the cholesterol metabolites, oxysterols. There are 2 LXR receptors encoded by distinct genes: LXRα is most highly expressed in the liver, adipose, kidney, adrenal tissues, and macrophages and LXRβ is ubiquitously expressed. Despite differential tissue distribution, these isoforms have 78% homology in their ligand-binding domain and appear to respond to the same endogenous ligands. Work over the past 10 years has shown that the LXR pathway regulates lipid metabolism and inflammation via both the induction and repression of target genes. Given the importance of cholesterol regulation and inflammation in the development of cardiovascular disease, it is not surprising that activation of the LXR pathway attenuates various mechanisms underlying atherosclerotic plaque development. In this brief review, we will discuss the impact of the LXR pathway on both cholesterol metabolism and atherosclerosis. (Arterioscler Thromb Vasc Biol. 2010;30:1513-1518.)

Key Words: ATP-binding cassette transporter ■ atherosclerosis ■ lipoproteins ■ macrophages

Liver X receptors (LXRs) act as “cholesterol sensors,” working in a converse manner to sterol response element binding proteins (SREBPs) to lower cholesterol levels via the increased expression of target genes associated with reverse cholesterol transport, cholesterol conversion to bile acid, and intestinal cholesterol absorption. These genes include members of the family of ATP-binding cassette (ABC) transporters (apos) E/C1/CII/CIV, and cholesterol 7α-hydroxylase. In addition, LXRs have been shown to drive fatty acid (FA) and triglyceride (TG) synthesis via an upregulation of genes, including SREBP1c, FA synthase, and acetyl coenzyme A carboxylase, to which the increase in TG levels associated with LXR agonists in vivo has been attributed. Given that raising TG levels could antagonize the otherwise attractive effects of LXR agonists, it was initially unclear whether LXR agonists would be pro- or antiatherosclerotic in vivo.

Effects of LXR Agonists on Atherosclerosis

Studies in various models of atherosclerosis have now clearly established that treatment with an LXR agonist results in attenuation of atherosclerosis in vivo (Table). Initial studies showed that the synthetic agonist GW3965 inhibited lesion development in both apoE−/− and low-density lipoprotein receptor (LDLR)−/− mice.1 Subsequent work has confirmed these findings using a variety of LXR agonists and additional mouse models, including the apoE−/3 Leiden mouse.2-9 Importantly, the beneficial effect of LXR activation is not sex specific, because antiatherosclerotic effects have been observed in both male and female mice. In some studies, the attenuation of atherosclerosis was observed in association with a reduction total cholesterol and/or elevation in high-density lipoprotein cholesterol, each associated with reduced cardiovascular risk.1,2,5,7 Studies using the LXR agonists, N,N-dimethyl-3β-hydroxy-cholenamide (DMHCA) or WAY-252623, observed a reduction in atherosclerosis in the absence of effects on SREBP1c and hepatic lipogenesis, whereas other studies observed an attenuation of atherosclerosis despite an increase TG levels.6,7 These observations raise the possibility that some of antiatherosclerotic effects of LXR agonists may be independent of systemic lipid metabolism and could be attributed to direct actions on the vascular wall (Figure).

Indeed, treatment with an LXR agonist was also associated with modulation of the plaque per se in many studies, attenuating inflammatory gene expression and E-selectin, intracellular adhesion molecule-1, interleukins (ILs), and fibrous cap thickness.1,8 Interestingly, Levin et al2 demonstrated that, despite an increase in TG levels, T0901317 was associated with not only a reduction but also a regression of atherosclerotic lesions. Similar effects were demonstrated by Dai et al9 and Dai and coworkers,10 who also reported a concomitant increase in Niemann–Pick C1 mRNA and protein expression in the aorta, liver, and intestine, which the authors suggested was responsible for the reduction in atherosclerosis.9 Verschuren et al9 also demonstrated that in addition to mediating athero-protective effects, TO901317 was associated with regression of atherosclerotic plaque, suggesting that LXRs not only attenuate pathways associated...
### Table Effects of LXR Agonists/LXR Genetic Manipulation in Mouse Models of Atherosclerosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Background, Diet</th>
<th>Findings</th>
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| TO901317² | LDLR⁻/⁻, WD     | ↓ 70% lesion area  
|           |                 | 62% regression of aortic lesion area  
|           |                 | ↓ CD68 and ↑ ABCAI mRNA in aortic lesions  
|           |                 | ↓ macrophages and ↑ collagen content  
|           |                 | ↓ plasma TC, ↑ plasma TG |
| TO901317⁴ | LDLR⁻/⁻, WD     | ↓ atherosclerosis in innominate artery and RC  
|           |                 | ↑ LC thickness of fibrous cap  
|           |                 | ↑ plasma VLDL-C, TC, TG |
| ATI-829⁵  | LDLR⁻/⁻, WD     | ↓ atherosclerosis in innominate artery and RC  
|           |                 | ↑ LC thickness of fibrous cap, ↓ macrophages  
|           |                 | no change in plasma Tgs, Tcs |
| TO901317⁶ | LDLR⁻/⁻, AD     | ↓ aortic root atherosclerosis  
|           |                 | ↑ plasma HDL-C, lesion ABCAI |
| GW3965¹   | LDLR⁻/⁻, WD     | ↓ en face atherosclerosis: 53% males; 34% females; ↓ 35% aortic root lesion area |
|           |                 | ↓ plasma TC |
| GW3965¹   | ApoE⁻/⁻, chow   | ↓ aortic root atherosclerosis: 47% males |
|           |                 | ↑ plasma TG, lesion ABCAI; ↓ plasma VLDL-C |
| WAY-252623⁶ | LDLR⁻/⁻, HFHC | ↓ en face atherosclerosis |
|           |                 | No change serum TC, TG |
| DMHCA⁷    | ApoE⁻/⁻, WD     | 58.3% regression en face atherosclerosis |
|           |                 | ↑ plasma TC, HDL-C levels |
|           |                 | ↑ NPC1, ABCAI in aorta, liver, intestine |
| TO901317⁸ | ApoE3Leiden, WD, RD | ↓ en face and aortic root lesion area  
|           |                 | ↓ plasma TC, (females)  
|           |                 | ↓ aortic root lesion no., severity (WD)  
|           |                 | ↓ E-selectin, ICAM-1, CD44 (WD)  
|           |                 | Promotes regression (RD) |
| Nil¹¹     | LXRαβ⁻/⁻, chow  | ↑ caspase-3, BAX, CCR7, ABCAI/GI (RD) |
|           |                 | Lipid accumulation in aortic root  
|           |                 | ↓ serum TG, HDL-C, ↑ LDL-C |
| Nil¹²     | LXRα⁻/⁻, apoE⁻/⁻, WD | ↑ en face and aortic root lesion area  
|           |                 | ↑ peripheral cholesterol accumulation  
|           |                 | ↓ en face and aortic root lesion area  
|           |                 | ↓ peripheral cholesterol accumulation  
|           |                 | No change in plasma TG levels |
| GW3965¹²  | LXRα⁻/⁻, apoE⁻/⁻, WD | ↑ en face and aortic root lesion area (LXRα⁻/⁻,) |
|           |                 | NS effect on atherosclerosis (LXRβ⁻/⁻)  
|           |                 | ↓ aortic root lesion area in both strains |
|           |                 | ↓ en face atherosclerosis in LXRβ⁻/⁻/LDLR⁻/⁻ only  
| LXRα⁻/⁻, LDLR⁻/⁻ BMT, | LDLR⁻/⁻, WD | ↑ en face atherosclerosis  
| LXRα⁻/⁻, LDLR⁻/⁻ BMT¹³ | LXRα⁻/⁻, LDLR⁻/⁻, WD | ↓ en face atherosclerosis  
| LXRαβ⁻/⁻ BMT¹⁵ | ApoE⁻/⁻, LDLR⁻/⁻ | ↑ aortic atherosclerosis (both strains)  
|           |                 | ↑ cholesterol accumulation in isolated macrophages |
|           |                 | No change in plasma TC |
| LXRαβ⁻/⁻ BMT TO901317² | LDLR⁻/⁻, WD | ↑ aortic lesion area (vehicle) |
|           |                 | No effect of TO901317 on lesion area |
| Macrophage LXRα Tg¹⁶ | LDLR⁻/⁻, SSD | ↑ 83% lesion area in braciocephalic artery |
|           |                 | ↑ ability to efflux and ↑ production of iNOS in isolated macrophages |
|           |                 | No change in plasma lipids, TC or TG |

BMT, bone marrow transplant; CCR, chemokine receptor; HDL-C, high density lipoprotein cholesterol; HFHC, high fat, high cholesterol; ICAM, intracellular adhesion molecule; INOS, inducible nitric oxide synthase; LC, left coronary-related sinus; LPS, lipopolysaccharide; Nil, not treated; NPC1, Niemann–Pick C1 protein; NS, not significant; RC, right coronary-related sinus; RD, regressive cholesterol-depleted diet; SSD, semi-synthetic diet, 0.02% cholesterol; TC, total cholesterol; Tg, transgenic; VLDL-C, very low-density lipoprotein cholesterol; WD, western diet.
with lesion progression but also promote modulation of the plaque itself, resulting in a reversal of plaque accumulation. This is highly relevant to the clinical setting in which individuals commonly have established lesions before presentation for treatment of cardiovascular disease.

Gene deletion studies further support an antiatherosclerotic role for LXR. Although little phenotype was observed on deletion of either LXRα or LXRβ in wild-type mice fed a chow diet for 18 months, deletion of both isoforms together in 1 study was associated with reduced serum TGs and high-density lipoprotein cholesterol and increased cholesterol content of LDL particles. These double knockout mice exhibited lipid accumulation in the aortic root in the subendothelium and in lipid-laden foam cells, demonstrating that even in the absence of proatherogenic stimuli, namely elevated dietary cholesterol, the absence of both LXR isoforms results in the initiation of atherosclerosis.

Studies by Bradley et al examined the relative contribution of the LXR isoforms to atherosclerosis in the setting of hypercholesterolemia. They demonstrated that LXRα deficiency on an apoe−/− background was associated with accumulation of cholesterol in peripheral tissues and accelerated atherosclerosis both en face and at the aortic root, suggesting that LXRβ is not sufficient to compensate for LXRα deletion in the context of hypercholesterolemia. However, on activation of LXRβ via administration of GW3965, cholesterol accumulation and atherosclerosis were attenuated without the concomitant increase in plasma TG levels seen in LXRα−/−apoE−/−-treated mice. More recently, Bischoff et al performed similar studies on LDLR−/− mice. LXRα deletion was associated with an increase in en face and aortic root atherosclerosis, as well as decreased plasma total cholesterol and TG. Little effect was seen on these parameters with LXRβ deletion. On administration of T0901317, TG were increased in LXRβ but not LXRα mice, and no change in plasma total cholesterol was seen in either group. Aortic root lesions were reduced by T0901317 in both LXRα−/− and LXRβ−/− strains. However, in contrast to Bradley et al, T0901317 did not attenuate en face atherosclerosis in LXRα−/−LDLR−/− mice. Interestingly, isolated macrophages from LXRα−/− mice in this study demonstrated reduced upregulation of ABCA1 and ABCG1 mRNA expression in response to T0901317 compared with those from LXRβ−/− mice. These findings suggest a particularly important role for LXRα in maintaining cholesterol homeostasis in the setting of hypercholesterolemia.

**LXRs and Macrophages**

Uptake of modified lipids, primarily modified LDL, such as oxidized LDL, via scavenger receptors on macrophages is critical to the formation of foam cells. Subsequent accumulation leads to the formation of fatty streaks and ultimately advanced atherosclerotic lesions. It is well established that LXRs antagonize this process by promoting cholesterol efflux via the upregulation of the ABC family transporters, resulting in enhanced reverse cholesterol transport. Indeed, one would anticipate that enhanced reverse cholesterol transport accounts for much of the antiatherogenic effects observed with LXR agonists. An important role for the macropage LXR pathway in atherosclerosis susceptibility was established by Tangirala et al, who showed that transplantation of bone marrow lacking LXRα and LXRβ expression into apoE−/− and LDLR−/− recipient mice strongly increased lesion development. Moreover, isolated LXRαβ null macrophages displayed increased accumulation of cholesterol. The importance of the LXR pathway in macrophages on the development of atherosclerosis is also supported by work demonstrating that overexpression of LXRα in a macrophage-specific manner in LDLR−/− mice was associated with a reduction in atherosclerosis in the absence of changes in plasma lipid levels.

Levin et al have further reported that T0901317 had no effect on atherosclerotic lesion development in LDLR−/− mice with bone marrow devoid of LXR, suggesting that most of the atherosclerotic protection afforded by LXR agonists are derived from effects on hematopoetic cells. However, T0901317 was only administered for 6 weeks in this study,
and thus, one might speculate that other effects may have been seen over a longer treatment period. In contrast to these studies, Bischoff et al.\textsuperscript{13} recently reported that LDLR\textsuperscript{−/−} mice transplanted with LXRa\textsuperscript{−/−}/LDLR\textsuperscript{−/−} bone marrow exhibit increased en face atherosclerosis. However, this was not as great as the level of atherosclerosis in global LXRa\textsuperscript{−/−}/LDLR\textsuperscript{−/−} mice receiving the same bone marrow, suggesting that LXRa deficiency in extrahematopoietic cells are also involved in the development of atherosclerosis. This was further confirmed by studies that restored LXRa expression in hematopoietic cells via bone marrow transplant into LXRa\textsuperscript{−/−}/LDLR\textsuperscript{−/−} mice. This manipulation attenuated atherosclerosis but not to the level seen in LDLR\textsuperscript{−/−} mice. These studies raise the possibility that LXRs may exert antiatherogenic effects on cell types other than macrophages critical to the development of atherosclerotic plaques, perhaps including liver, intestine, endothelial cells, and smooth muscle cells (SMCs) (see below).

**Antiinflammatory Effects of LXR**

LXRs can influence macrophage biology not only via modulation of lipid metabolism but also via effects on innate immunity. The release of cytokines from macrophages results in recruitment of monocytes, cross-talk with T cells, perpetuates cellular activation, and further promotes atherosclerotic lesion development.\textsuperscript{17} The antiinflammatory effect of LXRs were first described by Joseph et al.,\textsuperscript{18} who demonstrated that LXR activation attenuated *Escherichia coli* or lipopolysaccharide-induced expression of proinflammatory molecules, including IL-6, inflammatory nitric oxide synthase and cyclooxygenase-2 in macrophages from wild-type but not LXR null mice. Interestingly, mice deficient in any of these molecules exhibit increased atherosclerosis, suggesting that the powerful antiinflammatory effects of LXRs may contribute to their antiatherosclerotic effects. Mechanistically, the antiinflammatory effects of LXR have been attributed to nuclear inhibition of nuclear factor\textsuperscript{κ}B signaling via a process known as transrepression.\textsuperscript{19} Subsequent studies demonstrated that LXR also attenuates expression of the nuclear factor\textsuperscript{κ}B target gene matrix metalloproteinase-9 both in vivo and in vitro.\textsuperscript{18,20} Matrix metalloproteinase-9 has been shown to be localized to macrophage-rich areas within atherosclerotic lesions and is associated with enhanced extracellular matrix degradation, influencing SMC migration, neointima formation, and plaque instability. The regulation of matrix metalloproteinase-9 by LXR is consistent with the observed increase in collagen content in plaques of LXR ligand-treated LDLR\textsuperscript{−/−} mice.\textsuperscript{2}

Integration of lipid metabolism and immunity via the LXR pathway was further demonstrated in studies by Castrillo et al.,\textsuperscript{21} who demonstrated that bacterial pathogens, such as *E. coli* and influenza A, which signal via the TLR-3/4 pathway, can downregulate LXR signaling, resulting in reduced ABC transporter expression and efflux of cholesterol, an effect known to exacerbate atherosclerotic lesions formation. More recent studies demonstrate that LXRs can also modulate the TLR2/TLR4/MyD88 pathway.\textsuperscript{22} *Chlamydia pneumoniae*-induced atherosclerosis, which can be attenuated by TLR2, TLR4, or MyD88 deficiency, was accelerated in the absence of LXRa. Infected LXRa\textsuperscript{−/−}/apoE\textsuperscript{−/−} mice exhibited increased atherosclerosis with lesions rich in dendritic cells and cholesterol, as well as and higher plasma IL-6 levels compared with LXRa\textsuperscript{−/−}/apoE\textsuperscript{−/−} mice or uninfected LXRa\textsuperscript{−/−}/apoE\textsuperscript{−/−} mice.

Another recent discovery was that LXR can also promote apoptotic cell clearance. Phagocytosis of apoptotic cells results in LXR activation because of cholesterol loading, leading to an increase of the LXR target gene and apoptotic cell receptor Mer.\textsuperscript{23} LXR activation by apoptotic cells was shown to promote further clearance of apoptotic cells and to concomitantly suppress inflammatory pathways.\textsuperscript{23} In contrast, LXR null macrophages were defective in their ability to induce Mer expression and phagocytose apoptotic cells and exhibited an induction of the proinflammatory mediators IL-1β and monocyte chemoattractant protein-1. Interestingly, loss of Mer expression and defective apoptotic cell clearance have both previously been linked to accelerated atherosclerosis.\textsuperscript{24,25} Together, these studies illustrate that LXR regulates a number of immune and inflammatory pathways that have the potential to modulate atherosclerotic lesion development.

**LXRs and Endothelial Cells**

The importance of the endothelium in the initiation of atherosclerotic plaque development has been well described. Indeed, endothelial cells have been demonstrated to be metabolically active cells capable of responding to the surrounding environment by modulating expression of cell surface receptors and releasing soluble agents that influence the subendothelial layer. The effects of the LXR pathway on the endothelium have been less well studied than other cell types, yet it is possible that they may contribute to the antiatherosclerotic effects mediated by LXR agonists. Endothelial cells express at least LXRβ, and it has been reported that synthetic LXR agonists can mediate antiinflammatory and antiadhesive effects in this tissue. As in other cells, activation of LXR results in upregulation of ABCA1 in the endothelium.\textsuperscript{26,27} Conversely, oxidized LDL, both minimally and extensively modified, was shown to attenuate ABCA1 expression as well as the production of the endogenous LXR ligand, 27-hydroxycholesterol.\textsuperscript{28} Interestingly, the expression of LXRs, as well as their target genes, appear to be differentially expressed throughout the aorta. In the atherosclerotic prone arch, a region of turbulent flow, LXR was found to be expressed 5-fold lower than in the thoracic aorta, a region of laminar flow.\textsuperscript{29} In vitro studies confirmed a direct upregulation of LXRα and LXRβ, as well as their targets, ABCA1, lipoprotein lipase, and apoE, in response to high, but not low, laminar flow. These studies suggest that in areas of high flow, as seen in healthy arteries, upregulated LXR expression could mediate antiatherosclerotic effects. Interestingly, laminar shear stress has also been shown to upregulate stearoyl-coenzyme A desaturase-1, another LXR target gene and the rate limiting enzyme in the conversion of saturated FAs to monounsaturated FAs.\textsuperscript{30,31} Accumulation of nonesterified FAs is associated with endothelial dysfunction via lipidotoxic, apoptotic, and proinflammatory pathways. In human, aortic endothelial cells T0901317 was associated with increased stearoyl-coenzyme A desaturase-1 expression and attenuated palmitate-induced lipidotoxicity, apoptosis, and IL-6 and IL-8 expression.\textsuperscript{32}

As mentioned above, LXRs are known not only for their induction of target genes but also their transrepressive effects.
LXRs can mediate antiinflammatory effects via interference with the TLR pathway. However, much of these effects have been characterized in macrophages.\textsuperscript{19} T0901317 and GW3965 were found to attenuate lipopolysaccharide-induced expression of intracellular adhesion molecule-1 and vascular cell adhesion endothelial-1 in human umbilical vein and artery endothelial cells.\textsuperscript{33} Similar effects were observed in vivo, with administration of T0901317 to apoE-Leiden mice associated with an attenuation of levels of intracellular adhesion molecule, as well as E-selectin and CD44 in the vessel wall.\textsuperscript{9}

**LXRs and Vascular SMCs**

SMCs play a critical role in the vasculature, regulating contractile function. In the setting of vascular disease, SMCs are involved in plaque stabilization, migrating to form a fibrous cap over the plaque, preventing it from rupture. LXR\(\beta\) and perhaps low levels of LXR\(\alpha\) are expressed in human coronary artery SMCs, and limited studies in VSMCs have demonstrated that LXRs can influence proliferation, contractility, apoptosis, and calcification.\textsuperscript{34–38} Blaschke et al\textsuperscript{14} demonstrated that the LXR ligand T1317 attenuated vascular SCM proliferation and that administration of this agent protected against neoIntima formation following balloon injury. Interestingly, angiotensin II (AT) has been shown to promote proliferation, as well as vasoconstriction, fibrosis, inflammation, and formation of reactive oxygen species and advanced glycation endproducts. Inhibition of this pathway via AT type I receptor antagonism is associated with reduced atherosclerotic lesions.\textsuperscript{37} Both T0901317 and 22(R)-hydroxycholesterol attenuated AT type I receptor mRNA and protein, which was associated with a subsequent reduction of downstream signaling.\textsuperscript{38} Moreover, in Sprague–Dawley rats, treatment with GW3965 blunted AT-induced increases in blood pressure in the absence of changes in heart rate. Other effects mediated by AT were not assessed. 25-Hydroxycholesterol was shown to upregulate skeletal muscle LIM 1 protein in aortic SMCs, associated with an increase in \(\alpha\)-smooth muscle actin and the cell cycle regulator p27\(^{\text{Kip1}}\), suggestive of enhanced differentiation.\textsuperscript{39} This is in contrast with the abovementioned findings with T1317. However, the effect of synthetic LXR agonist and the requirement for LXR expression was not examined, raising the possibility of an LXR-independent mechanism. Finally, LXR ligands, both endogenous and synthetic, have been shown to affect vascular calcification, although whether this may contribute plaque stabilization or promote their rupture remains to be established.\textsuperscript{36,40,41}

**LXR-Dependent Mechanism for Control of Cholesterol Uptake**

As outlined above, the function of LXR in cellular cholesterol efflux and ABC transporter expression has long been appreciated. Recent work has uncovered a novel mechanism by which LXR also modulates cellular cholesterol accumulation.\textsuperscript{42} Zelcer et al\textsuperscript{14} demonstrated that in the setting of high cellular cholesterol LXR induces the expression of an E3 ubiquitin ligase termed Idol (inducible degrader of the LDLR). Idol posttranslationally modifies LDLR, resulting in its degradation and subsequent attenuation of LDL cholesterol binding and uptake. The LXR-Idol pathway provides a complement to the SREBP2 pathway, which increases LDLR transcription under conditions of low cholesterol to enhance LDL cholesterol uptake. Interestingly, the LXR-Idol pathway appears to operate in many different cell types, including macrophages, hepatocytes, and fibroblasts. Similar effects were seen in vivo, with administration of GW3965 associated with upregulation of Idol expression in various tissues, including macrophages, spleen, and liver. In vitro studies demonstrated that cotransfection of Idol and LDLR was associated with enhanced ubiquitination and degradation of the LDLR via a lysosomal pathway. Adenoviral expression of Idol in wild-type mice resulted in elevated plasma LDL cholesterol levels, essentially mimicking the phenotype of the LDLR\(^{−/−}\) mice, one of the most common models of atherosclerosis.

Subsequent studies have revealed that Idol also targets the 2 most closely related members of the LDLR family, very low-density lipoprotein receptor and apoER2, for degradation in a similar manner to that of LDLR.\textsuperscript{43} Interestingly, the Drosophila Idol homolog, DNR-1, was also able to degrade human LDLR, indicating that Idol is an evolutionarily conserved mechanism for regulation of lipid uptake. Many questions remain to be answered, including whether there is compensation by the SREBP pathway, how Idol interacts with LDLR, and which other proteins are involved in the degradation of LDLR/VLDLR/apoER2. Future studies will no doubt address many of these issues. Given that LDL carries \(\sim70\%\) of the cholesterol in the plasma, and that elevated LDL cholesterol levels are associated with increased coronary heart disease, the discovery of a new pathway that regulates LDL cholesterol levels may have therapeutic implications as a novel drug target.

**Conclusion**

The last 10 years have seen major advances in our understanding of LXR biology. Numerous studies have revealed that LXRs lie at the intersection of lipid metabolism, innate immunity, and inflammation, all pathways fundamental to the development of atherosclerotic lesions and cardiovascular disease. Future studies will continue to assess whether manipulation of these pathway may have utility in the treatment of cardiovascular disease.

**Disclosures**

None.

**References**


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