Dihydropyridine calcium channel blockers (CCBs) are widely used agents for patients with hypertension. Dihydropyridine CCBs lower blood pressure mainly through vasodilation and reduction of peripheral resistance, and several clinical studies have demonstrated that they have clinical benefits in patients with cardiovascular diseases. In addition, some studies have indicated that dihydropyridine CCBs have anti-atherogenic effects beyond their blood pressure-lowering effects. In fact, several studies using atherosclerotic model animals have revealed that dihydropyridine CCBs suppress atherosclerotic lesion formation. It is well known that the production of reactive oxygen species (ROS) is involved in the progression of atherosclerosis by stimulating the production of inflammatory factors such as chemokines, cytokines and adhesion molecules. Dihydropyridine CCBs can suppress ROS generation and subsequent inflammatory actions in vascular cells and arterial walls. Furthermore, several reports have revealed that dihydropyridine CCBs suppress the expression of adhesion molecules, thereby inhibiting monocyte adhesion to endothelial cells, which is thought to be an early step in the pathogenesis of atherosclerosis. In smooth muscle cells, dihydropyridine CCBs suppress cell proliferation and migration \textit{in vitro} and \textit{in vivo}. In macrophages, dihydropyridine CCBs decrease cholesterol accumulation and intracellular cholesterol esterification, and increase cholesteryl ester hydrolysis. Moreover, dihydropyridine CCBs suppress the expression of matrix metalloproteinases, which affects the stability of atheromatous plaques. Interestingly, recent studies have revealed that the anti-atherosclerotic effects of dihydropyridine CCBs are mediated, at least in part, via the activation of peroxisome proliferator-activated receptor-\(\gamma\). In this review, we focus on the anti-atherosclerotic effects of dihydropyridine CCBs beyond their blood pressure-lowering effects.


\textbf{Key words;} Dihydropyridine calcium channel blocker, Atherosclerosis, Hypertension

The initiation of molecular and cellular events in atherogenesis is triggered by endothelial dysfunction, resulting in decreased nitric oxide (NO) production, increased expression of cell adhesion molecules, including intracellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1, and increased production of inflammatory cytokines in endothelial cells (ECs)\textsuperscript{2-4}). In particular, inflammation is thought to be one of the major processes that accelerates the progression of atherosclerosis. Proinflammatory factors, such as oxidized low-density lipoprotein (LDL), stimulate the release of cytokines from diseased vessels. This process leads to the accumulation of monocytes and monocyte-derived macrophages, migration and proliferation of smooth muscle cells, and formation of fibrous tissue that eventually results...
in the formation of mature atherosclerotic plaque. Since a number of these atherogenic responses in vessels are mediated by the disruption of calcium homeostasis, there has been interest in the potential role of calcium channel blockers (CCBs) as anti-atherogenic agents. This hypothesis has been extensively examined in a variety of cellular and animal models of atherosclerosis.

Clinical events of ischemia are often caused by an increase in vascular tone or by a loss of reactivity to normal physiologic stresses. Excessive vasoconstriction and vasospasm can lead to plaque rupture and vessel occlusion in patients with CAD. As a counter-effect of these effects on the vessel wall, vascular ECs play a pivotal role in the control of vasodilation by specifically mediating the release of NO generated by NO synthase (NOS). The release of NO from the endothelium is induced by various factors, including shear stress caused by blood flow; however, the system for increasing flow capacity is impaired in atherosclerotic states. In fact, higher responses to vasoconstrictor agents and lower responses to NO-mediated vasodilation are observed in abnormal arteries. Abnormal vasoconstriction can directly lead to plaque rupture by destabilizing the thinning fibrous cap enriched with inflammatory cells, resulting in thrombus formation. In fact, the Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function (ENCORE I) study revealed that nifedipine improved endothelium-dependent vasodilation in patients with CAD. On the other hand, the Conduit Artery Function Evaluation (CAFÉ) study, which is a sub-study of the Anglo-Scandinavian Cardiac Outcomes (ASCOT) trial, is a well-recognized study linking improved central aortic pressure and vasodilation to superior clinical outcomes for dihydropyridine CCBs; therefore, agents that attenuate vasoconstriction and vasospasm, such as CCBs, may have an important role in reducing episodes of ischemia.

CCBs were approved for the treatment of hypertension in the 1980s. Since then, the use of CCBs has increased markedly because they are effective for lowering blood pressure and have few side effects. CCBs are heterogeneous and can be classified into three main classes, phenylalkylamines, benzothiazepines and dihydropyridines. The first-generation drugs in these three classes are verapamil, diltiazem and nifedipine, respectively. The three major classes differ in their molecular structures, sites and modes of action on calcium channels, and effects on various other cardiovascular functions. Among them, dihydropyridine CCBs are widely used as anti-hypertensive agents because of their strong vasodilator action, high vasoselectivity and reduced cardiac depression.

Dihydropyridine CCBs have been reported to produce clinical benefits in CAD patients that might be independent of blood pressure changes. In fact, in vivo and in vitro studies have demonstrated that dihydropyridine CCBs induce NO production in coronary microvessels and inhibit smooth muscle cell (SMC) migration and proliferation. In the present review, we focus on the benefits of dihydropyridine CCBs for the progression of atherosclerosis beyond their blood pressure-lowering effects.

Clinical Studies on the Regression or Prevention of Atherosclerosis by Dihydropyridine CCBs

Dihydropyridine CCBs have been shown to possess anti-atherogenic properties in various clinical studies, revealing slowed progression and decreased formation of new lesions. Waters et al. reported that treatment with nicardipine had no effect on advanced coronary atherosclerosis but retarded the progression of minimal atherosclerotic lesions, and stepwise logistic regression analysis revealed a correlation between the blood pressure-lowering effect and the retarded progression of atherosclerotic lesions. The International Nifedipine Trial on Anti-atherosclerotic Therapy (INTACT) study and its 6-year follow-up demonstrated an appreciable and statistically significant reduction in angiographically detected new coronary lesions in patients with coronary heart disease treated with nifedipine. In two subprotocols of the Intervention as a Goal in Hypertension Treatment (INSIGHT) study, nifedipine treatment prevented an increase in intima-media thickness in the carotid artery and significantly slowed the progression of coronary calcification compared with the diuretic co-amilozide in hypertensive patients. In another subprotocol of the INSIGHT study, nifedipine was shown to be as effective as co-amilozide in reducing cardiovascular complications in patients with hypertension and diabetes. Furthermore, treatment with nifedipine was associated with lower incidences of both vascular and non-vascular deaths, as well as a lower incidence of type 2 diabetes mellitus. The Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) study reported that nifedipine was as effective as angiotensin-converting enzyme inhibitors in reducing the incidence of cardiac events in high-risk hypertensive patients. The 3-year Prospective Randomized Evaluation of the Vascular Effect of Norvasc Trial (PREVENT) involving 825 patients examined the effect of amlodipine on the progression
of atherosclerosis, and found that amlodipine therapy was associated with significant slowing of the progression of carotid artery atherosclerosis. The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) and Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation (NORMALISE) trials reported that amlodipine treatment, compared to placebo, resulted in fewer ischemic events after 18 months of therapy; however, there was no difference between amlodipine and enalapril in the improvement of arterial lumen dimensions. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCO MPLISH) trial reported that combination therapy with benazepril and amlodipine was superior to therapy with benazepril and hydrochlorothiazide in reducing cardiovascular events in patients with hypertension. The Coronary Angioplasty Amlodipine Restenosis Study (CAPARES) revealed that amlodipine therapy initiated 2 weeks before percutaneous transluminal coronary angioplasty (PTCA) did not reduce luminal loss, but significantly reduced the incidence of repeated PTCA and composite major adverse clinical events during the 4-month follow-up period after PTCA compared with placebo. The European Lacidipine Study on Atherosclerosis (ELSA) showed that lacidipine was more effective at reducing the rate of intima-media thickness progression than the β-blocker atenolol.

On the other hand, several clinical studies have investigated the effect of combination therapy with Dihydropyridine CCBs and HMG-CoA reductase inhibitors (statins) in patients with hypertension. The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) trial is a randomized, double-blind, multicenter trial that compared the efficacy of amlodipine plus atorvastatin with that of placebo over 3.3 years and evaluated data from patients who had received atorvastatin 10 mg once daily or placebo in addition to their antihypertensive regimen. This trial demonstrated that the relative risk of nonfatal myocardial infarction and fatal coronary heart disease was reduced by 36% in the group receiving atorvastatin plus either an antihypertensive regimen compared with the group receiving placebo plus either antihypertensive regimen. In the Regression Growth Evaluation Statin Study (REGRESS), coadministration of the dihydropyridine CCBs amlodipine or nifedipine with pravastatin resulted in significant reductions in the appearance of new angiographic lesions. Moreover, the ENCORE I trial demonstrated that combination therapy with nifedipine and cerivastatin improved endothelial function in patients with CAD. These clinical studies suggest the benefit of combination therapy with Dihydropyridine CCBs and statins in patients with hypertension.

Anti-Atherosclerotic Mechanisms of Dihydropyridine CCBs

Anti-Atherosclerotic Effects of Dihydropyridine CCBs in Animal Models

Several studies have reported that many dihydropyridine CCBs suppress the progression of atherosclerotic lesion formation in atherosclerotic model animals (Table 1). In fact, it has been reported that amlodipine, benidipine, nicardipine and nifedipine suppressed the progression of atherosclerosis in high cholesterol-fed atherosclerotic model rabbits. Furthermore, azelnidipine, lacidipine and nifedipine suppressed the progression of atherosclerosis in normal chow-fed and Western-type diet-fed apolipoprotein E-deficient mice. On the other hand, CCBs suppressed neointima thickening in vascular injury model animals (Table 2). Nakano et al. reported that azelnidipine suppressed neointima thickening in the injured femoral artery of high cholesterol diet-fed monkeys. Benidipine or lacidipine suppressed neointima thickening in the injured carotid artery of C57BL/6 mice or white rabbits fed normal chow. Interestingly, most of these studies showed that dihydropyridine CCBs did not affect blood pressure. These findings suggest the possibility of applying dihydropyridine CCBs as a protective tool against atherosclerotic lesion formation and vascular remodeling beyond their blood pressure-lowering effects.

Anti-Oxidative Effects of Dihydropyridine CCBs

The production of reactive oxygen species (ROS) together with inflammatory factors, such as chemokines, cytokines and adhesion molecules, is increased in atherosclerotic lesions. Several dihydropyridine CCBs, including nifedipine, azelnidipine, benidipine, lacidipine, amlodipine and manidipine, have been reported to suppress ROS generation in in vitro and in vivo studies (Fig. 1). One of the mechanisms of the anti-oxidative effects of dihydropyridine CCBs has been reported to be mediated through the inhibition of NADPH oxidase. On the other hand, nifedipine have been reported to scavenge O$_2^-$ directly in endothelial cells. Amlodipine has also been reported to scavenge O$_2^-$ by mediating membrane physico-chemical interactions. In a clinical study, nifedipine treatment attenuated circulating
On the other hand, oxidative modification of LDL and membrane lipids contributes to foam cell formation, endothelial dysfunction and destructive inflammatory processes associated with atherosclerosis. Both in vitro and in vivo studies have demonstrated increased plasma levels of lipoperoxides and isoprostanes, increased plasma antioxidant capacity, and restored NO bioavailability in patients with hypertension. Moreover, lercanidipine treatment attenuated LDL oxidation in hypertensive patients with type 2 diabetes mellitus. On the other hand, oxidative modification of LDL and membrane lipids contributes to foam cell formation, endothelial dysfunction and destructive inflammatory processes associated with atherosclerosis. Both in vitro and in vivo studies have demonstrated...

<table>
<thead>
<tr>
<th>Animal models</th>
<th>CCBs</th>
<th>Dose</th>
<th>Decrease of lesion size</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NZW rabbit (male) (high-cholesterol diet)</td>
<td>Amlodipine</td>
<td>2 mg/kg/day</td>
<td>41%</td>
<td>21</td>
</tr>
<tr>
<td>ApoE−/− mice (male) (Western-type diet)</td>
<td>Azelnidipine</td>
<td>3 or 10 mg/kg/day</td>
<td>3 mg: 46% 10 mg: 50%</td>
<td>22</td>
</tr>
<tr>
<td>NZW rabbit (male) (high-cholesterol diet)</td>
<td>Benidipine</td>
<td>10 mg/kg/day</td>
<td>71%</td>
<td>23</td>
</tr>
<tr>
<td>ApoE−/− mice (female) (Western-type diet)</td>
<td>Lacidipine</td>
<td>3 or 10 mg/kg/day</td>
<td>3 mg: 43% 10 mg: 50%</td>
<td>24</td>
</tr>
<tr>
<td>ApoE−/− mice (female) (Western-type diet)</td>
<td>Lacidipine</td>
<td>0.3, 1 or 3 mg/kg/day</td>
<td>0.3 mg: 10% 1 mg: 17% 3 mg: 53%</td>
<td>25</td>
</tr>
<tr>
<td>ApoE−/− mice (female) (Western-type diet)</td>
<td>Lacidipine</td>
<td>1 or 3 mg/kg/day</td>
<td>1 mg: 66% 3 mg: 71%</td>
<td>26</td>
</tr>
<tr>
<td>Dutch-belted rabbits (male) (high-cholesterol diet)</td>
<td>Nicardipine</td>
<td>40 mg/kg/day</td>
<td>49%</td>
<td>27</td>
</tr>
<tr>
<td>Dutch-belted rabbits (male) (high-cholesterol diet)</td>
<td>Nifedipine</td>
<td>40 mg/kg/day</td>
<td>59%</td>
<td>27</td>
</tr>
<tr>
<td>NZW-rabbits (male) (high-fat diet)</td>
<td>Nifedipine</td>
<td>16 mg/kg/day</td>
<td>58%</td>
<td>28</td>
</tr>
<tr>
<td>WHHL rabbits (male) (high-fat diet)</td>
<td>Nifedipine</td>
<td>40 mg/kg/day</td>
<td>59%</td>
<td>29</td>
</tr>
<tr>
<td>ApoE−/− mice (male) (normal diet)</td>
<td>Nifedipine</td>
<td>10 mg/kg/day</td>
<td>52%</td>
<td>30</td>
</tr>
</tbody>
</table>

CCBs, calcium channel blockers; NZW rabbits, New Zealand White rabbits; WHHL rabbits, Watanabe heritable hyperlipidemic rabbits; ApoE−/− mice, apolipoprotein E-deficient mice.

<table>
<thead>
<tr>
<th>Animal models</th>
<th>CCBs</th>
<th>Dose</th>
<th>Decrease of I/M ratio</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monkey (male) (high-fat diet)</td>
<td>Azelnidipine</td>
<td>3 or 10 mg/kg/day</td>
<td>3 mg: 50% 10 mg: 41%</td>
<td>22</td>
</tr>
<tr>
<td>C57BL/6J mice (male) (normal diet)</td>
<td>Benidipine</td>
<td>3 mg/kg/day</td>
<td>63%</td>
<td>31</td>
</tr>
<tr>
<td>White rabbit (both) (normal diet)</td>
<td>Lacidipine</td>
<td>5 mg/kg/day</td>
<td>83%</td>
<td>32</td>
</tr>
</tbody>
</table>

CCBs, calcium channel blockers; I/M ratio: intima/media ratio.
Anti-Atherogenicity of CCBs

Anti-Inflammatory Effects of Dihydropyridine CCBs

Current knowledge indicates that inflammation is part of the molecular basis of atherosclerosis. Several reports have revealed that dihydropyridine CCBs exert anti-inflammatory effects on various vascular cells (Fig. 1). Azelnidipine has been reported to suppress tumor necrosis factor (TNF-α)-induced interleukin (IL)-8 and monocyte chemoattractant protein (MCP)-1 expression in human umbilical vein ECs (HUVECs). Manidipine was found to suppress TNF-α-induced IL-6 and IL-8 expression in human ECs and human THP-1 macrophages. Nifedipine was shown to suppress lipopolysaccharide (LPS)-induced MCP-1 expression in macrophages, and angiotensin II-induced MCP-1 expression in SMCs. Benidipine was reported to suppress TNF-α- or IL-1β-induced MCP-1 and IL-8 expression in human aortic ECs. On the other hand, several reports have revealed that dihydropyridine CCBs can suppress TNF-α-induced cardiovascular cells. Azelnidipine has been reported to suppress cytokine-induced expression of inflammation-related genes, such as VCAM-1, ICAM-1 and E-selectin, resulting in reduced adhesion of THP-1 monocytes. Furthermore, lacidipine, lercanidipine and amlodipine were shown to suppress TNF-α- or oxidized LDL-induced ICAM-1, VCAM-1 and E-selectin expression in HUVECs. Nuclear factor (NF)-κB is a transcription factor involved in immune-related gene expression. NF-κB mediates the cytokine-induced expression of inflammation-related genes, such as TNF-α, MCP-1, ICAM-1 and VCAM-1, all of which are implicated in atherosclerosis. NF-κB is also redox-sensitive, and cytokine-induced generation of ROS is at least partly responsible for activation of the factor by immune stimuli; therefore, inhibition of NF-κB has potential as a pharmaceutical target for the prevention of vascular events. Recent reports have revealed that dihydropyridine CCBs can suppress the transcriptional activation of NF-κB in macrophages, ECs, mesangial cells and hepatic cells; therefore, it is suggested that inactivation of NF-κB by dihydropyridine CCBs may be one of their anti-atherosclerotic effects. It is well understood that activation of NF-κB induces the expression of inducible nitric oxide synthase (iNOS). In fact, dihydropyridine CCBs were reported to suppress iNOS expression and subsequent NO release in macrophages.

Anti-atherosclerotic Effects on Vascular Cells

Other anti-atherosclerotic effects of dihydropyridine CCBs have been reported in vascular cells (Fig. 1).
In ECs, benidipine was found to prevent lysophosphatidylcholine-induced apoptosis of ECs via inhibition of ROS\(^7\). Nifedipine was also shown to suppress EC apoptosis\(^7\). Ando \textit{et al}\(^8\) reported that benidipine increased EC differentiation of endothelial progenitor cells. These findings suggest that dihydropyridine CCBs have several protective effects toward vascular ECs.

On the other hand, the migration and proliferation of vascular SMCs of the synthetic phenotype in the intima are thought to result in the progression of intimal hyperplasia\(^8\), \(^9\). Several studies have shown that dihydropyridine CCBs can suppress SMC proliferation and migration \textit{in vitro}\(^8\), \(^9\) and \textit{in vivo}\(^8\). Moreover, the change in vascular SMCs from a differentiated state to a dedifferentiated state, termed phenotypic modulation, is a critical event that promotes intimal hyperplasia in atherosclerosis and restenosis after angioplasty\(^9\), \(^9\). Arakawa \textit{et al}\(^7\) reported that benidipine prevented the dedifferentiation of SMCs. These findings suggest that dihydropyridine CCBs act as anti-atherogenic agents by suppressing SMC proliferation, migration and dedifferentiation.

In macrophages, dihydropyridine CCBs were reported to influence cellular cholesterol metabolism\(^9\), \(^9\). It has been shown that dihydropyridine CCBs decrease cholesterol accumulation\(^9\) and intracellular cholesterol esterification\(^9\), \(^9\), and increase cholesteryl ester (CE) hydrolysis\(^9\) in macrophages. A dihydropyridine CCB-induced increase in CE hydrolysis was also observed in SMCs\(^9\). In addition, it was found that dihydropyridine CCBs increase CE hydrolysis and decrease cholesterol accumulation in human aortic tissues\(^9\); therefore, these effects of dihydropyridine CCBs may act as anti-atherogenic effects in the vessel wall. On the other hand, we\(^7\) and other groups\(^9\), \(^9\) reported that dihydropyridine CCBs induce ATP-binding cassette-transporter-A1 (ABCA1) expression in macrophages. Since ABCA1 is involved in the control of apolipoprotein AI-mediated cholesterol efflux from macrophages\(^9\), dihydropyridine CCBs may improve atheromatous plaque via ABCA1-mediated cholesterol efflux.

Macrophages, and other cells present in the vessel wall, are capable of degrading the extracellular matrix by phagocytosis or by secreting proteolytic enzymes, especially members of the matrix metalloproteinase (MMP) family\(^9\), resulting in atheromatous plaque rupture. It has been reported that dihydropyridine CCBs suppress the expression of MMP-2 and MMP-9 in macrophages\(^9\), \(^9\). Similarly, amlo- dipine can inhibit MMP-1 expression in ECs\(^9\); however, Roth \textit{et al}\(^7\) found that dihydropyridine CCBs increased the proteolytic activity of MMP-2 and decreased the activity of tissue inhibitor of metalloproteinase-2, resulting in collagen deposition in the extracellular matrix of SMCs. On the other hand, Anacak \textit{et al}\(^7\) found that lacidipine did not inhibit wall injury-mediated MMP-9 expression in the carotid artery of rabbits. Thus, further studies are needed to clarify the effects of dihydropyridine CCBs on the stability of plaques.

**Nifedipine-Mediated Anti-Atherogenic Effects Via Activation of Peroxisome Proliferator-Activated Receptor-γ (PPARγ)**

Our recent report demonstrated that nifedipine can activate PPARγ, which is a member of the nuclear hormone receptor family of ligand-dependent transcription factors\(^7\), and is a regulator of adipogenesis\(^9\), in macrophages\(^7\) (Fig. 2). In its mechanism on PPARγ activation, nifedipine does not act as a direct PPARγ ligand, but suppresses PPARγ phosphorylation by inhibiting ERK1/2 activity, thereby activating PPARγ phosphorylation via inactivation of ERK1/2, thereby activating PPARγ in macrophages. Nifedipine-mediated PPARγ activation shows anti-atherogenic effects, at least in part, by suppressing MCP-1 expression and inducing ABCA1 expression. PPARγ, peroxisome proliferator-activated receptor-γ; ERK1/2, extracellular signal-regulated kinase 1/2; ABCA1, ATP-binding cassette protein A1; MCP-1, monocyte chemoattractant protein-1.

![Fig. 2. Summary of nifedipine-mediated PPARγ activation in macrophages.](image)
PPARγ \(^{35}\) (Fig. 2). Recent studies have revealed that PPARγ is expressed in macrophages \(^{109}\), ECs \(^{110}\), vascular SMCs \(^{111}\) and atherosclerotic lesions \(^{112, 113}\), and it has many anti-atherogenic effects on these cells \(^{114}\).

In addition, PPARγ agonists suppressed the progression of atherosclerosis in atherosclerotic model mice \(^{115-119}\). Clinical studies have also indicated the protective effects of PPARγ activation against the progression of atherosclerosis \(^{120-123}\); therefore, activation of PPARγ may suppress the progression of atherosclerosis. We recently revealed that nifedipine not only activates PPARγ in macrophages but also suppresses the acceleration of atherosclerosis in apoE \(^{-/-}\) mice (Table 1) \(^{35}\). Our recently proposed novel mechanism for nifedipine-mediated PPARγ activation is supported by other reports using the PPARγ antagonist GW9662 \(^{124, 125}\). Regarding these findings, Tukuda et al. \(^{126}\) reported that nifedipine significantly decreased the serum insulin level in KK-A\(^{y}\) mice, a mouse model of type 2 diabetes. On the other hand, other dihydropyridine CCBs were reported to improve glucose intolerance in KK-A\(^{y}\) mice \(^{127}\) and increase the glucose infusion rate in hypertensive patients \(^{128}\); therefore, treatment with dihydropyridine CCBs may be useful for hypertensive patients with type 2 diabetes or metabolic syndrome. Taking all these findings into consideration, nifedipine may show anti-atherogenic effects not only by class effects of CCBs but also by nifedipine-specific and unique actions, such as PPARγ activation.

Conclusions

It is well recognized that the mechanisms of the anti-atherosclerotic effects mediated by dihydropyridine CCBs are mainly caused by their anti-hypertensive actions; however, recent studies have revealed that dihydropyridine CCBs also have direct anti-atherosclerotic effects on vascular cells. The progression of atherosclerosis is mediated by endothelial injury, activation of macrophages and abnormalities of vascular SMC function, and several \textit{in vivo} studies have demonstrated that dihydropyridine CCBs have the ability to protect against endothelial injury, inactivate macrophages and improve SMC abnormalities. Many \textit{in vitro}, \textit{in vivo} and clinical studies have proposed the validity of dihydropyridine CCBs for preventing the progression of atherosclerosis; therefore, dihydropyridine CCBs may work in a synergistic fashion with other established treatments, including HMG-CoA reductase inhibitors, to effectively improve outcomes in patients with hypertension.

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