Do antilipidemic agents reduce blood pressure?

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Abstract:
Currently, the prevalence of hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HL) is high, and these diseases are important risk factors for cardiovascular disease (CVD). Furthermore, patients with CVD often have more than one of these diseases. Generally, patients take multiple drugs for each disease. Therefore, clinicians must pay attention to drug interactions. Although HT, DM, and HL are different diseases, they share some of the same pathophysiological mechanisms and ultimately lead to the same cardiovascular events.

Currently, most patients with CVD are treated with 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins), and various beneficial pleiotropic effects of statins have been reported since the 1990s.

In this review, we evaluate the additional effects of antihyperlipidemic agents on blood pressure (BP).

Key words:
Statin, Fibrate, Blood pressure, Ambulatory blood pressure monitoring

1. Introduction

Because various types of lipid-lowering agents have been available for several years, studies have reported on the clinical effects of these agents. Particularly, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), fibrates, and ezetimibe are often administered to lower lipid levels. However, many patients with hyperlipidemia (HL) often have other lifestyle diseases, such as diabetes mellitus (DM) and hypertension (HT).

HT, DM, and HL have been shown to share some of the same pathophysiological mechanisms, and all these diseases increase the risk for cardiovascular events⁷. It is important for physicians to fully understand the interactions among the drugs used to treat these diseases. Evidence shows that lipid-lowering agents, particularly statins, have pleiotropic effects beyond improvement of lipid profiles⁷. Therefore, verification of the effects of lipid-lowering drugs on blood pressure (BP) is desirable, which is significant for physicians based on the data reported to date.

In this review, we would like to explore the pathophysiological mechanisms common to HT and HL, and discuss the possibility that lipid-lowering agents may affect BP.

2. Pathophysiology and clinical aspects

2-1. HT

Because BP is regulated by the product of vascular resistance and stroke volume, drugs that reduce vascular resistance and suppress cardiac output have been developed as antihypertensive agents. However, recent evidence shows that lipid-lowering agents may also have antihypertensive effects.

The role of inflammation as an important underlying process contributing to the initiation and progression of atherosclerosis and its clinical manifestations is well established⁸. Recent data indicated a strong relationship between essential HT and the inflammatory process. Therefore, inflammation is speculated to be a key feature in the initiation, progression, and clinical implications of essential HT. In addition, several inflammatory mediators are speculated to be associated with an increased risk for HT. An understanding of inflammatory modulation by C-reactive protein, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and chemokines is important because these modulators may influence therapeutic responses, as well as clinical outcomes in patients with HT⁹. Therefore, several

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therapeutic approaches targeting BP may have beneficial effects on inflammation that may lead to further clinical benefits.

In addition, increasing evidence shows that activation of the renin-angiotensin-aldosterone system (RAAS) and enhanced local production of angiotensin II (Ang II) is implicated in the pathophysiology of inflammation. Because Ang II increases BP, angiotensin-converting-enzyme inhibitors and Ang II receptor blockers are excellent antihypertensive agents. In addition, Ang II can regulate the inflammatory process, specifically by increasing vascular permeability, participating in the recruitment of inflammatory cells and their adhesion to the activated endothelium, and regulating cell growth and fibrosis. Reactive oxygen species (ROS) is implicated at each stage of inflammation and activate multiple intracellular signaling molecules and transcription factors associated with inflammatory responses, such as nuclear factor-kappa B and activator protein-1. Other components of the RAAS, including aldosterone and/or mineralocorticoid receptors, induce the production of ROS and participate in vascular inflammation. Several studies suggest the role of endothelin-1 (ET-1), which is a strong vasoressor, as an important mediator of chronic inflammation, and there is an increasing interest in the relationship between ET-1 and ROS. These mechanisms involving inflammation and vasoreactive mediators may have great impact on future therapeutic strategies to treat HT.

2.2. HL

HL is common in patients with HT, DM, and atherosclerosis. Epidemiologic studies have shown a strong relationship between serum lipid levels and risk of CVD. HL is also associated with inflammation. Therefore, it is reasonable that the vicious cycle induced by lipid abnormalities can be stopped by reducing inflammation, and this hypothesis was proposed by Ross. Multifactorial intervention strategies aimed at simultaneously controlling BP, blood glucose, and lipid profiles may be necessary to achieve maximal reductions in cardiovascular risk. HL and metabolic abnormalities are strongly associated with atherosclerosis and poor cardiovascular outcomes.

Because HL, including hypercholesterolemia and hypertriglyceridemia, is one of the most important risk factors for atherosclerosis, statins have long been used for protection against coronary artery disease (CAD) because they strongly lower low-density lipoprotein cholesterol (LDL-C). Emerging evidence from both laboratory studies and clinical trials has shown the pivotal role of inflammation in the initiation and exacerbation of atherosclerosis, a major cause of CAD. Although the pharmacotherapy of HL with statins has been shown to improve lipid profiles and prevent CVD, lifestyle modifications that emphasize weight loss and regular exercise are also essential. The beneficial effect of statins apart from cholesterol reduction lies in their pleiotropic properties. Many studies have shown that statins have a beneficial effect on blood vessels, and statins have been suggested to show efficacy against HT.

3. Possible mechanisms of lipid-lowering drugs for lowering BP

3-1. HMG-CoA reductase inhibitors (statins)

Atherosclerosis has been speculated to be caused by inflammation because inflammatory mechanisms are important participants in the pathophysiology of HT, and that inflammation will further exacerbate HT; hence, the anti-inflammatory effects of statins may lower BP indirectly. In fact, several reports show that statins suppress sympathetic nerve activity (SNA). Because this effect was not observed with ezetimibe, it is considered one of the multifaceted effects of statins, regardless of the extent of lipid reduction. Suppressing SNA obviously suppresses the increase in BP. This effect on SNA is remarkable in pathological conditions, such as heart failure, wherein SNA is increased. The effect is more pronounced in lipophilic statins than in hydrophilic statins. However, the results of a double-blind trial showed that muscle SNA was not reduced in patients with heart failure treated with atorvastatin, but these findings have not yet been confirmed.

Many studies reported a possible effect of antihyperlipidemic drugs on BP. Statin treatment for 12 months did not decrease BP in patients with HT. In addition, a randomized trial indicated that pravastatin combined with conventional antihypertensive drug therapy did not lower BP compared with drug therapy alone over a 2.6-year treatment period in patients with mild HT. However, most clinical and experimental studies have suggested that statins may modify BP. A meta-analysis of randomized trials showed that statins had a slight but statistically and clinically significant effect on BP, and that this effect was not related to age, changes in serum cholesterol, or length of the trial. The effect of statin treatment on BP was greater in patients with a relatively higher BP. The effect of statin therapy on SBP and DBP was -4.0 mmHg and -1.2 mmHg in patients whose basal SBP and DBP was >130 mmHg and >80 mmHg, respectively, compared with -0.9 mmHg on DBP in control subjects.

Statins has been well known to exert pleiotropic effects on vascular cells, including eNOS activation in endothelial cells, inhibition of proliferation and migration of vascular smooth muscle cells, anti-inflammatory actions, down-regulation of angiotensin II receptors, and antioxidant actions, resulting in improved endothelial function and reduction of BP in vivo.

Because statins may interact with the RAAS, statins may lower arterial BP when administered alone or together with antihypertensive drugs acting via the RAAS. Moreover, lipophilic statins have been shown to reduce muscle SNA by 12%-30% in patients with HT. Because SNA is usually higher during daytime, statins may affect daytime BP more than nighttime BP. In contrast, statin use might be associ-
ated with an increased risk of sleep disturbances, including insomnia, hallucinations, and nightmares\(^{32,34}\). Statins with high lipophilicity are speculated to cause a higher rate of central nervous system disorders compared with hydrophilic statins\(^{35,37}\). Milionis et al. suggested that the mechanism by which statins reduce BP is largely unrelated to their lipid-lowering effects\(^{38}\). Bautista et al. reported that statins reduced BP by cholesterol-independent mechanisms and found that the reduction was greater in patients with a higher BP and in those with a lower level of LDL-C\(^{39}\).

As mentioned above, statins are speculated to have effects of lowering BP; however, whether the reduction in BP by statins is clinically meaningful is still unclear. Therefore, future intervention studies are necessary\(^{40}\).

### 3-2. Fibrates

Fibrates are known to activate peroxisome proliferator-activated receptor (PPAR)-alpha, and there has been concern that they may increase BP. Several studies found slight reductions in BP during fibrate treatment\(^{41-45}\). Fibrates can enhance endothelial NO production and inhibit endothelin-1 expression\(^{44,45}\). Bezafibrate can rapidly reduce BP in rats\(^{46,48}\), and fibrates can directly inhibit the activation of vascular smooth muscle cells and their proliferation\(^{49-51}\). Treatment with fibrates resulted in improved lipid profile and endothelial function in patients with type 2 DM or HL\(^{52-59}\). Therefore, they may have a small BP-lowering activity in patients with HT.

As mentioned previously, fibrates can improve endothelial function\(^{58-60}\) and relax vascular smooth muscle cells\(^{60}\). A meta-analysis showed improvement of endothelial dysfunction with fibrates both with short- and long-term intervention\(^{61}\). However, gemfibrozil improved lipid profiles but did not improve vascular function in patients with chronic kidney disease (although atorvastatin also had similar results)\(^{61}\).

Unfortunately, data on the effect of fibrates on SNA are unclear. Although suppression of elevated SNA may be reduced if postprandial HL is suppressed, it has not yet been proven.

However, docosahexaenoic acid (DHA), a PPAR\(\alpha\) activator, reduces BP in some hypertensive models\(^{62-65}\). One of the mechanisms for lowering blood pressure is that PPAR\(\alpha\) activator DHA can improve endothelial dysfunction in Ang II-induced HT by modulating NADPH oxidase activity and inflammation in the vascular wall\(^{66}\). For these reasons, fibrates can also lower BP; however, no evidence supports a clinically significant reduction in BP.

### 3-3. Ezetimibe

Many studies reported that ezetimibe improves vascular endothelial dysfunction\(^{64,66}\), although whether the effect was as good as\(^{60}\), superior to\(^{70}\), or weaker than\(^{12,71}\) the effect of statins is controversial. However, the inhibitory effect of simvastatin on SNA was not observed with ezetimibe\(^{71}\). In a study wherein ezetimibe was combined with simvastatin, BP was further decreased by 6 mmHg in the ezetimibe combination group compared with simvastatin alone\(^{72}\). Because ezetimibe is new on the market, many studies administered this agent in combination with statins, and an antihypertensive effect of monotherapy with ezetimibe has not yet been established. Thus, further prospective intervention studies are necessary.

### 4. Conclusions

In this review, we examined the effects of lipid-lowering drugs on BP from the aspect of the pathophysiology of HT and HL. These diseases are important contributors to atherosclerosis, and therapeutic agents that improve lipid profiles has been well established to result in vascular protection and improvements in vascular function. Furthermore, lipid-lowering agents possibly lower BP, but the clinical significance of this effect is uncertain. However, because prevention and improvement of atherosclerosis is a major goal in lifestyle-related diseases, these effects should be fully understood by clinical physicians.

Conflicts of Interest
JO and FU belong to the endowed department by Fukuda Denshi Co, Ltd. KN received remuneration, including lecture fees from AstraZeneca, Astellas Pharma Inc, Nippon Boehringer Ingelheim Co, Ltd, Pfizer Inc, MSD K.K., Daiichi Sankyo Company, Ltd, Kowa Pharmaceutical Co, Ltd, Takeda Pharmaceutical Co, Ltd, Novartis Pharmaceuticals Japan, Mitsubishi Tanabe Pharma Corporation, and Daippon Sumitomo Pharma Co, Ltd. KN also received scholarship funds or donations granted by Astellas Pharma Inc, Nippon Boehringer Ingelheim Co, Ltd, Daiichi Sankyo Company, Ltd, Takeda Pharmaceutical Co, Ltd, Mitsubishi Tanabe Pharma Corporation, and MSD K.K.

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