*Editorial Comment*

# Cross Talk among Substances Can Answer Questions Raised by Clinical Trials

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It is well known that atherosclerosis is a pivotal risk for cardiovascular events in hypertensive patients. It has also been clinically proved that lowering blood pressure together with controlling lipid abnormality can protect against vascular damage. Among antihypertensive drugs, blocking agents against the renin-angiotensin-aldosterone (RAA) system are very potent; in some cases, they might even exhibit so-called "beyond blood pressure effects." The RAA system directly affects atherogenic factors, such as oxidative stress, inflammation (*1*, *2*), and possibly others. On the other hand, multiple clinical trials have revealed the importance of lipid lowering in preventing atherosclerosis. In addition to clinical trials, basic research has revealed both RAS regulation and control of macrophage foaming *via* the reduction of cholesterol or normalization of cholesterol metabolism. So far, it seems that the RAS and lipid metabolism independently promote atherosclerosis. In this issue of *Hypertension Research*, Kanome *et al*. (*3*) demonstrated cross-talk between lipid metabolism and the RAA system with a focus on angiotenisn II type 1 (AT1) receptor–mediated effects. They show that AT1 receptor activation promotes lipid accumulation in monocyte-macrophages by inducing acyl-CoA:cholesterol acyltransferase-1 (ACAT1). Sharing with urotensin II and serotonin, G protein/c-Src/PKC/MAPK pathway, those are part of downstream of AT1 receptor, upregulated ACAT1. The findings present a novel aspect of the interaction between the RAA system and lipid metabolism.

In a clinical setting, ACAT1 inhibitors (*e.g.*, avasimibe or pactimibe) did not show significant clinical effects on secondary prevention (*4*, *5*). It has been discussed that ACAT1 inhibitors do not show additive effect on statins. Although the precise rate of co-administration of RAA inhibitors is not described, around 50% of the cohort in those studies is hypertensive, and a certain number of cohorts could be treated with RAA inhibitors. The article by Kanome *et al*. (*3*) gives us new insight into why ACAT1 inhibitors fail to show satisfactory effects in clinical trials as expected from basic research. The cohorts treated with RAA inhibitors could already show lower ACAT1 levels, and thus further inhibition of ACAT1 may not yield further beneficial effects.

Recently, statins, anti-platelets, and RAA inhibitors have become commonly used in high-risk patients. Therefore, clinical trials for newly developed drugs do not always prove drug efficacy, despite beneficial effects suggested by animal experiments. This discordance might be due to the unresolved cross talk among physiologically active substances that regulate common factors in hypertensive organ damage, such as inflammation, oxidative stress, and share stress. Further investigations are required to prevent inappropriate clinical trials and analyses.

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