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Hirata, Ken-ichi

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Editorial

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New Evidence of Probucol on Cardiovascular Events

Ken-ichi Hirata

The Cardiovascular Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

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Although intensive cholesterol lowering therapies with statins or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to reduce cardiovascular events (CVE), it is difficult to prevent CVE completely[1]. Therefore, additional effective pharmacological intervention is necessary to improve "residual risks" in combination with statins. Probucol, a diphenolic compound, was developed to reduce low density lipoprotein-cholesterol (LDL-C) levels without LDL receptor activity modulation before the development of statin. One of the unique characteristics of probucol it its potent anti-oxidant property, and the LDL particles from probucol-treated patients were strongly protected from oxidation[2, 3]. Probucol has been used for patients with dyslipidemia with efficacy and safety profiles especially in Japan. In addition, probucol reportedly reduced atherosclerotic plaque formation in WHHL rabbits, an animal model of familial hypercholesterolemia (FH)[4], and it is characterized by its ability to cause xanthoma regression.

There have been few studies on the effect of probucol treatment on the prevention of cardiovascular events. Clinical trials and meta-analysis demonstrated that probucol is effective in reducing the risk of restenosis and incidence of MACE after percutaneous transluminal intervention[5]. In addition, a cohort study named probucol observational study illuminating therapeutic impact on vascular events (POSITIVE) has also revealed the secondary-preventive effects of probucol in patients with heterozygous FH[6]. A POSITIVE study evaluated the long-term effects of probucol treatment on cardiovascular events in 410 patients with heterozygous FH. This study has demonstrated that long-term probucol treatment reduced secondary cerebro- and cardiovascular events in FH. Therefore, probucol has been used for the treatment and prevention of cardiovascular diseases especially in patients with homozygous FH during the past few decades.

However, probucol has been recognized to be harmful for clinical use because of its adverse effects to reduce high-density lipoprotein (HDL)-cholesterol (HDL-C) and QT prolongation on electrocardiograms. A randomized controlled trial "Probucol Quantitative Regression Swedish Trial (PQRST)," was performed in Sweden to examine whether administration of probucol to hypercholesterolemic patients may reduce femoral atherosclerosis or not[7]. Although treatment of patients with probucol for 3 years decreased LDL-C by 12% and HDL-C by 24%, respectively, probucol treatment did not increase lumen volume significantly. In PQRST, probucol administration in addition to diet therapy and cholestyramine treatment did not inhibit atherosclerosis progression in the femoral arteries. Finally, the United States and Europe quitted the use of probucol because of the reduction of serum HDL-C.

In the current PROSPECTIVE study, Yamashita, *et al.* analyzed 876 Japanese patients with coronary artery diseases (CAD) and dyslipidemia with LDL-C level ≥ 140 mg/dl without medication or those treated with lipid-lowering drugs randomly assigned to two groups by adjusting LDL-C level, followed up more than 3 years[8]. They have shown that probucol tended to reduce cardiovascular events (CVE) in CHD patients treated with statins, but the inhibitory effects of probucol on CVE were not statistically significant. They concluded that probucol might be effective for secondary prevention of CVE with conventional lipid-lowering therapy. Unfortunately, the sample size of

Address for correspondence: Ken-ichi Hirata, The Cardiovascular Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
E-mail : hiratak@med.kobe-u.ac.jp
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this study may be underpowered to prove the hypothesis.

Another important finding in the current study may be that the reduction of serum HDL-C by probucol does not increase CVE, but rather tended to decrease them. Although several epidemiological studies have revealed that HDL-C is a negative risk factor for CVE, clinal trials on increased HDL-C levels by cholesterol ester transfer proteins (CETP) inhibitors or niacin have failed to translate HDL-C elevation into reduced clinical outcomes[9]. In addition, recent studies have demonstrated the importance of HDL functionality, rather than HDL-C levels in the development of CAD. Recently, the mechanisms of pharmacological actions of probucol have been elucidated with a focus on HDL metabolism. The HDL-C reducing effect by probucol may be mediated by suppression of ABCA1, a membrane protein essential for HDL production. Other possible mechanism is the enhancement of the reverse cholesterol transport. Probucol has been shown to decrease serum HDL-C levels through enhancement of plasma CETP activity and increase of scavenger receptor class B type I (SR-BI) expression on the liver[10]. The reduction of HDL-C by probucol may be explained by both an enhanced transfer of cholesteryl esters from HDL to apolipoprotein B-containing lipoproteins mediated by CETP and increased uptake of cholesteryl esters from HDL into the liver via SR-BI. HDL-C reduction may not be a "side effect" but it most likely might reflect a mechanism of action of probucol. Probucol could be reconsidered as an option at least in case statins, which are known to be effective in lowering low density lipoproteins (LDL) and CAD risk, are not effective. Probucol is indicated for dyslipidemia with a high LDL-C level in JAS guideline 2017. In any case, because no large-scale clinical studies have been conducted, probucol use is limited to certain situations such as combination therapy with statins or in monotherapy in patients with statins intolerance. The IMPACT trial in patients with CHD is ongoing in Korea and China with a similar protocol. However, the primary endpoint of IMPACT is the changes in carotid IMT, and the secondary endpoint is the rate of cerebro- and cardiovascular events.

In summary, the current PROSPECTIVE study in addition to previous trials demonstrated that probucol may be effective for prevention of secondary cerebro- and cardiovascular events, aside from its application in conventional lipid-lowering therapy despite a marked reduction of HDL-C, although the differences of CVE were not statistically significant. A meta-analysis of PROSPECTIVE and IMPACT, or additional clinical trials should be required in future to establish the evidence of probucol on CVE.

Conflicts of Interest

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