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Current States of Clinical Perspectives on Medication for Dyslipidemia

Bando H[ab*]

[a]Tokushima University / Medical research, Tokushima, Japan
[b]Integrative Medicine Japan (IMJ), Shikoku Island Division, Tokushima, Japan

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Corresponding author: Bando H, Tokushima University, Medical Research, Tokushima, Japan; Tel: +81-90-3187-2485; E-mail: pianomed@bronze.ocn.ne.jp;
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Abstract

Current topics for dyslipidemia are described. Elderly people receiving statin (n=326,981) for 6.8 years showed reduced hazard ratio (HR) as total mortality 0.75, and cardiovascular mortality 0.80. Taking n-3 unsaturated fatty acids >3g daily reduced relative ratio (RR) as sudden death 0.70, stroke 0.74 and cardiac death 0.82. As LDL-C is reduced every 1.0 mmol/L (38.67 mg/dL), cardiovascular event will be reduced by 21%. The efficacy of inclisiran has been reported for reducing LDL-C value. In large RCTs of ORION 10/11 studies, patients with atherosclerotic cardiovascular disease (ASCVD) receiving inclisiran for 510 days showed decreased LDL-C ratio as 53.8%/49.2%.

Keywords: Dyslipidemia; Inclisiran; Statin; Atherosclerotic Cardiovascular Disease (ASCVD); LDL-C

Commentary

In recent years, various medical developments have been found in dyslipidemia [1]. What about the clinical effects of statins on the elderly and people with low cardiovascular risk? It seems not so satisfactory in the light of actual life extension. In the elderly, high level of LDL-C is not the only factors affecting the risk of developing atherosclerosis. For cardiovascular risk, the effects of n-3 unsaturated fatty acids may increase in a dose-dependent manner. However, in actual practice, the clinical effect is not apparent. What is the effect of improving the prognosis of dyslipidemia agents other than statins, such as inclisiran? [2]. In this articles, current topics concerning dyslipidemia will be described. A cohort study was reported that examined the effect of statin treatment in the elderly on the primary prevention of cardiovascular disease [3]. The study included 326,981 US veterans aged >75 (mean 81.1 years, 97% male, 91% white). After 6.8 years follow-up, cardiovascular mortality per 1000 man-years was 22.6 for statin users and 25.7 for non-users. Propensity score matching-corrected hazard ratio (HR) was 0.75 for total mortality, 0.80 for cardiovascular mortality, and 0.92 for arteriosclerotic cardiovascular events, which were significantly lower for statin users. In this study, special group of veterans was analyzed. Then, these results cannot be generalized, and the external validity is not always high [3]. Patients receiving statin treatment themselves may potentially have higher health levels than those who do not.

A secondary analysis of Aspirin in Reducing Events in the Elderly (ASPREE) study was reported on the efficacy of statins in healthy elderly people [4]. ASPREE is an RCT that examined the effect of aspirin on healthy life expectancy in 19,114 people aged 65 and over. This secondary analysis included 18,096 ASPREE participants aged 70 years and older (median 74.2 years, 56.0% female). The group who was taking statins at the start of the study was compared to the group who was not taking statins. Survival situation without disability (combined outcomes of total mortality, dementia, and persistent physical dysfunction) was examined. A median follow-up of 4.7 years showed no significant difference between statin use and unimpaired survival (HR 0.92).

A systematic review was also reported on the cardiovascular prognosis of statins in the frail elderly [5]. Six cohort studies were included in the review, and no RCTs that met the acceptance criteria were reported. In addition, no studies have been reported examining the effects on primary prevention or the results on cardiovascular events. Some studies in the secondary prevention showed a reduced risk of death (HR 0.28) [5].

In general, the effect of a drug is often indicated by a relative ratio of event incidence. In particular, cardiovascular drugs are rarely evaluated from their effects on life extension. Under these circumstances, a meta-analysis was reported that examined the effect of statins on life extension using previously reported RCT data [6]. Nineteen placebo-controlled RCTs in at least 1000 subjects were included. As a result, the number of days of postponement of events (days and [95% CI]) during statin follow-

up compared to placebo was 9.27 days [3.6-14.91] for cardiovascular death, 1.5 days [-2.2-5.3] for non-cardiovascular death, 18 days [12.1 to 24.1] for myocardial infarction and 6.1 days [2.86 to 09.39] for stroke [6]. Thus, a meta-analysis revealed the life-prolonging effect of statins. In other words, it should be noted that the research results shown as relative ratios tend to be estimated with the drug effect as an issue. Considering the practical life-prolonging effect, it seems to be smaller than the level expected so far.

Several systematic review meta-analyses have been reported on the effects of n-3 unsaturated fatty acids on cardiovascular disease. Rizo et al. conducted a review [7], including a double-blind RCT 17 study (n=83,617) with a follow-up period of 1 year or longer. As a result, it has been shown that the higher the dose of n-3 unsaturated fatty acids, the greater the benefit obtained. Less than 1 g daily did not reduce the risk of cardiovascular disease. At 2 g daily, a significant reduction in cardiac death was shown. The relative risk is RR = 0.55. Furthermore, administration of 3 g or more per day reduces the risk of sudden death (0.70), stroke (0.74) and cardiac death (RR: 0.82) [7].

A systematic review was reported on the factors affecting the medication adherence of cardiac statins [8]. Evaluating nine reviews, high social and economic status, high education levels, and middle-aged age had a positive impact on medication adherence. On the other hand, reduced medication adherence was observed in women and young, older, non-white races, low socio-economic status, new statin users, high out-of-pocket costs, experience of reverse effects, dosage/dose complexity, high potent level of statins, smoking and drinking habits, poor efficacy, and distrust of medical care [8]. The efficacy of inclisiran has been reported in patients with elevated LDL-C value. ORION-10 study in patients with atherosclerotic cardiovascular disease (ASCVD) was conducted. Successively, ORION 11 study in patients with ASCVD or at risk equivalent to ASCVD was investigated [9]. Both trials were RCTs comparing the inclisiran (284 mg) group and the placebo group, which were followed for 540 days. Inclisiran was injected subcutaneously on days 1 and 90, and every 6 months thereafter, and the ratio of change in in LDL-C was investigated as the primary outcome. As a result, the LDL-C level on day 510 decreased by 53.8% in the ORION-10 study and 49.2% in the ORION-11 study. Both were significantly different compared to the placebo ($p<0.001$). On the other hand, inclisiran showed more adverse events at the injection site than placebo. Elevated LDL-C has brought atherosclerosis from pathophysiological development, and then lowering LDL-C would be important to reduce the risk of ASCVD. As LDL-C is reduced every 1.0 mmol/L (38.67 mg/dL), CV event will be reduced by 21% [10]. Among these circumstances, physiological regulator of LDL-C that is serine-protease PCSK9, would promote the degradation of LDL receptor. Cost-effectiveness of inclisiran was analyzed, based on the ORION-10 trial for the costs and outcomes [11]. As a result, the cost of inclisiran should be 60% lower than that of evolocumab. In summary, future research development concerning LDL-C will be expected so as to prevent ASCVD [12].

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