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Editorial

Current trends in the management of dyslipidemia for prevention against cardiovascular diseases

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From a historical point of view, adequate treatment for dyslipidemia has been discussed and changed for long. There are recently four common broadly used agents, which are I) statins, II) n-3 unsaturated fatty acids, III) ezetimibe and IV) fibrates. In this article, recent topics concerning dyslipidemia and these agents would be described.

When evaluating the effect of medical agents, it is generally expressed by the event occurrence rate of the active drug to placebo. This is shown by the numerical value of the Hazard Ratio (HR). However, this biomarker cannot indicate how long the event can be delayed in the future. Under such circumstances, an impressive study on statins has been reported.

Firstly, statin agents have been broadly used for long. There is a study summarized from 16 Randomized Controlled Trials (RCTs) for statin administration [1]. As a result, the average survival time was prolonged by 12.6 days (95% CI: 7.1-18.0) by the statin administration. Furthermore, it showed 10.2 days for the primary preventive group and 17.4 days for the secondary preventive group [1].

Two papers have been recently published on the efficacy of statins for the elderly. One is a paper that analyzed 28 RCTs [2]. The subjects included 186,854 patients with a median follow-up of 4.9 years. When the value of LDL-C decreased by 1.0 mmol/L (38.7 mg/dL), the ratio of major cardiovascular events decreased by 21% (Rate Ratio, RR: 0.79). This reduction in risk shows a similar trend at almost all ages. As their age became higher, the effective degree became lower. There was no statistically significant difference in the primary prevention group for over 70 years.

Another study was a summary of 23 meta-analyses investigating changes in lipids and cardiovascular outcomes in 65 years and older 60,194 subjects [3]. As a result, the administration of statins for primary prevention reduced coronary artery disease (RR: 0.79) and myocardial infarction (RR: 0.45), while no significant changes in total mortality (RR: 0.95) and cardiovascular fat (RR: 1.01). There was no significant risk reduction for stroke (RR: 0.78). Besides, the administration of statins for secondary prevention significantly reduced total death (RR: 0.80), cardiovascular disease (RR: 0.68), myocardial infarction (RR: 0.68) and revascularization (RR: 0.68). On the other hand, fibrate did not show a significant risk reduction in stroke, cardiovascular death or cardiovascular disease.

There was a compared report for continuation and discontinuation groups with statin treatment [4]. A total of 120,173 patients with good adherence were followed up for 2.4 years on average. The discontinued group showed a 33% increase in hospitalization for all cardiovascular events (HR: 1.33), associated with hospitalization for coronary events (HR: 1.46) and cerebrovascular disease events (HR: 1.26) [4]. Furthermore, a meta-analysis of 45 studies was published for the background of patients unable to continue taking statins [5].

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As a result, the influencing factors included low income (Odds Ratio, OR: 1.20), smoking (OR: 1.14), higher medical payment (OR: 1.61), multidrug combination (OR: 1.04), dementia (OR: 1.18), respiratory disease (OR: 1.05) [5].

There has been a novel project, which is Statins in Reducing Events in the Elderly (STAREE). It is a world-first study conducted by Universities across Australia on the effects of statins on healthy aging [6]. The characteristic points would be I) it is funded by public health research grants, II) it does not accept funding from pharmaceutical companies to reduce influence and bias, III) its findings will directly benefit current and future generations of Australians [6].

Secondly, n-3 unsaturated fatty acids have been used. As to the efficacy for cardiovascular disease, there have been some reports of a randomized, double-blind, placebo-controlled trial.

The first is the Vitamin D and Omega-3 Trial (VITAL) [7]. A total of 25,871 subjects were compared between the n-3 administration group and the placebo group. Major cardiovascular events (a composite of myocardial infarction, stroke or death from cardiovascular causes) were examined. At a median follow-up of 5.3 years, there were no significant differences between the two groups (HR: 0.92) [7].

The second is the Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT) [8]. It was a multicenter, randomized, double-blind, placebo-controlled trial, with 8,179 subjects taking statins. For the EPA group, icosapent ethyl 4 g/day was provided for comparison with the placebo group. Outcomes were studied as the primary endpoint, including a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization or unstable angina. Following both groups for 4.9 years, the risk for cardiovascular events was significantly reduced by 17.2% in the EPA group and 22.0% in the placebo group (HR: 0.75) without a significant difference between them [8].

Furthermore, there is a systematic review meta-analysis of the RCT. The purpose was to examine the effect of Omega-3 Fatty acids on mortality, morbidity and adverse events in patients with acute myocardial infarction (AMI) [9]. The results from 24,414 patients in 10 studies showed no significant difference in total mortality (RR: 0.86), but significantly reduced risk in cardiovascular death (RR: 0.77) and acute myocardial infarction (RR: 0.77) [9].

On the other hand, there is a Study of Cardiovascular Events in Diabetes (ASCEND), in which the effect of n-3 unsaturated fatty acid was not observed [10]. A total of 15,480 diabetic patients without a history of cardiovascular disease were followed for 7.4 years. As a result, the occurrence of serious vascular events was 8.9% in the n-3 group and 9.2% in the placebo group, with no significant difference (RR: 0.97) [10].

Regarding the above reports of n-3 unsaturated fatty acids, the results differ due to various factors such as differences in subject characteristics, differences in high risk, the dosage of ethyl icosapentate and so on. These studies have different method protocols. In VITAL and ASCEND, subjects showed a lower risk of cardiovascular events and received 1 g/day of n-3 unsaturated fatty acids [7,10]. On the other hand, in REDUCE-IT, subjects showed a higher risk for cardiovascular events and received 4 g/day of ethyl icosapentate [8]. Thus, it is necessary to compare the details of the intervention content for several studies. Based on the results of REDUCE-IT, American Heart Association (AHA) has rated n-3 unsaturated fatty acids as an effective and safe option to reduce triglyceride as monotherapy or as an adjunct to other lipid-lowering drugs [11].

The third agent is ezetimibe. There have been reports of RCTs such as SEAS [12], SHARP [13] and IMPROVE-IT [14]. Recently, a meta-analysis of 26 RCTs has been reported [15]. Whether the combination of statins and ezetimibe has a benefit over statin alone is still under investigation.

Recent topics include reports of the efficacy of ezetimibe in the elderly [16]. It is a multicenter, prospective, randomized, open-label, blinded end-point evaluation conducted at 363 medical institutions in Japan. It was Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75). Totally 3,796 subjects were randomly assigned to the ezetimibe group (10 mg once daily) versus the control group. The primary outcome was a composite of sudden cardiac death, myocardial infarction, coronary revascularization or stroke. As a result of follow up to 4.1 years, the ezetimibe group showed a significant reduction of the primary outcome (HR: 0.66). Secondary outcomes showed significantly reduced values, which were the incidences of composite cardiac events (HR: 0.60) and coronary revascularization (HR: 0.38) [16]. However, it should be noted that this study is an open-label study and soft endpoint includes coronary revascularization. Therefore, effectiveness may have been overestimated.

Fourth agents are fibrates. They have a potentially beneficial effect on primary prevention, secondary prevention and reduced risk of cardiovascular disease. However, the clinical effect for total and cardiovascular mortality have not been identified [17,18]. Furthermore, Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have also been reported to reduce cardiovascular risk, but their effect on mortality risk has been uncertain [19,20].

In summary, recent topics on oral agents for dyslipidemia were introduced. We hope that this article will serve as a reference for the drug treatment of patients with various conditions in the future.

Conflict of interest

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