

Time to consider an Asian guideline for management of dyslipidemia?

Atherosclerotic vascular disease is the major cause of morbidity and mortality in patients with diabetes mellitus. It is well established that patients with diabetes tend to show atherogenic lipid profiles related to insufficient insulin action, including the appearance of small dense low-density lipoprotein (LDL), an increase in the amount of remnant lipoproteins, and a decrease in and functional disability of high-density lipoproteins (HDL). Indeed, patients with type 2 diabetes have been shown to benefit from lipid-lowering therapy in terms of prevention of cardiovascular events, as well as the decline in renal function. Cholesterol-lowering therapy reduces the relative risk ratio of cardiovascular events to a similar degree in diabetic and non-diabetic subjects. However, the actual benefit is expected to be greater in patients with diabetes, as they show a higher absolute risk, resulting in a lower number of patients that need to be treated. Therefore, it is important to properly manage not only blood sugar and blood pressure, but also lipids, from the earliest stage of disease as possible.

Lipid treatment guidelines for both diabetic and non-diabetic subjects have been established in the USA and Europe, primarily based on results from epidemiological studies and clinical trials^{1,2}. In many Asian countries, management of dyslipidemia is carried out according to these guidelines in daily clinical practice. The Japan Atherosclerosis Society published

original guidelines for the prevention of atherosclerotic cardiovascular diseases, including those for patients with diabetes as well, based on results from both Japanese and Western studies, taking into account that the risk for developing coronary artery disease is lower in Japanese compared with Western populations³.

The Western and Japanese guidelines are similar in their basic concepts. For example, both recommend lifestyle modification focusing on adequate diet, increased physical activity, smoking cessation and weight loss in obese patients as the first-line therapy. A reduction in excessive calorie and saturated fat intake, increase of omega-3 fatty acids and viscous fiber in the diet are recommended in every guideline. Pharmacological therapy, primarily with statins, is generally used when the lipid management goals cannot be achieved by lifestyle modification alone.

In contrast, the idea of therapeutic targets, management goal level and the way to use lipid-lowering drugs are not identical between the Western and Japanese guidelines (Table 1). In the Western guidelines, diabetes is considered to indicate a high risk for cardiovascular disease (CVD) practically equivalent to that of patients with overt CVD. Therefore, it is recommended to reduce the LDL cholesterol (LDL-C) level below 100 mg/dL (2.6 mmol/L) in type 2 diabetes patients without evident CVD

Table 1 | Comparison of lipid management goals for diabetic patients in the USA, Europe and Japan

	LDL-C goals (mg/dL)			Alternative goals to LDL-C		TG (mg/dL)	HDL-C (mg/dL)	Type 1 diabetes
	Without CVD	With overt CVD	Alternative goals in case drug-treated patients do not reach the target value	Non-HDL-C (mg/dL)	Apo-B (mg/dL)			
USA ¹	<100	<70*	30–40% reduction	LDL-C goals +30 (mg/dL)	<80–90	<150	>40 in men >50 in women	Similar lipid-lowering goals as in type 2 diabetes, particularly if having other cardiovascular risk factors
Europe ²	<100	<70*	ND	LDL-C goals +30 (mg/dL)	<80–100	<150	>40 in men >45 in women	<30% LDL-C reduction with statins in the presence of microalbuminuria and renal diseases
Japan ³	<120†	<100†	20–30% reduction	LDL-C goals +30 (mg/dL)	ND	<150	≥40	ND

Apo-B, apolipoprotein B; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; ND, not described.

*For the patients with overt CVD or without CVD who are over the age of 40 years and have one or more other CVD risk factors.

†In the Japanese guideline, LDL-C goal of <100 mg/dL is applicable to subjects with prior coronary artery disease; and those with stroke or peripheral artery disease are recommended to achieve the goal of <120 mg/dL.

(primary prevention). Patients with diabetes with prior CVD are advised to lower their LDL-C more intensively to below 70 mg/dL (1.8 mmol/L), because of the high risk of recurrent events (secondary prevention). The values of these lipid treatment goals have been shown by the results of clinical studies mainly carried out in Europe and the USA.

The Japanese guideline recommends a LDL-C level below 120 mg/dL (3.1 mmol/L) for patients with diabetes without prior coronary artery disease (CAD), and below 100 mg/dL for patients with CAD, regardless of whether they have diabetes. The major reasons for setting milder goals in the Japanese guidelines compared with those in Western guidelines are as follows. (i) As in Western countries, Japanese patients with diabetes also show a higher relative risk of developing CAD and stroke by two- to threefold compared with the subjects with normal glucose tolerance. However, the absolute risk of developing CAD is lower in Japan by 30–70% compared with the USA and Europe⁴. No evidence to date shows that cardiovascular risk in Japanese patients with diabetes without prior CAD is as high as that in non-diabetic subjects with history of CAD either. (ii) The results of large-scale randomized trials to evaluate the outcome of intensive lipid lowering are currently lacking in Japan. Therefore, it is still uncertain whether LDL-C lowering below 100 mg/dL benefits Japanese patients with diabetes for primary prevention, and especially whether the use of high-dose statin outweighs the risk of adverse effects. Risk stratification within a diabetic population; for example, the presence of multiple risk factors or microvascular complications, might be informative in identifying patients who require more intensive treatment. Regarding secondary prevention of diabetes, many Japanese cardiologists in fact already aim at lowering LDL-C below 70 mg/dL. Because several clinical trials are now ongoing to examine the effect of intensive lipid lowering therapy on preventing CVD in type 2 diabetes patients in Japan, it is possible that the Japanese guidelines will also adopt stricter management goals in the future.

As mentioned earlier, lifestyle modification plays a central role in the management of dyslipidemia in patients with diabetes, irrespective of the different guidelines. When such an approach is insufficient to achieve the lipid goals, drug therapy is considered. In cases where the LDL-C target value could not be achieved even with use of statins, a reduction of LDL-C by 30–40% in the USA and 20–30% in Japan, respectively, has been proposed as an alternative goal. In addition, the USA and European guidelines recommend the use of statins in patients with diabetes with overt CVD, or in subjects without CVD who are over the age of 40 years and have one or more other CVD risk factors. Such recommendations are not yet included in the Japanese guidelines because of the lack of evidence in an Asian population.

Because patients with diabetes remain at high risk of cardiovascular events, even at the LDL-C goal, and often have accompanying low HDL cholesterol (HDL-C) and high triglyceride (TG) levels, it is important to care for these lipid param-

eters as well. To date, however, clinical trial evidence is limited on the effectiveness of interventions targeting these variables on further reducing the cardiovascular risk. Therefore, HDL-C and TG are currently regarded as secondary targets in lipid management. A HDL-C value of 40 mg/dL or more is recommended in all guidelines, with higher goals for females in the Western guidelines. It might also be important to consider not only the amount of HDL, but also its function; for example, cholesterol efflux, anti-oxidative and anti-inflammatory capacity, to establish HDL-C as a true therapeutic target⁵. For TG, a value <150 mg/dL is suggested in all guidelines. Non-HDL-C is now also being widely used as a target secondary to LDL-C in subjects with high TG. Apolipoprotein B, carried by both LDL and TG-rich lipoproteins, is another useful parameter included in the USA and European guidelines, but not yet in the Japanese guidelines.

Finally, most of the clinical trial evidence for lipid management in cardiovascular prevention has been obtained for type 2 diabetes patients after middle age, and very little exists for type 2 patients under the age of 40 years or for type 1 patients at any age. In the USA guidelines, it is recommended that similar lipid-lowering goals should be considered in type 1 diabetes patients as in type 2 diabetes patients, particularly if they have other cardiovascular risk factors. The European guidelines recommend lowering the LDL-C by at least 30% in type 1 diabetes patients, using statins as the first choice, and if necessary, with drug combinations, irrespective of the basal LDL-C concentration in the patients. Currently, there is no specific recommendation for the LDL-C management goal of type 1 diabetes patients in the Japanese guidelines, and this is one of the fields where Asian evidence is required.

Concerning the recent accumulation of both epidemiological and clinical trial data in Asia, it will be beneficial to further analyze them and consider what is the most suitable way to evaluate and treat dyslipidemia in Asian patients with diabetes to safely and efficiently prevent cardiovascular disease. In other words, the time is ripe for there to be specific guidelines developed from data on Asians, by Asians, for the Asian population to achieve longevity and better quality of life.

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