Intensive lipid-lowering therapy in high-risk diabetic patients

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Hypertension, dyslipidemia, and diabetes mellitus (DM) are major risk factors for atherosclerotic diseases, and there are several recommendations for their treatment. Regarding low-density lipoprotein cholesterol (LDL-C) levels, the European Society of Cardiology/European Atherosclerosis Society cholesterol guidelines recommend a target LDL-C level <55 mg/dl in patients with very high risk and <70 mg/dl in patients with high cardiovascular (CV) risk [1]. Regarding intensive lipid-lowering therapy, Khan et al. performed a meta-analysis of 11 randomized controlled trials (130,070 patients) comparing intensive lipid-lowering therapy (LDL-C < 70 mg/dl) and less-intensive lipid-lowering therapy (LDL-C ≥ 70 mg/dl) [2]. Compared with the less-intensive lipid-lowering therapy, intensive lipid-lowering therapy was significantly associated with the lower risk of all-cause mortality [risk ratio (RR) 0.94 (95% confidence interval 0.89–1.00), $P = 0.04$], CV mortality [RR 0.90 (0.81–1.00), $P = 0.04$], myocardial infarction [RR 0.80 (0.72–0.90), $P < 0.001$], cerebrovascular events [RR 0.81 (0.73–0.90), $P < 0.001$], and major adverse cardiovascular events (MACEs) [RR 0.89 (0.84–0.93), $P < 0.001$]. Although concerns exist that extremely low levels of LDL-C can enhance the risk of cancer, DM, and hemorrhagic stroke, there are no significant differences between intensive lipid-lowering and less-intensive lipid-lowering therapies in terms of cancer, DM, or hemorrhagic stroke. The researchers concluded that treatment to achieve LDL-C levels below 70 mg/dl using intensive lipid-lowering therapy can safely reduce the risk of mortality and MACEs.

DM patients tend to have multiple risk factors, not only hyperglycemia but also hypertension, dyslipidemia, and insulin resistance. DM patients develop microvascular complications, including retinopathy, nephropathy and neuropathy, and

macrovascular complications, such as stroke, coronary artery disease (CAD), and peripheral artery disease (PAD) [3]. To prevent these diabetic complications, glycated hemoglobin A1c (HbA1c) less than 7.0%, systolic blood pressure (SBP) lower than 130 mmHg, diastolic blood pressure (DBP) lower than 80 mmHg, LDL-C lower than 120 mg/dl, high-density lipoprotein cholesterol (HDL-C) 40 mg/dl or greater, triglycerides lower than 150 mg/dl, and non-HDL-C lower than 150 mg/dl are recommended for DM patients in all guidelines in Japan [4–6]. Furthermore, LDL-C lower than 100 mg/dl and non-HDL-C lower than 130 mg/dl are recommended for DM patients with CAD, and LDL-C lower than 70 mg/dl and non-HDL-C lower than 100 mg/dl are recommended for high-risk DM patients with CAD in Japan (Fig. 1). Although DM patients undergo revascularization procedures for CAD or PAD, the outcomes are less favorable than those of non-DM patients. Therefore, intensive preventive therapy through the combination of diet, exercise, and optimal medical therapy is important for DM patients to reduce their CV risk and prevent CV events and disability.

To explore the potential benefits of treat-to-target therapy in very high-risk DM patients, Itoh et al. investigated the incidence of CV events with intensive lipid-lowering therapy (LDL-C < 70 mg/dl, $n = 2518$) or standard lipid-lowering therapy (LDL-C 100–120 mg/dl, $n = 2524$) in DM patients with hypercholesterolemia, diabetic retinopathy, and no history of CAD [7]. The standard versus intensive statin therapy for hypercholesterolemic Patients with diabetic retinopathy (EMPATHY) study used a multicenter, prospective, randomized, open-label, blinded end point (PROBE) design. The primary outcome was the composite incidence of CV events, including cardiac, cerebral, renal, and vascular events, or CV-associated death. They found no significant decrease in CV events or CV-associated deaths with intensive therapy, possibly because the between-group difference in LDL-C was lower than they expected (27.7 mg/dl at 36 months of treatment).

Then, to identify patients who will benefit from intensive statin therapy among high-risk DM patients without prior CV diseases, Shinohara et al. reported the subanalysis of the

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Fig. 1 Multiple risk factors and complications in DM patients. DM diabetes mellitus, CAD coronary artery disease, PAD peripheral artery disease, HbA1c glycated hemoglobin A1c, BP blood pressure, LDL-C

low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglyceride, ↓ progression, T protection. *DM patients without CAD, #DM patients with CAD, \$high-risk DM patients with CAD

EMPATHY study [8]. The 4980 patients enrolled in the EMPATHY study were divided into BP $\geq$ 130/80 mmHg (SBP $\geq$ 130 mmHg and/or DBP $\geq$ 80 mmHg, $n = 3335$) and BP < 130/80 mmHg ($n = 1645$) subgroups according to baseline BP levels. Intensive statin therapy with a target LDL-C of <70 mg/dl significantly reduced the primary outcome compared with standard statin therapy with a target LDL-C of 100–120 mg/dl in DM patients with BP $\geq$ 130/80 mmHg but not in those with BP < 130/80 mmHg. Their findings suggested that intensive BP control (BP < 130/80 mmHg), similar to intensive LDL-C control (LDL-C < 70 mg/dl), is also useful for the prevention of CV events in high-risk DM patients with hypertension and hypercholesterolemia. Combined optimal therapy is important for high-risk patients with multiple risk factors.

Hypertriglyceridemia is an important residual risk factor for CV diseases in DM patients after the reduction of LDL-C with statin, ezetimibe, and proprotein convertase subtilisin kexin 9 antibody inhibitors. Fibrates, nicotinic acids, and n-3 polyunsaturated fatty acids are used for the treatment of hypertriglyceridemia. In patients with hypercholesterolemia and hypertriglyceridemia, combined therapy with statins and fibrate is recommended by JAS guidelines, and these treatments can be carefully combined [6]. The creatine kinase level and liver and renal function need to be checked before and after this combined therapy to screen for rhabdomyolysis or liver and renal dysfunction.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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