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Paradigm Shift of the Strategy on Diabetic Nephropathy in Recent Decade

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Editorial

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Editorial

Almost 20 years ago, it was reported that pancreas transplantation can reverse the lesions of diabetic nephropathy in patients with type 1 diabetes [1] and intensive blood-glucose control decreases the risk of microvascular complications in patients with type 2 diabetes [2] in 1998. Steno 2 study revealed that the intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria slowed progression to nephropathy, and progression of retinopathy and autonomic neuropathy in 1999 [3]. Since then, the strict multifactorial intervention has been accepted to be most effective approach for prevention of diabetic microvascular complications.

KDIGO Clinical Practice Guideline Diabetes and CKD described the characteristics of DKD (diabetic kidney disease) such as absence of diabetic retinopathy, fast decline of renal function, refractory hypertension, acute renal failure after starting the renin-angiotensin-aldosterone system (RAS) blockade and so on in 2007 [4]. This variability of renal disease in patients with diabetes mellitus has changed the strategy on diabetic nephropathy such as the strict multifactorial intervention in recent decade.

Blood Glucose Control

10 years ago, it was reported that there were no significant effects of intensive glucose control (HbA1c 6.5% vs 7.3%) on major macrovascular events although the type of glucose control reduced the incidence of nephropathy [5]. In addition, it was also reported that the use of intensive therapy to target normal glycated hemoglobin levels (HbA1c 6.4% vs 7.5%) for 3.5 years increased mortality and did not significantly reduce major cardiovascular events [6]. It was reconfirmed by other report that intensive therapy (HbA1c 6.9% vs 8.4%) could not achieve any beneficial effects in terms of major cardiovascular events and the rate of death from any causes [7].

It is reported recently that sodium-glucose cotransporter 2 inhibitor such as empagliflozin [8] and canagliflozin [9] was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care. The glycated hemoglobin level in the drug-treated group was more than 7% in both trials. For now, there is no specific rationale to recommend strict glucose control in patients with diabetes mellitus.

Blood Pressure Control

There is no consensus of target blood pressure level in patients with diabetic mellitus to prevent vascular complications. Less than 140/90 was recommended by JNC8 and ASH/ISH in 2014 [10], which is little bit higher than JSH criteria in 2014 (less than 130/80), because of the influence of ACCORD-BP trial [6]. It was reported in 2015 that targeting a systolic blood pressure of less than 120 mmHg, as compared with less than 140 mmHg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause (SPRINT trial) [11]. ACC/AHA recommended less than 130/80 as targeting blood pressure in 2017 [12]. However, ADA recommended less than 140/80 in 2018, same as previous guideline level, because SPRINT trial excluded people with diabetes mellitus [13]. Recently, secondary

analyses of these two trials (ACCORD and SPRINT) revealed that intensive lowering of systolic blood pressure increased the risk of incident chronic kidney disease in people with and without type 2 diabetes [14]. Further examination must be waited to answer the question of target blood pressure in people with diabetic mellitus.

Lipid Management

In 2008, it was reported that patients with diabetes and coronary heart disease marked reduction in cardiovascular events with intensive lipid lowering [15]. It was reported recently that when added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes in the patients after acute coronary syndromes [16]. After that, it has been thought that lowering LDL cholesterol to levels below previous targets provided additional benefit. However, it is still uncertain whether aging people with diabetic mellitus could get same advantage, especially as primary prevention.

When both the population composition and the disease constitution are changing in aging society, guideline is not an absolute golden rule, but one of the indicators as greatest common divisor. We must think about offering most appropriate treatment for each individual patient with different clinical conditions.

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