

Management for Hypertension in Patients with T2D

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Abstract

Healthy life expectancy (HLE) is useful for management of hypertension in type 2 diabetes (T2D) patients. During development of anti-hypertensive agents (AHAs), comparative study for Angiotensin-neprilysin inhibition vs enalapril against heart failure (HF) was found. The project was Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Clinical Trial. It was designed to compare the effect of the angiotensin receptor-neprilysin inhibitor (ARNI) in patients with symptomatic HF with reduced ejection fraction (HFrEF). Novel marker would be urinary cyclic guanosine monophosphate/B-type natriuretic peptide (ucGMP/BNP), reflecting the response ability to natriuretic peptides.

Keywords: healthy life expectancy (HLE); Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF); angiotensin receptor-neprilysin inhibitor (ARNI); Heart failure with reduced ejection fraction (HFrEF); cyclic guanosine monophosphate /B-type natriuretic peptide (ucGMP/BNP)

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Commentary

In recent years, various discussion have been found for the correlation among diabetes, hypertension, cardiovascular disease in the light of life expectancy and mortal rate. Several healthy plans were observed in the light of healthy life expectancy (HLE) [1]. Some determinants and priority were identified for extending HLE in Japanese local governments. Latest HLE values in average were found as 79.2/83.8 years (male/female) by the analyses of simple and multiple regression. In order to analyze the relationships among cardiovascular health (CVH), CVH-related HLE and mortality risk, applicants with/without type 2 diabetes (T2D) were investigated [2]. They included 310 thousand applicants with 56.6 years in average. Several markers were measured for BMI, lipids, blood glucose (BG), blood pressure (BP), diet, activity, smoking and sleep. Comparing the results of diabetic/non-diabetics, additional life years at 50 years showed 9.79/5.58 years for men, and 24.21/10.18 years for female, respectively.

For long, the following phrase has been well-known, that is “the lower, the better”. It may indicate three aspects in the clinical practice. First is applicable to most cases of dyslipidemia. However, its quality improvement has been important, and the involvement of residual factors also needs to be considered. Second is the adequate control of BG [3]. However, hypoglycemia would be exceptional situation. It is important to know how to make lowering BG depending on each person and occasion. Third is BP control, in which “the lower the better”

would be preferable. However, we have to debate which anti-hypertensive agents (AHAs) will be applied and which BP level will be recommended.

From the results of United Kingdom Prospective Diabetes Study (UKPDS), the suppression effects of diabetic complication were observed by the adequate BP control [4]. For 9-year follow up, average BP was decreased from 154/87 to 144/82 mmHg. By lowering BP level, the risk suppression was obtained in the following: total mortality -18%, acute myocardial infarct -21%, total diabetic complication -24% (p=0.005), and development of microangiopathy -37% (p=0.009). These results have been known widely, which became the milestone of diabetic therapeutic management for long. For control of BP, preferable goal has been used for <130/80 mm Hg in T2D patients. However, the results of Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial could not show apparent beneficial data for lowering BP. For optimal BP, 38 thousand participants were analyzed [5]. Then, lowering BP brought 10% reduction for all-cause mortality, in which 0.90 of odds ratio, 0.83-0.98 of confidence interval, as well as 17% reduction for stroke development. Consequently, treatment goal of systolic BP for 130-135 mmHg would be acceptable.

During clinical development of AHAs, meaningful comparative report for Angiotensin-neprilysin inhibition vs enalapril against HF was found [6]. The former showed reduced risk of hospitalization by heart failure (HF) by 21% and reduced symptoms of HF significantly. The project was named as PARADIGM-HF Clinical Trial (Prospective Comparison of

ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure). It was designed to compare the effect of the angiotensin receptor-neprilysin inhibitor (ARNI) LCZ696 with enalapril in patients with symptomatic HF with reduced ejection fraction (HFrEF). It included 8442 cases associated with class II, III, or IV HF and also an ejection fraction of 40% or less [6]. As a result, LCZ696 showed the superiority to enalapril for decreasing the risks of hospitalization and death. These studies were supported by Novartis. Neprilysin has preferable clinical efficacy on diabetic nephropathy. For double-blind, randomized PARADIGM-HF, comparative study was conducted for sacubitril/valsartan and enalapril in 8399 cases. The former showed slower decline rate of eGFR as -1.3 versus -1.8 mL/min per 1.73m^2 /year with $p < 0.0001$ [7].

T2D becomes the independent risk factor for HF progression. A combined sacubitril/valsartan shows improved mortality and morbidity for patients with HFrEF in comparison with enalapril. These two agents were provided and compared for 3778 diabetic cases [8]. The former showed better HbA1c improvement as 0.26% vs 0.13% for 1 year, and the between-group reduction became 0.14% for 3 years. Thus, the former has more clinical efficacy of reducing HbA1c level. Consequently, hypertensive T2D patients may show less legacy effect on BP compared with BG. However, maintaining strict BP can generally control suppressive diabetic complications. The adequate goal would be less than 130/80 mmHg. If the case has proteinuria, the agents of renin-angiotensin system (RAS) inhibitors would be recommended for the first choice. The current agent contains the combination of these two elements, and then it will be expected to contribute applicable control of BP and HF, that are diabetic complications [8].

The treatment for HF has been based on New York Heart Association (NYHA) classification. Combined factors of PARADIGM-HF, NYHA and N-terminal pro B-type natriuretic peptide (NT-proBNP), 8326 cases were studied [9]. By the stratification of NT-proBNP, cases of NYHA class I with elevated NT-proBNP ($n=175$) showed higher event rate than cases with low NT-proBNP from other NYHA class. The results of HR were 3.43 vs I, 2.12 vs II, and 1.37 vs III, respectively. Consequently, NYHA classification may be rather limited for differentiating mild HF condition.

A recent report showed the impressive findings for PARADIGM-HF trial [10]. The novel diagnostic measure is to calculate the ratio of urinary cyclic guanosine monophosphate (ucGMP) to B-type natriuretic peptide (BNP). It seems to reflect the response ability for tissues to natriuretic peptides. The ucGMP/BNP ratio and clinical efficacy of sacubitril/valsartan were studied for 1 month and 8 months with randomization. The results of ucGMP/BNP ratio were categorized into the tertiles. Cases with higher tertiles showed lower outcome risk. The comparative data of hazard ratio were 1.0 in tertile 1, 0.57 in tertile 2, and 0.54 in tertile 3. Consequently, higher ucGMP/BNP ratio seems to have better outcomes in the cases with HF and reduced ejection fraction. Furthermore, sacubitril/valsartan group increased the

ratio in comparison with enalapril group.

In summary, it is expected that beneficial ARNI contributes hypertensive T2D patients. Furthermore, related research will be developed with providing wellness and happiness to everyone.

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