

Perspective of the β -blockers for the patients with diabetes and heart failure

Abstract

Patients with diabetes and heart failure have been increasing due to Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) study. β -blockers showed significantly suppressed cardiovascular events in the strict glycemic control group. Sodium-glucose Cotransporter-2 Inhibitors (SGLT2i) seem to be beneficial for diabetes and heart failure. Clinical efficacy of β -blockers would be suggested from three studies including Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial, Canagliflozin cardiovascular Assessment Study (CANVAS) and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study. Further discussion will be expected with research in detail.

Keywords: Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) study, Canagliflozin cardiovascular Assessment Study (CANVAS), Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study, The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study, sodium–glucose cotransporter 2 (SGLT2) inhibitors

Volume 8 Issue 4 - 2020

Hiroshi Bando^{1,2}¹Tokushima University / Medical Research, Tokushima, Japan²Japan Low Carbohydrate Diet Promotion Association, Kyoto, Japan

Correspondence: Hiroshi BANDO, Tokushima University / Medical Research, Nakashowa 1-61, Tokushima 770-0943 Japan, Tel +81-90-3187-2485, Email pianomed@bronze.ocn.ne.jp

Received: August 15, 2020 | **Published:** August 31, 2020

Introduction

In the world, the social environment and lifestyle are changing, and then diabetic patients has been increasing rapidly.¹ Diabetes is a significant risk factor for ischemic heart disease due to arteriosclerosis. Therefore, myocardial ischemia, angina and myocardial infarction may develop and lead to heart failure.² It means the combination of metabolic and cardiovascular diseases, resulting in a serious situation. In fact, the prevalence of diabetes with heart failure patients is increasing. There was the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) study with randomly selected 1677 patients.³ According to the JCARE-CARD survey, the ratio of diabetes with heart failure was 30% and it increased to 44% associated with acute heart failure.

On the other hand, β -blockers are widely used in clinical settings and their effects are known.⁴ β -blockers for diabetics have long been controversial.⁵ The reasons include that the adverse effects on glucose metabolism and the subjective symptoms of hypoglycemia are difficult to detect. However, the effect of heart failure and improvement of prognosis seems to be greater than the disadvantage, and then β -blockers for diabetes have not been so limited.⁶ This article describes the effects of β -blockers on these subjects based on previous evidence.

Diabetes mellitus with hypoglycemia leads to cardiovascular events due to increased stimulation of sympathetic nerves. If this response is suppressed by β -blockers, it may have a protective effect on the cardiovascular system.⁷ A sub-analysis of the ACCORD study was performed and reported the differences in the use of β -blockers.⁸ Those who took β -blockers had significantly suppressed cardiovascular events in the strict glycemic control group compared to the standard group. Overall mortality was not increasing and administration of β -blockers appeared to be beneficial. However, in the ACCORD trial,

the number of heart failure complications at the time of enrollment was low at about 6%, and then discussion is still necessary.

There was another study from the data of US National Health and Nutrition Examination Survey 1999- 2010.⁹ The relationship was investigated between use of β -blockers and all-cause mortality in patients with diabetes (n=28409) and without diabetes (n=14,684). As a result, DM with β -blockers showed Hazard Ratio (HR) 1.60 compared to no meds, DM and coronary heart disease (CHD) with β -blockers showed HR 1.64 compared to no meds, and non-DM with β -blockers showed Hazard Ratio (HR) 0.68 compared to no meds. Several factors are involved in these data with necessary discussion.

In recent years, Sodium-glucose Cotransporter-2 Inhibitors (SGLT2i) have been widely used in clinical practice.¹⁰ From the evidence of these clinical trials, it is possible to suggest the pathophysiological situations of diabetes and heart failure. The following three studies are compared and summarized in Table 1. There was The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial. It targets diabetic patients with cardiovascular disease.¹¹ Initially 10.1% of the participants had heart failure. However, its criteria for heart failure were not so clear, and then it seems that more cases with heart failure may be included.¹² For the treatment group vs control group, the usage rate of β -blockers was 65.2% vs. 64.2%, which were rather low. One reason is considered to be the wide range of target patients and the low rate of heart failure.

The subjects of the Canagliflozin cardiovascular Assessment Study (CANVAS) are diabetic patients with a history of cardiovascular disease or high risk of diabetes.¹³ Canagliflozin was administered to 10142 subjects, and the effect was examined. Initially, heart failure was associated with 14.4% and β -blockers in 70.4%. On the other hand, β -blockers were administered at 50.6% in cases without heart failure.

Table 1 Mega study concerning SGLT2 inhibitors

	EMPA-REG OUTCOME	CANVAS Program	DAPA-HF
Medicine	empagliflozin	canagliflozin	dapagliflozin
Journal, year	N Engl J Med 373:2117	N Engl J Med 377:644	N Engl J Med 381:1995
Authors	Zinman B, 2015	Neal B, 2017	McMurray JJV, 2019
Society	European Society for the Study of Diabetes (EASD)	American Diabetes Association (ADA)	European Society of Cardiology (ESC)
subjects	T2DM with CV	CV / high risk DM	HFrEF
number	7,020	10,142	4,744
ratio with diabetes	100%	100%	41.80%
HbA1c	8.10%	8.20%	N/D
ratio with heart failure	10.10%	14.40%	100%
ejection fraction	N/D	N/D	less than 40%
taking β -blockers in heart failure	N/D (total 65.2%)	70.40%	96.00%
reference number	10)	12)	13)

There was a Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study.¹⁴ It was phase 3, placebo-controlled trial, and included 4744 patients with New York Heart Association (NYHA) class II, III, or IV heart failure, showing an ejection fraction (EF) of 40% or less. They are heart failure with reduced ejection fraction (HFrEF), including diabetes and non-diabetes, and were received either dapagliflozin or placebo. Among them, the administration rate of ACE inhibitor/ARB was 80% or more, and the β -blocker was administered to almost all cases, in the treatment group vs control group as 96.0% vs 96.2%. Diabetes was associated with 41.8%, and β -blockers were usually administered. DAPA-HF study was different from the former two. DAPA-HF was planned after SGLT2i was proved to be effective for heart failure. Therefore, it is suggested that the cases with heart failure were probably treated by cardiologist, and were prescribed β -blocker already.

There was a Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study.¹⁵ Totally 2368 cases with both T2DM and heart disease were randomly assigned to i) prompt revascularization with intensive medical therapy or ii) intensive medical therapy alone. It concluded that there was overall no significant difference in the rates of death and major cardiovascular events. For this sub-analysis, clinical efficacy of β -blocker was investigated.¹⁶ Among them, 2244 T2DM cases were studied, with or without history of myocardial infarction (MI)/heart failure (HF). In cases with diabetes and CHD, β -blockers showed efficacy in reducing all-cause mortality in those with MI/HFrEF (HR 0.60) but not in those without MI/HFrEF (HR 0.91). From various investigations above, they have recently updated elective coronary angiography.¹⁷

In summary, there are some important points as follows: i) Both diabetes and heart failure are increasing, ii) β -blockers for diabetic seem to be beneficial, but still with controversial discussion due to the situation, iii) SGLT2i may have effects for diabetes and also heart failure with expected further research in the future.

Acknowledgments

None.

Conflicts of interest

None.

Funding

None.

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