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ORIGINAL ARTICLE

Effects of Teneligliptin on the Progressive Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes Mellitus in Open-Label, Marker-Stratified Randomized, Parallel-Group Comparison, Standard Treatment-Controlled Multicenter Trial (TOPLEVEL Study): Rationale and Study Design

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Abstract

Background and Aims Diabetes mellitus (DM) can cause left ventricular (LV) diastolic dysfunction, leading to heart failure with preserved ejection fraction (HFpEF). Dipeptidyl peptidase IV (DPP-IV) inhibitors have failed to reduce hospitalization due to HF in type 2 DM (T2D) patients in a large-scale clinical trial, despite their cardiovascular protective effects. Therefore, it is important to investigate whether DPP-IV inhibitors can improve LV diastolic dysfunction in T2D patients. The aim of the study was to evaluate whether teneligliptin, the strongest of the DPP-IV inhibitors, improves LV dysfunction or prevents the worsening of LV diastolic function in T2D patients.

Methods The TOPLEVEL study is designed as an open-labeled, marker-stratified randomized, parallel-group comparison, standard treatment-controlled multicenter study. TOPLEVEL includes two marker-defined subgroups to give treatment recommendations for T2D patients with normal ($E/e' < 8$) or impaired LV diastolic function ($E/e' \geq 8$), where E/e' is the ratio of peak velocity of early transmitral diastolic filling by echocardiography to early diastolic mitral annular velocity by tissue Doppler echocardiography as LV diastolic function. Patients are randomly assigned to either teneligliptin (20 or 40 mg) or the standard treatment group. All patients are followed up for 2 years. The primary endpoint measure is the change in E/e' from baseline and 2 years after enrollment.

Conclusion and Perspectives TOPLEVEL is a clinical trial of teneligliptin targeting LV diastolic dysfunction in T2D patients. This study demonstrates the effectiveness of DPP-IV inhibitors on LV diastolic dysfunction, an important surrogate endpoint to predict the cardiovascular outcomes of HFpEF (UMIN000014589).

Keywords Left ventricular diastolic dysfunction · Type 2 diabetes mellitus · DPP-IV inhibitors · Teneligliptin

Introduction

The prevalence of diabetes mellitus (DM) has increased rapidly not only in Japan but also worldwide because of the marked changes in diet and living environment. This has resulted in about 22.1 million people with DM or suspected DM in Japan according to statistics released in 2007 by the Japanese Ministry of Health, Labor and Welfare. The most pressing issue for type 2 DM (T2D) is the progression of atherosclerosis and cardiovascular diseases such as acute coronary syndrome or stroke. T2D is also a potent independent risk factor of increased left ventricular (LV) mass [1, 2], LV diastolic dysfunction [3, 4], and heart failure (HF), especially

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HF with preserved ejection fraction (HFpEF) [5]. The prevalence of HFpEF markedly increases to more than 50% of the population of HF, whereas the mortality and morbidity in HFpEF patients are similar to those in HF patients with reduced EF [6]. Furthermore, there are no effective drugs for patients with HFpEF; this is in contrast with HF with reduced EF, for which there are a number of effective drugs such as angiotensin-converting-enzyme inhibitors and beta-blockers. Recently, dipeptidyl peptidase IV (DPP-IV) inhibitors have become available for T2D patients. Studies of DPP-IV inhibitors have provided evidence of cardiovascular protection [7, 8], suggesting that DPP-IV inhibitors can prevent the occurrence of HFpEF or improve the pathophysiology of HFpEF. Because several large-scale clinical trials have yielded negative results, indicating that DPP-IV inhibitors are not able to reduce the incidence of hospitalization due to HF in patients with T2D [9], we have now reached an unresolved clinical question as to the ability of DPP-IV inhibitors to improve LV diastolic function in T2D patients.

Therefore, we aimed to investigate whether teneligliptin [10], the strongest DPP-IV inhibitor, improves LV diastolic dysfunction or prevents the progression to diastolic dysfunction in T2D patients. If the present study shows that teneligliptin has a positive effect on LV diastolic dysfunction, this would suggest that DPP-IV inhibitors may be effective in treating HFpEF in T2D patients.

Methods and Design

Purpose

The purpose of the present study is to determine (1) whether teneligliptin improves LV diastolic dysfunction and (2) whether teneligliptin prevents progressive worsening of LV diastolic function in T2D patients.

Study Design

The TOPLEVEL study is designed as an open-label, marker-stratified randomized multicenter study. Because the aim of the study is to provide recommendable treatment for each marker-defined subgroup of T2D patients in parallel, the trial is desiged to assess the effects of teneligliptin simultaneously in two marker-defined subgroups, i.e., T2D patients with a higher or lower E/e′ ratio of LV diastolic function, where E is the early filling velocity on transmitral Doppler and e′ is the early relaxation velocity on tissue Doppler. For T2D patients with low E/e′ (< 8.0), we evaluated whether teneligliptin can prevent worsening of LV diastolic function (TOPLEVEL-1); for T2D patients with high E/e′ (≥ 8.0), we investigated whether teneligliptin can improve LV diastolic dysfuncton (TOPLEVEL-2).

Intervention Groups

Study drug (teneligliptin) group: teneligliptin hydrobromide hydrate, TENELIA® tablets, 20 mg.

Control group: antidiabetic drugs except for DPP-IV inhibitors.

Eligibility Criteria

The following eligibility criteria were designated for TOPLEVEL-1 and TOPLEVEL-2 studies. All the relevant medical and nonmedical conditions should be considered when deciding whether the protocol is suitable for a particular subject. Patients must provide written informed consent before participating in the study procedure.

Inclusion Criteria

Patients eligible for the trial must comply with all of the following at the time of randomization:

1. Evidence of an informed consent document from patients who sufficiently understand the contents of the examination and signed the documented consent form of their own free will.
2. Asian men and women who are at least 20 years of age and less than 85 years at the time of informed consent.
3. T2D patients who require treatment with antidiabetic drugs, or T2D patients who have received antidiabetic drugs and are able to change the drugs.
4. Patients whose LV ejection fraction is $\geq 40\%$ as measured by echocardiography, left ventriculography, cardiac magnetic resonance imaging examination, or cardiac nuclear scanning within 1 year before informed consent.

Exclusion Criteria

Patients were excluded from enrollment if they met any of the key criteria listed below:

1. Patients with type 1 diabetes.
2. Patients with slowly progressive insulin-dependent DM characterized by positive islet-associated autoantibodies such as glutamic acid decarboxylase antibody, insulinoma-associated protein-2 antibody, islet cell antibody, and insulin antibody.
3. Patients with DM caused by obvious genetic factors.
4. Patients with secondary DM such as DM caused by endocrine disorders and liver disease.
5. Patients with diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome.

6. Patients with serious infection, severe trauma, or awaiting any operation.
7. Patients with severe hepatic dysfunction with AST, ALT, or γGTP threefold of the upper limit of the normal at informed consent.
8. Patients with hypophyseoprivic or adrenal insufficiency.
9. Patients with malnutrition, starvation, irregular dietary intake, lack of dietary intake, or weakness.
10. Patients who cannot tolerate vigorous exercise or who are not suitable for enrollment, as judged by the investigator or subinvestigators.
11. Patients with excessive alcohol intake or drug abuse.
12. Patients with a history of intestinal obstruction.
13. Patients with evidence of QT prolongation on an electrocardiogram. Corrected QT (QTc) ≥ 0.44 s; QTc interval (s) = QT interval (s) / √[RR interval (s)].
14. Patients with a history of HF as defined by the New York Heart Association (NYHA) classification class III or IV at the beginning of the study.
15. Patients with a history of acute coronary syndrome, percutaneous coronary intervention, or cardiac surgery within 6 months.
16. Patients who have undergone mitral valve plasty or replacement, or with severe mitral annular calcification.
17. Patients receiving teneligliptin before the enrollment.
18. Patients receiving DPP-IV inhibitors and who cannot stop the drug.
19. Patients currently breast feeding.
20. Patients who are pregnant or with the possibility of pregnancy.
21. Patients with a diagnosed life expectancy < 3 years.
22. Patients with a history of an allergy to teneligliptin.
23. Patients who have participated or plan to participate in a clinical study of another investigational drug.
24. Patients who are deemed inappropriate to participate in the study for any other reason, as determined by the investigator or subinvestigators.

Outcome Measures

The outcome measures are common in TOPLEVEL-1 and -2 studies.

Primary Outcome Measures

Change in the values of E/e′ between baseline and 2 years after assignment.

Secondary Outcome Measures

1. All-cause death for 2-year follow-up.
2. Cardiac death for 2-year follow-up.
3. All-cause hospitalization for 2-year follow-up.
4. Hospitalization due to cardiovascular events for 2-year follow-up.
5. Hospitalization due to worsening of HF for 2-year follow-up.
6. Presence of new or additional treatment for HF for 2-year follow-up.
7. Change in values of E/A between baseline and 2 years after assignment, where E/A is the ratio of peak velocity blood flow from gravity in early diastole (E) to peak velocity flow in late diastole caused by atrial contraction (A).
8. Change in values of deceleration time between baseline and 2 years after assignment.
9. Change in values of left atrium volume (LAV) between baseline and 2 years after assignment.
10. Change in values of LV end-diastolic diameter (LVDd), LV end-systolic diameter (LVDs), and LV fractional shortening (%FS) between baseline and 2 years after assignment.
11. Change in values of the left ventricular mass index between baseline and 2 years after assignment.
12. Change in values of NYHA classification functional class between baseline and 2 years after assignment.
13. Change in plasma NT-proBNP levels between baseline and 2 years after assignment.

Methods

Assignment of Interventions

All patients who provide written informed consent for participation and who fulfill the inclusion criteria will be randomly assigned to either the control or the teneligliptin group with a 1:1 allocation in both TOPLEVEL-1 and -2, according to a computer-generated randomization schedule using a covariate-adaptive randomization method (Pocock-Simon method). The method includes the following as randomization factors: duration of DM (< 5 years or ≥ 5 years), sex (male or female), and medical histories of hypertension in TOPLEVEL-1; and E/e′ (> 15 or ≤ 15), gender (male or female), and medical histories of hypertension in TOPLEVEL-2.

Treatment Procedure

First, enrolled patients are requested to follow standard treatment for T2D, as previously discussed [11]. After enrollment, patients are to be treated as the plasma HbA1c levels less than 7.0%.

Second, the treatment strategy for each group is as follows.

Teneligliptin Group

(1) For patients who start DM drugs for the first time, teneligliptin is administered at a dose of 20 mg and can be increased up to 40 mg per day as necessary. If the treatment of T2D with teneligliptin is not satisfactory, other antidiabetic drugs, except for other DPP-IV inhibitors, can be added.
(2) For patients who have already received a DPP-IV inhibitor except for teneligliptin, physicians are required to change the DPP-IV inhibitor to 20 or 40 mg of teneligliptin per day. For patients who have already taken antidiabetic drugs except for DPP-IV inhibitors, physicians are required to change one of the antidiabetic drugs to 20 or 40 mg of teneligliptin per day. If the treatment of T2D is not satisfactory, physicians can increase the dose of teneligliptin up to 40 mg per day or add another antidiabetic drug except for other DPP-IV inhibitors. In both cases (1) and (2), glucagon-like peptide-1 (GLP-1) receptor agonists are not permitted because sufficient efficacy and safety for such a combination therapy have not yet been established.

Control Group

(1) For patients starting diabetic drug therapy for the first time, antidiabetic drugs except for DPP-IV inhibitors are administered.
(2) For patients who have already received a DPP-IV inhibitor, physicians are required to change the DPP-IV inhibitor to the antidiabetic drugs except for DPP-IV inhibitors. If the treatment of T2D is not satisfactory, physicians are required to increase the dose of antidiabetic drugs and add or change the other antidiabetic drugs, except for other DPP-IV inhibitors.

Third, any concomitant medication/therapy can be used during this study. Physicians are required to pay attention to the notes in the package insert of teneligliptin.

Finally, all enrolled patients are to be followed up with scheduled examinations for 2 years. Echocardiography is performed before the start of the study as well as 48 and 96 weeks after the start of the study. The schedule of this study is shown in Fig. 1 and Table 1.

Sample Size

Sample size was calculated on the basis of the primary hypothesis, separately for each marker-defined subgroup. For both TOPLEVEL-1 and -2 studies, one interim analysis was prospectively planned for futility and efficacy stoppings. For TOPLEVEL-1, the maximum total sample size of 530 patients (265 patients per group) provides 80% power to detect a mean difference of 0.50 with a 2.0 standard deviation (SD) in change from baseline in the E/e′ ratio at 2 years by a one-tailed test at a 2.5% significance level, where the Lan-DeMets error-spending method [12] is used, and the O'Brien-Fleming-type boundary is selected for both futility and efficacy stoppings. The interim analysis is planned at the time of 50% data accumulation, and the critical boundary for futility is nonbinding. For TOPLEVEL-2, similar to TOPLEVEL-1, the maximum sample size of 403 (265 patients per group) is calculated to detect a mean difference of − 1.0 with a 3.5 SD change from baseline in the E/e′ ratio at 2 years with 80% power at a 2.5% one-tailed significance level. The results of the interim analysis can be taken into account for a preplanned recalculation of the required sample size, where the Cui-Hung-Wang statistic [13] is used to evaluate the calculation to control for the type I error rate. If the sample size recalculation leads to the conclusion that a 1.5 times larger patient sample is required, the study is stopped, as the related treatment group difference is judged to be of minor clinical importance.

Risk-Based Monitoring and the Data and Safety Monitoring Committee

The risk-based monitoring of study sites will be implemented to ensure that the study protocols are properly conducted. A monitoring procedure has been separately created for a detailed monitoring-related plan. Auditing by a third party who is not participating in this study will ensure the reliability of the study results. Auditing will be performed according to the separately specified and documented procedure. Records and medical information identifying the patient will be kept confidential during monitoring and auditing. Moreover, when new safety information-related issues arise, the Protocol Steering Committee or the Independent Data Monitoring Committee will discuss the issues, including possible study discontinuation or continuation; the ethical review committee at each study site will also confirm each patient's intention to continue participating in the study.

Statistical Analysis

Analyses will be performed on the basis of the intention-to-treat principle. The teneligliptin group will be compared against the standard treatment group for all analyses. In TOPLEVEL-1, for the primary endpoint, i.e., a change from baseline in E/e′ at 2 years, the analysis of covariance will be used to calculate an adjusted mean difference and 95% confidence interval, where baseline E/e′ will be included as a covariate. For subgroup analyses, we will use regression methods with appropriate interaction terms (respective subgroup × treatment group). Secondary endpoints will be

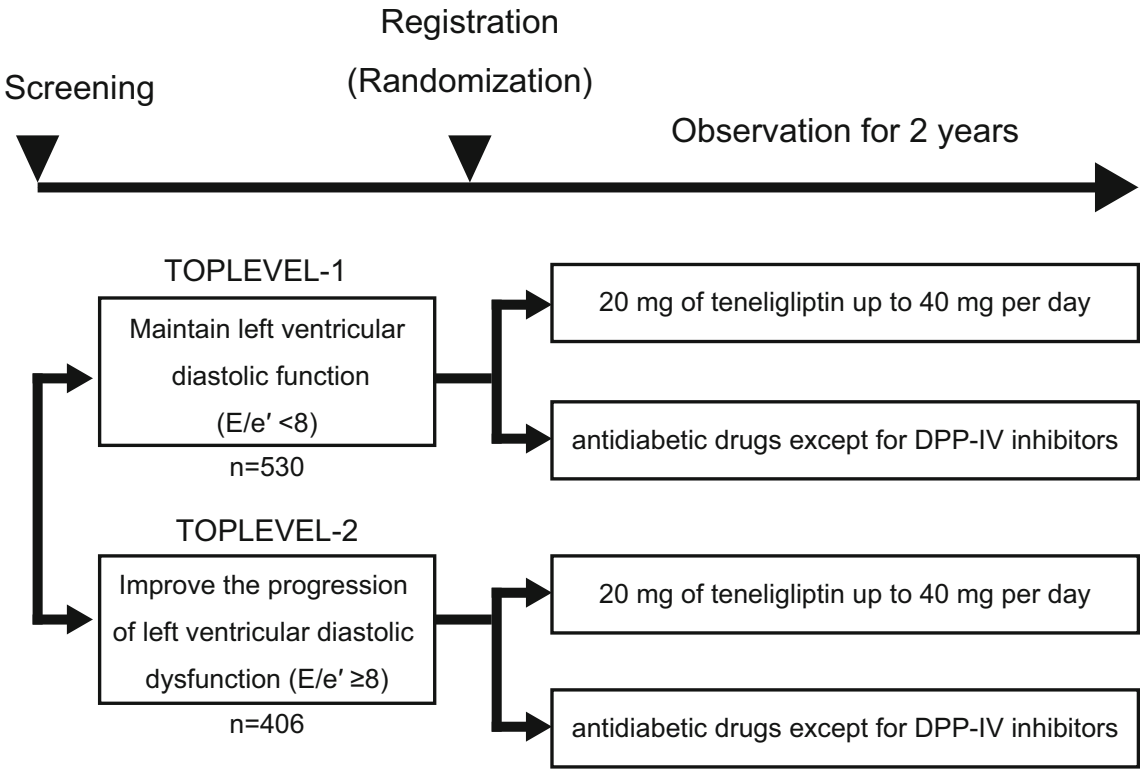

Fig. 1 Study protocol of the present study

analyzed descriptively; categorical variables will be assessed using a Chi-squared test or Fisher's exact test, whereas continuous variables will be assessed with the Student's *t* test or Wilcoxon rank-sum test as appropriate. For time-to-event variables, the Kaplan-Meier method will be used to estimate the survival curves, and the log-rank test will be used to compare the curves between the treatment groups. Analyses of the primary endpoint may be affected by the number of withdrawals from the trial. We will report the reasons for withdrawal for each randomization group and compare the reasons qualitatively. We will also assess the potential effect of any missing data on results via sensitivity analysis of the augmented data

Table 1 Schedule of data acquisition

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Regular visit
	Screening	Echocardiography	Baseline 0 weeks	48 weeks	96 weeks	
Acceptable range				44–52 weeks	92–100 weeks	
Informed consent	○					
Background	○			○	○	
Body height	○					
Body weight	○		○	○	○	○
Blood pressure	○		○	○	○	○
Pulse rate	○		○	○	○	○
Blood and urinary test	○			○	○	○
12-lead electrical cardiogram	○			○	○	
NYHA class	○			○	○	
Echocardiogram		○		○	○	
Clinical endpoint	○			←	—	→
Adverse event				←	—	→
Treatment compliance				○	○	○

NYHA, New York Heart Association

sets. Dropouts will be included in the analysis by modern imputation methods for missing data, if necessary. In TOPLEVEL-2, all analyses will be performed similarly to TOPLEVEL-1, except that the primary endpoint is only compared and not included as a covariate. All tests were two-tailed, and a P value of < 0.05 was considered to be statistically significant. All analyses will be performed using statistical analysis software SAS, version 9.3 or later for Windows (SAS Institute, Cary, NC). The statistical analysis plan, which will include a more technical and detailed elaboration of the principal features stated in the protocol, will be prepared separately and finalized before the interim analysis.

Current Status

The first patient was enrolled in June 2015. We recruited 44 hospitals that specialize in T2D diagnosis and echocardiography. As of December 2018, we have enrolled 53 and 258 patients for TOPLEVEL-1 and TOPLEVEL-2 studies, respectively, and will recruit the remaining patients with T2D.

Concerning TOPLEVEL-1, the enrollment speed seems to be slow. We have had a difficulty to find T2D patients without impaired LV diastolic function, since T2D patients usually suffered from LV diastolic dysfunction. Nevertheless, we will analyze the data even if the number of the enrollment does not reach the target number especially in TOPLEVEL-1, and we will obtain important information whether DPP4 inhibitors are effective for the improvement of LV diastolic dysfunction. Such an information is needed because the large-scale trials show negative results for the improvement of hospitalization due to HF, and HFpEF is becoming the big issue in cardiology worldwide.

Discussion

The major concerns of T2D patients are not only the progression of T2D along with microangiopathy, neuropathy, and nephropathy but also the progression of macroangiopathy. T2D is one of the major risk factors for coronary artery diseases, including acute myocardial infarction [14], and several investigators (including us) have demonstrated that DM also impairs the myocardium [1, 2, 15, 16], eventually culminating in HF. The pathophysiology of HF in T2D patients is mainly characterized as impaired LV diastolic function, such as E/e′ > 15 after an adjustment of risk factors for HF [3] followed by HFpEF. Indeed, E/e′ positively correlates with plasma HbA1c levels in T2D patients [4].

The question then becomes, how does T2D cause LV dysfunction? T2D causes vascular [17] and myocardial [18] impairment, and it is conceivable that myocardial impairment affects LV diastolic distensibility, increasing LV filling pressure and thus leading to HFpEF. The question is whether vascular impairment affects LV diastolic function. Some clinical studies [17, 19] suggest a robust relationship between the elevation in vascular load and worsening diastolic function. Elzinga and Westerhof showed that aortic peak, mean flow speed, and volume decrease when aortic resistance increases or capacitance decreases, and the early onset of aortic valve opening [20], early opening of the aortic valve, and early timing of LV ejection slow down LV relaxation [21]. This indicates that changes in vascular compliance may alter LV relaxation properties via changes in the LV ejection mode. Accumulating lines of evidence have inspired us to test the hypothesis that treatment of T2D improves abnormalities in both ventricular and vascular stiffness, and thus improves LV diastolic dysfunction, or prevents worsening of LV diastolic function in T2D patients in the present study.

Before answering these questions, we must solve the most important question as to whether the E/e′ ratio is the most suitable predictor of HFpEF, especially as we set the primary endpoints using the E/e′ ratio. Interestingly, previous studies have reported a significant association between the E/e′ ratio and the time from diabetes diagnosis; the E/e′ ratio increased by 0.23 for every 1 year after the onset of diabetes, the E/e′ ratio ≥ 15 was a significant predictor of all-cause mortality in diabetic patients [22], and increases in the E/e′ ratio by 1 unit increased the probability for the onset of HF by 3% [3]. Furthermore, the E/e′ ratio is reported to increase by 1.64 units in T2D patients during an 8-year follow-up [23]. Several clinical studies [24–26] have identified the tissue Doppler index E/e′ as an independent predictor of future cardiovascular events in patients with HFpEF. The E/e′ ratio has been widely accepted clinically to estimate LV filling pressure [27] and diastolic dysfunction. Despite the argument of the limitation of E/e′ to be sensitive to diastolic function [28, 29], E/e′ also persists as the routine parameter to assess diastolic function in patients with HFpEF in the recent European Society Cardiology guidelines [30], with other multistep echocardiographic assessments. In accordance with the recent guidelines, we added several parameters for the assessment of diastolic function in this study, such as E/A, left atrial volume, and TR velocity.

The next question is what kind of DM drugs would become the candidate for the clinical trial. In basic studies [31–33], DPP-IV inhibitors are reportedly cardioprotective, independent of the improvement in T2D, because GLP-1, BNP, adenosine, and SDF-1a, which provide potent cardioprotection, are involved in the pharmaceutical effects of DPP-IV inhibitors. Furthermore, some of the DPP-IV inhibitors have an effect on cardiac function in animal experiments [7, 8]. In the myocardium, GLP-1 receptors are not expressed in the heart [34], hinting that DPP-IV inhibitors may not affect myocardial properties. However, GLP-1 receptors may be upregulated in the heart with T2D patients; therefore, DPP-IV inhibitors may affect the myocardium via several DPP-IV inhibitor-induced hormonal actions [31, 35, 36] other than GLP-1. Furthermore,

DPP-IV inhibitors may affect endothelial cells and increase the NO [37] or adenosine [32] levels, which affect the myocardium in a paracrine manner. Therefore, we hypothesize that teneligliptin, the strongest DPP-IV inhibitor, may prevent the deterioration of LV dysfunction or improve the already deteriorated LV function. To test this hypothesis, we decided to test the effects of teneligliptin in T2D patients in the present TOPLEVEL study.

Large-scale clinical trials have failed to show the benefit of several DPP-IV inhibitors in preventing the onset of HF. Because T2D causes HF, it is not conceivable that DPP-IV inhibitors have no effect on the pathophysiology of HF. DPP-IV inhibitors may have unknown factors modulating the pathophysiology of HF. It is therefore of utmost importance to determine whether teneligliptin can improve the LV diastolic dysfunction often seen in T2D-induced HFpEF in TOPLEVEL study.

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Availability of Data and Materials To avoid potential bias of the analysis, the data set supporting the conclusions of this article will not be available until the final report of this trial is published.

Compliance with Ethical Standards

Conflict of Interest Persons from Mitsubishi Tanabe Pharma Corporation were not involved in conducting this study and analysis, and the intentions of Mitsubishi Tanabe Pharma Corporation are not reflected in the results or interpretations of this study.

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