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Short Communication

Clinical Implications of The Direct Comparison of Dulaglutide Versus Tirzepatide

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Abstract

It is unclear which incretin-based therapy has the best impact on reduction of cardiovascular (CV) outcomes and mortality. The SURPASS-CVOT trial was the first randomized trial to directly compare the effects of 2 incretin-based therapies, tirzepatide and dulaglutide, on such outcomes in patients with type 2 diabetes and atherosclerotic CV disease. After 4 years of follow-up, tirzepatide was non-inferior to dulaglutide in incidence of a composite of death from CV causes, myocardial infarction (MI), or stroke (the primary outcome). While statistical superiority of tirzepatide over dulaglutide was not achieved, there was a trend toward decrease incidence of individual CV events with tirzepatide and a remarkable 16% decrease in all-cause mortality versus dulaglutide. Tirzepatide was more effective than dulaglutide in lowering body weight, glycated hemoglobin levels and systolic blood pressure. Gastrointestinal (GI) adverse effects were more common with tirzepatide (42.5%) versus dulaglutide (35.9%). The main limitation of the SURPASS-CVOT trial is the comparison of maximum doses of tirzepatide (15mg) with sub-maximal doses of dulaglutide (1.5 mg), but this limitation is unlikely to significantly change the results of the study. Overall, tirzepatide is preferred over dulaglutide in patients with high CV risk.

Kew Words: tirzepatide; dulaglutide; cardiovascular events; mortality; surpass-cvot

Introduction

In the well-designed megatrial called the REWIND, dulaglutide, an agonist of glucagon-like peptide receptor-1 (GLP-1) was shown to decrease the incidence of CV events in patients with type 2 diabetes and high CV risk at baseline [1]. No similar trials were conducted with tirzepatidfe, the dual agonist of the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. Therefore, it is unclear which incretin-based agent to start with in clinical practice. The recently published SURPASS-CVOT trial is the first study with hard outcomes to compare head-to-head 2 incretin-related drugs: tirzepatide versus dulaglutide [2]. The purpose of this mini-review is to provide an appraisal on the SURPASS-CVOT trial and apply its results to clinical practice.

Overview of the SURPASS-CVOT trial

The SURPASS-CVOT trial is a mega trial (n=13,165), in which the authors randomized patients with type 2 diabetes and atherosclerotic cardiovascular (CV) disease in a 1:1 ratio to receive once weekly tirzepatide or dulaglutide in a double-blin fashion on top of their usual diabetes therapy. Thus, sodium-glucose transporters 2 inhibitors (SGLT2i) were taken by 33.8% and 41.1%, metformin by 71.4% and 78.8%, and insulin by 39.2% and 47.8% in the tirzepatide and dulaglutide groups, respectively [2]. Patients' mean age was 64.1 years, 29.0% were women, with mean glycated hemoglobin levels (HbA1c) of 8.4%. Most subjects were obese with a mean weight of 92.6 kg, and mean body mass index (BMI) of 32.6 kg/m^2, respectively [2]. Baseline characteristics were generally well-balanced between the study arms. Median follow-up was 4.0 years. The primary outcome of the adequately powered SURPASS-CVOT trial was a composite of death from CV causes, myocardial infarction (MI), or stroke and was tested for noninferiority of tirzepatide to dulaglutide [2].

Results of the SURPASS-CVOT trial

A primary end-point event occurred in 12.2% (n=801) and 13.1% (n=862) in the tirzepatide and dulaglutide groups, respectively. These results yielded a hazard ratio (HR) for death from CV causes, MI, or stroke of 0.92 (95.3% CI, 0.83 to 1.01; P=0.003 for noninferiority), i.e. tirzepatide was noninferior to dulaglutide. Meanwhile, tirzepatide was not superior to dulaglutide (P=0.09 for superiority) [2]. Therefore, the study results suggest no significant difference between tirzepatide and dulaglutide in terms of their impact on the primary endpoint. However, inspection of the individual components of the primary outcome showed a trend toward reduction in such outcomes in the tirzepatide group (table 1). In addition, there was an remarkable reduction in risk of all-cause death by 16% in the tirzepatide group, HR 0.84 (95% CI, 0.75 to 0.94) and less reduction in the estimated glomerular filtration rate (eGFR) by an average of 3.17 ml/min/1.73 m^2 in the tirzepatide group (table 1). Regarding the intermediate metabolic

outcomes, except for changes in low-density lipoprotein cholesterol (LDL-C) concentrations, tirzepatide was clearly superior to dulaglutide in amelioration of HbA1c values, weight, and systolic blood pressure (table 1).

End point	Tirzepatide (15 mg) (n=6586)	Dulaglutide (1.5 mg) (n=6579)	Hazard ratio (95% CI)	Difference (95% CI)
Primary end point (death from cardiovascular causes, myocardial infarction, or stroke)	12.2%	13.1%	0.92 (0.83 to 1.01)	
Death from cardiovascular causes	5.6%	6.2%	0.89 (0.77 to 1.02)	
Myocardial infarction	4.7%	5.4%	0.86 (0.74 to 1.00)	
Stroke	3.5%	3.8%	0.91 (0.81 to 1.03)	
Death from any cause	8.6%	10.2%	0.84 (0.75 to 0.94)	
* eGFR (ml/min/1.73 m^2)	-5.7	-8.9		3.17 (2.09 to 4.26)
*Glycated hemoglobin	-1.66%	-0.88%		-0.78 (-0.84 to -0.72)
*Body weight (kg)	-11.6	-4.8		-6.8 (-7.1 to -6.5)
*Systolic blood pressure (mmHg)	-6.2	-4.1		-2.1 (-2.6 to -1.5)
**LDL-C (percentage)	-1.6%	-2.9%		1.3 (-0.2 to 2.8)

Values are means
*Changes from baseline to 36 months
LDL-C: low-density lipoprotein cholesterol
** Changes from baseline to 24 months

Table 1: Proportions of patients who experienced various outcomes in the SURPASS-CVOT trial

Safety of tirzepatide versus dulaglutuide in the SURPASS-CVOT trial

Overall, dulaglutide was tolerated slightly better than tirzepatide as reflected by drug discontinuation rates of 13.2% and 10.1% with tirzepatide and dulaglutide, respectively [2]. The most common adverse effects were GI (nausea, vomiting, diarrhea) occurring in 42.5% and 35.9% with tirzepatide and dulaglutide, respectively [2]. Severe hypoglycemia was recorded similarly with tirzepatide and dulaglutide, 0.7% of patients in each group [2].

Limitations of the SURPASS-CVOT trial

Despite its rigorous design, large size, relatively long-duration of follow-up and adequate statistical power, the SURPASS-CVOT trial failed to compare equivalent doses of tirzepatide and dulaglutide. Thus, tirzepatide was titrated up to its maximum doses of 15 mg/wk. On the other hand, dulaglutide was used at its submaximal dose of 1.5 mg/wk and not at its maximum effective doses of 4.5 mg/wk (2). In fact, in the randomized, double-blind, multinational AWARD-11 trial, Frias et al (3) compared dulaglutide doses of 1.5 mg. 3.0 mg, and 4.5 mg/wk in 1842 patients with type 2 diabetes (mean age 57 years, 49% women). After 36 months, compared with the dulaglutide-1.5 mg dose, the 4.5 mg-dose provided superior reductions in HbA1c values (difference -0.24%) and weight (difference -1.6 kg) (2). Although the differences between the 1.5 and 4.5 mg dulaglutide doses were small, they were statistically significant and virtually could have impact on CV outcomes after more prolonged duration.

More recently, Billings et al [4] compared dulaglutide dose escalation versus switching to tirzepatide 15 mg/wk among patients with type 2 diabetes inadequately controlled on dulaglutide 1.5 mg. After 40 weeks, tirzepatide was superior to maximum doses of dulaglutide 4.5 mg in lowering HbA1c values, -1.44% versus -0.67 (difference -0.77%, 95% CI -0.98 to -0.56; P< 0.001) and weight, -10.5 kg versus –3.6 kg, difference -6.9 kg, 95% CI, -8.3 to -5.5; P<0.001) [4]. Taken together, the results of the above 2 trials suggest that although the 4.5 mg dulaglutide dose is more effective than lower doses in lowering HbA1c values and weight, tirzepatide is still far more superior when compared with the highest effective doses of dulaglutide of 4.5 mg/wk.

Thus, if the SURPASS-CVOT trial had compared tirzepatide with dulaglutide at its highest dose of 4.5 mg (instead of 1.5 mg), the magnitude of difference between the 2 agents in intermediate outcomes would have been less substantial. Yet, regarding the primary outcome in the SURPASS-CVOT, it is hard to predict the results of comparing dulaglutide high-dose 4.5 mg with tirzepatide 15 mg, but probably the 2 drugs would be equivalent in that respect. Other limitations of the SURPASS-CVOT trial include not reporting the difference in albuminuria and diabetic retinopathy between the 2 study groups.

Clinical implications of the direct comparison of tirzepatide versus dulaglutide

Based on the available data and recent results of the SUPRPASS-CVOT trial, use of tirzepatide seems to be preferred over dulaglutide in patients with type 2 diabetes due to the following reasons. First, its impact on hard CV events is at least similar and not inferior to that of dulaglutide [2]. In particular, the 16% reduction in all-cause mortality with tirzepatide versus dulaglutide is noteworthy [2]. Second, tirzepatide was clearly superior to dulaglutide in improving glycemia control, lowering body weight and systolic blood pressure and slowing the decline in eGFR. Third, other trials have shown that tirzepatide exerted beneficial effects in patients with heart failure and obesity and those with obstructive sleep apnea [5,6]. Yet, when compared to dulaglutide, 2 disadvantages of tirzepatide should be emphasized namely, the slightly higher incidence of GI adverse effects and higher monthly cost with average wholesale price of $ 1,296 for tirzepatide and $ 1,185 for dulaglutide [7].

Conflict of interest

The author has no conflict of interest to declare

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