European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Tirzepatide decreases systolic and diastolic blood pressure

Tirzepatide is a newer glucose-lowering medication with agonist activity on the glucagon-like peptide (GLP)−1 receptor as well as on the glucose-dependent insulinotropic polypeptide (GIP) receptor. Tirzepatide exerts superior glycated hemoglobin (HbA1c) and overall plasma glucose lowering effects compared to GLP-1 agonists or basal insulin therapy. Furthermore, exploratory analyses have demonstrated that compared to insulin glargine, tirzepatide has a greater anti-albuminuric effects, and attenuates the decline in estimated glomerular filtration rate (eGFR). From a kidney perspective, in post-hoc analyses of data from SURPASS-4 clinical trial, eGFR decline by slope was less with tirzepatide compared to insulin glargine (−1.4 ml/min/1.73 m2 vs. −3.6 ml/min/1.73m2 in insulin glargine) similar to urinary albumin-to-creatinine ratio (95% CI, 26.0 to 48.7%). Although the exact mechanisms responsible for this nephroprotective profile are largely unknown, several factors may be responsible including better glycaemic control, suppression of pro-inflammatory cytokines, reactive oxygen species, and the renin-angiotensin-aldosterone system, decline in glomerular hypertension and reduction in body weight. Cardioprotective effects of tirzepatide may also be attributable actions on GLP-1 receptors inhibiting the formation, progression, and rupture of atherosclerotic plaques [1–5].

Multiple clinical trials have been performed in order to assess the efficiency and safety of tirzepatide therapy, and most of those studies have reported data regarding systolic and diastolic blood pressure (BP) and heart rate (Figs. 1a and 1b). In the SURPASS-1 trial (40-week placebo-controlled phase 3 randomized controlled trial (RCT), $n = 478$ participants with type 2 diabetes, mean HbA1c 7.94%), systolic BP declined by -4.7 to −5.2 mmHg in patients receiving tirzepatide compared to -2.0 mmHg decline in placebo group, with a statistically significant effect on systolic BP with tirzepatide at the 10 mg dose [6]. Another 40-week phase 3 RCT involving (SURPASS-2) 1879 patients with type 2 diabetes (mean HbA1c= 8.28%) receiving either tirzepatide (5 mg, 10 mg, 15 mg) or semaglutide, a GLP-1 analogue, demonstrates decline in systolic and diastolic BP significantly higher than semaglutide therapy (−3.6\ and −1.0 mmHg, respectively) [3]. Both trials reported a mean heart rate increase by 1–2 beats/minute [3,6].

The subsequent, SURPASS-III trial investigated the effect of tirzepatide as an add-on to metformin alone or combined with SGLT-2 inhibitors in 1437 patients with type II diabetes mellitus (mean HbA1c= 8.2%) on HbA1c, fasting plasma glucose level, body weight, systolic and diastolic BP, heart rate [7]. Statistically significant declines in systolic BP (-4.9 to -6.6 mmHg) and diastolic BP (-1.9 to -2.5 mmHg) were reported compared to insulin degludec [7]. Similarly, a significant decline in systolic BP (-2.8 to -4.8 mmHg) and diastolic BP (−0.8 to 1.0 mmHg) was been reported with tirzepatide therapy at varying dose formulations in a 52-week phase 3 parallel-group open-label RCT (SURPASS-IV) involving 1995 patients with type 2 diabetes receiving any combination of metformin, SGLT-2 inhibitors and sulfonylurea in which tirzepatide (5, 10, 15 mg) was compared with insulin glargine (1.3 mmHg increase in systolic BP, 0.7 mmHg increase in diastolic BP) [2]. SURPASS-V investigated the efficiency of tirzepatide as an add-on therapy to insulin glargine with or without metformin in patients with type 2 diabetes (mean HbA1c= 8.31%) over 40-weeks of clinical trial period [1]. This trial demonstrated significant declines in systolic BP (−6.1 to −12.6 mm Hg) and diastolic BP (−2.0 to −4.5 mm Hg) with tirzepatide compared to placebo (−1.7 and −2.1 mmHg) without changes in HR [1]. Another double-blind phase 3 RCT called SURMOUNT-1 investigated the effect of tirzepatide (5 mg, 10 mg, 15 mg) compared to placebo over 72-weeks period on weight reduction and illustrated that tirzepatide results in significant declines in systolic BP (mean= −7.2 mm Hg) and diastolic BP (mean= −4.8 mm Hg) compared to placebo (−1.0 mm Hg decline in systolic BP, −0.8 mm Hg decline in diastolic BP) [8]. A separate phase 3 trial conducted in 636 Japanese type 2 diabetes patients over 52-weeks demonstrated mean systolic BP decline of −6.5 to −11.0 mm Hg and mean diastolic BP decline of −3.2 to −5.6 mm Hg, effects which were greater compared to dulaglutide therapy [5]. On the other hand, a double-blind phase 2 RCT conducted on 318 participants assigned to variable doses of tirzepatide, dulaglutide or placebo has demonstrated no significant difference in terms of systolic BP, diastolic BP or heart rate between groups at week 26 [4]. To conclude, most RCTs conducted on tirzepatide therapy have demonstrated improvements in systolic and diastolic BP and probably reflex response as increased heart rate.

Even though exact underlying pathophysiology of cardioprotective effects of tirzepatide or GLP-1 receptor agonists are largely unknown, multiple hypothesis have been developed. Tirzepatide therapy leads to increased adiponectin production from adipose tissue which leads to inhibition of pro-inflammatory cytokines, inhibition of monocyte/macrophage activation and migration, inhibition of vascular smooth muscle cells, decline in reactive oxygen species formation in vascular endothelial cells along with increased nitric oxide production and activation of adenosine monophosphate-activated protein kinase. Furthermore, activation of GLP-1 or GIP signaling pathway leads to inhibition of caspase system resulting in the inhibition of apoptosis and activation of PI3K-AKT-mTOR pathway resulting in beta-cell proliferation. Moreover, increased peripheral insulin sensitivity, better glycaemic control, weight loss and reductions at BP all contribute to improvements with tirzepatide therapy [7–9]. Potentially, BP-lowering effects of tirzepatide therapy may be attributable to the effects of tirzepatide therapy on weight reduction, a component of metabolic syndrome, and increased peripheral insulin sensitivity. However, no clinical trial has investigated the timing and correlation of BP and weight lowering effects of tirzepatide therapy. There is clear need for future clinical studies investigating such relationship.

The major limitations of the studies investigating the effects of

https://doi.org/10.1016/j.ejim.2023.04.005
Received 26 February 2023; Received in revised form 30 March 2023; Accepted 7 April 2023

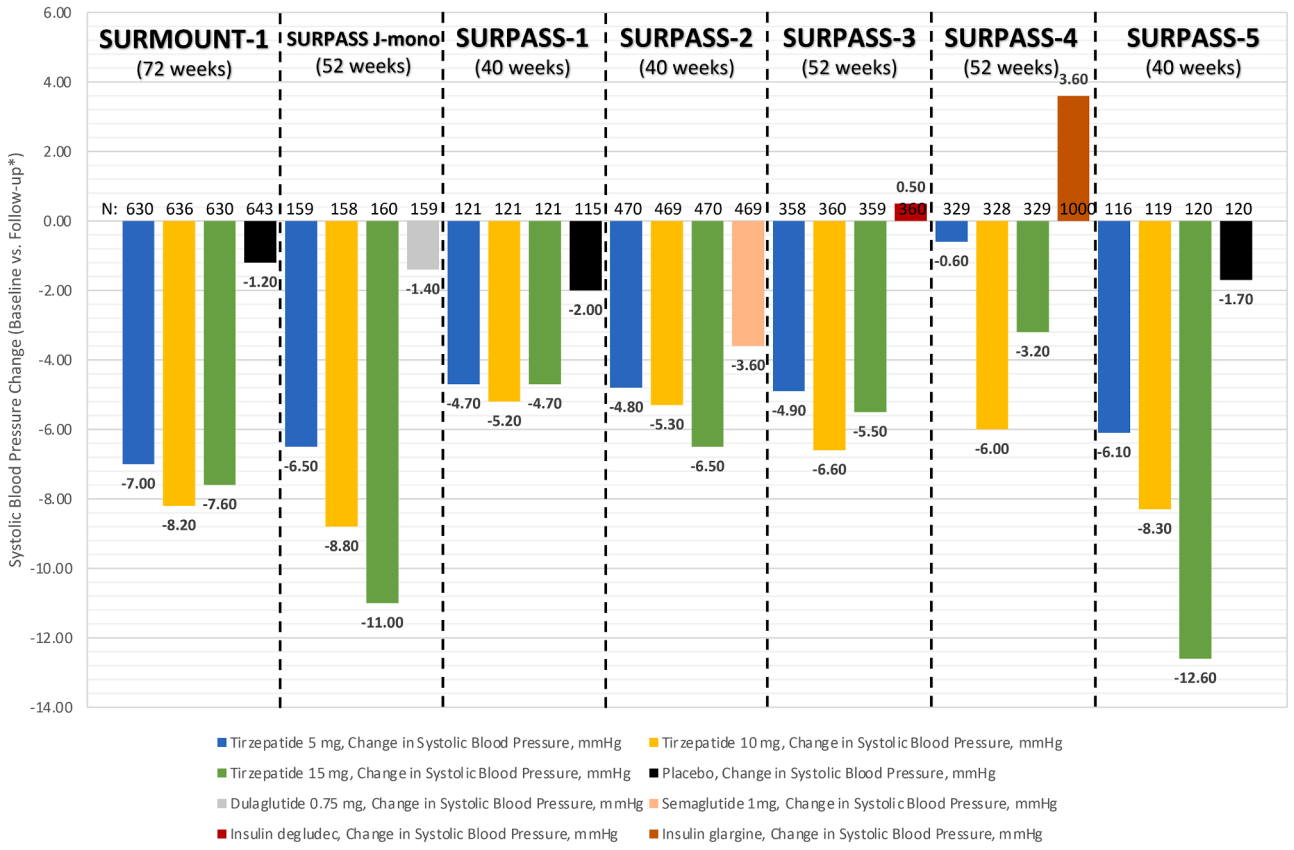

Fig. 1a. The changes in systolic blood pressure at baseline and at the end of the follow-up period reported in seven trials with tirzepatide are shown in the bar graph. The names of the trials and (the duration of their follow-up periods) are mentioned at the top of the graphs. The numbers of participants in each group are indicated above the bars as N.

tirzepatide therapy on BP and heart rate include the dependence on single office BP measurement at baseline and at the end of clinical trial which may increase the risk of bias via white-coat hypertension or masked hypertension. Additionally, no studies have utilized 24-hour ambulatory BP measurements as a tool for BP evaluation which may lead to misevaluation due to daytime variability of BP measurements. However, a subset study of SURMOUNT-1 trial investigated 24-hour ambulatory blood pressure monitoring among 494 participants (mean body-mass index= 37 kg/m^2) illustrates that tirzepatide decreased 24-hour systolic BP measurements and diastolic BP measurements at most doses that were studied [9]. Additionally, the BP-lowering effects of tirzepatide therapy have shown to be dose-dependent in certain clinical studies such as SURPASS-I in which tirzepatide therapy leads to statistically significant BP decline at 10 mg/week dose in contrast to multiple other clinical trials in which decline in BP is dose-independent. Even though it is speculative to address the exact underlying cause for such outcome, we may assume that it is largely due to the dependence of clinical trials on single office BP measurement and relatively short-term follow-up period. Subset study of SURMOUNT-1 trial in which 24-hour ambulatory BP measurements have been performed at baseline and at week 36 illustrates statistically significant decline in systolic and diastolic BP at all doses except the effects of 15 mg/week dose on diastolic BP.

The beneficial effects of tirzepatide therapy, a novel anti-diabetic medication, have been shown in terms of glycaemic control and weight loss in multiple clinical trials while our study has demonstrated that tirzepatide therapy leads to superior outcome in terms of systolic and diastolic BP compared to placebo and other anti-diabetic medications including metformin and GLP-1 analogues. Nevertheless, it is important not to overlook the potential detrimental effect on such blood pressure-reducing effect of tirzepatide in diabetic patients with autonomic nerve involvement leading to orthostatic hypotension which may be worsen by such anti-diabetic therapy. However, such potential condition has not been investigated or addressed in any clinical study and therefore it is currently only a hypothetical concern. Moreover, only few clinical trials have investigated the effects of tirzepatide therapy on renal outcomes such as eGFR or UACR and on long term cardiovascular outcomes. There is clear need for future studies investigating the renal and cardiovascular outcomes of tirzepatide therapy on large-scale studies.

Funding

No funding was received for this research.

Data availability statement

Our manuscript has no associated data.

CRediT authorship contribution statement

Sidar Copur: Conceptualization, Methodology, Writing – original draft. **Atalay Demiray:** Funding acquisition, Formal analysis, Data curation, Writing – original draft. **David Cherney:** Writing – review & editing, Resources, Writing – review & editing, Resources. **Katherine Tuttle:** Writing – review & editing, Resources. **Mehmet Kanbay:** Conceptualization, Methodology, Funding acquisition, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Resources.

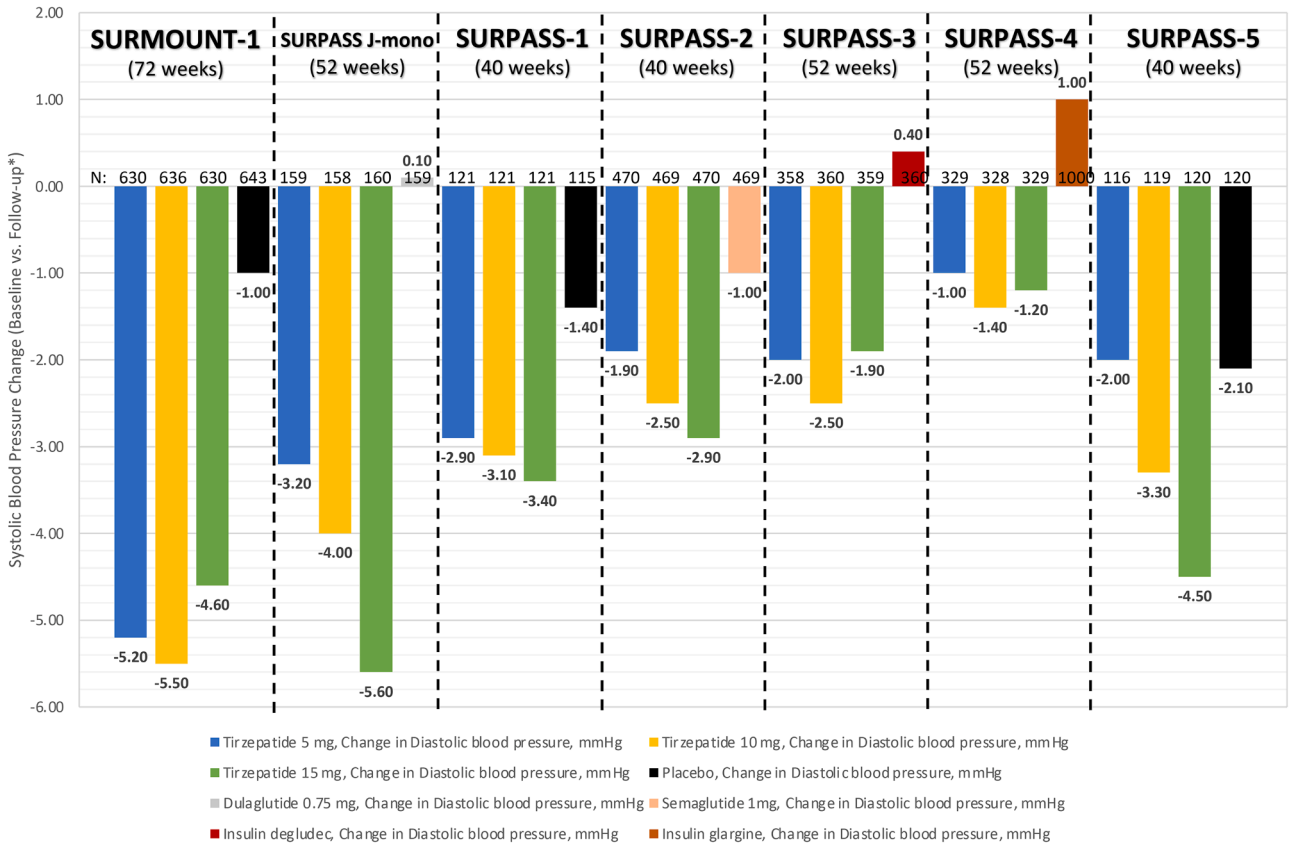

Fig. 1b. The changes in diastolic blood pressure at baseline and at the end of the follow-up period reported in seven trials with tirzepatide are shown in the bar graph. The names of the trials and (the duration of their follow-up periods) are mentioned at the top of the graphs. The numbers of participants in each group are indicated above the bars as N.

Declaration of Competing Interest

D.Z.I.C has received honoraria from Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, Abbvie, Janssen, Bayer, Prometic, BMS, Maze, Gilead, CSL-Behring, Otsuka, Novartis, Youngene, Lexicon and Novo-Nordisk and has received operational funding for clinical trials from Boehringer Ingelheim-Lilly, Merck, Janssen, Sanofi, AstraZeneca, CSL-Behring and Novo-Nordisk. KRT reports consultancy fees from AstraZeneca, Boehringer Ingelheim, Lilly, Goldfinch Bio, Novo Nordisk, and Travere; grant support from the National Institutes of Health (NIDDK, NHLBI, NIMHD), the Centers for Disease Control and Prevention, Bayer, Goldfinch Bio, and Travere; and speaker fees from AstraZeneca, Lilly, Janssen, and Novo Nordisk. Other authors have nothing to disclose.

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