Verapamil improves One-Year C-Peptide Levels in Recent Onset Type-1 Diabetes: A Meta-Analysis

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Abstract

Meta-analysis studying the role of verapamil in improving C-peptide in people with recent-onset type-1 diabetes (T1DM) has not been conducted to date. We undertook this meta-analysis to address this knowledge gap. Electronic databases were systematically reviewed for RCTs having individuals with T1DM receiving verapamil in the treatment arm and placebo in the control arm over the standard of care. The primary outcome was to evaluate changes in the C-peptide area under the curve (AUC) at a one-year follow-up. Secondary outcomes were to assess alterations in C-peptide AUC, glycated hemoglobin (HbA1c), blood pressure, heart rate, and side effects at different time intervals over a one-year follow-up. From the initially screened 27 articles, data from two RCTs (112 patients) satisfied the inclusion criteria and were analyzed. Compared to placebo, C-peptide AUC in individuals receiving verapamil was not different at three months [MD 0.17 nmol/L (95%CI: -0.05-0.38); $P = 0.13$; $I^2 = 86\%$] but significantly higher at 1-year [MD 0.27 nmol/L (95%CI: 0.19–0.35); $P < 0.01$; $I^2 = 12\%$]. The verapamil arm showed similar changes in HbA1C at three months [MD 0.23% (95%CI: -0.43–0.90); $P = 0.49$; $I^2 = 88\%$] and 1-year [MD 0.18% (95% CI: -0.74 – 1.10); $P = 0.70$; $I^2 = 89\%$] compared to placebo. Occurrence of treatment-emergent adverse events [Risk ratio (RR) 1.90 (95%CI: 0.52–6.91); $P = 0.33$; $I^2 = 63\%$], serious adverse events [RR 1.40 (95%CI: 0.50–3.93); $P = 0.53$], constipation [RR4.11 (95%CI: 0.93–18.13); $P = 0.06$; $I^2 = 0\%$], headache [RR0.48 (95%CI: 0.16–1.43); $P = 0.19$; $I^2 = 0\%$], severe hypoglycemia [RR 0.87 (95%CI: 0.06 – 13.51); $P = 0.92$] were comparable across groups. Verapamil was well tolerated, and its use over one year was associated with significant improvements in C-peptide AUC though the HbA1c remained unchanged.

Keywords: C-peptide, meta-analysis, safety, type-1 diabetes, verapamil

Introduction

Type 1 diabetes mellitus (T1DM) is characterized by the autoimmune destruction of pancreatic beta cells, leading to a state of absolute insulin deficiency, necessitating lifelong intensive insulin therapy to prevent end-organ damage and ensure optimal quality of life.[1] Therapies targeting preserving residual beta cell function in people with T1DM have been going on for decades with limited success. The beneficial impact of preserved residual beta cell function in T1DM includes a reduction of the total daily dose of insulin requirement, lesser glycemic variability, and reduced risk of hypoglycemia and end-organ damage.[2]

Among the several intracellular signaling pathways in pancreatic beta cells, thioredoxin-interacting protein (TXNIP) overexpression has been demonstrated to induce pancreatic beta cell apoptosis and glucotoxicity-induced beta cell death in culture and mouse models of T1DM.[3] In preclinical studies, verapamil, a calcium channel blocker, has been observed to reduce thioredoxin-interacting protein expression and beta-cell apoptosis.[4] Stimulated C-peptide estimation is an established method of assessing residual beta cell function in people with diabetes. Recently few randomized controlled trials (RCTs) have been published evaluating the impact of one-year verapamil

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therapy as compared to placebo on stimulated C-peptide levels in people with recent onset T1DM.[5,6] However, to date, no meta-analysis has been published evaluating the role of verapamil in improving pancreatic beta cell function in T1DM. Hence, this meta-analysis intends to critically analyze the potential role of verapamil in improving C-peptide levels in people with T1DM.

Methods

The protocol for the meta-analysis has been registered in Prospero with the registration number CRD42023405647. The meta-analysis was done using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[7] Using PICOS criteria, RCTs involving people with T1DM receiving verapamil in the study group and placebo/any other medication in the control group were considered for this meta-analysis.

The primary outcome of this meta-analysis was to evaluate the changes in the C-peptide area under the curve (AUC) at one year of follow-up. The secondary outcomes were alterations in C-peptide AUC at three months follow-ups, changes in glycated hemoglobin (HbA1C), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), hypoglycemia and side effects profile at three months and one year of follow-up.

We systematically searched Embase database, Web of Science, Cochrane Library, Medline (PubMed), clinicaltrials.gov, CNKI database, ctri.nic.in, and Google Scholar as either keywords or MESH terms: (verapamil) OR (calcium channel blocker) OR (CCB) AND (type-1 diabetes). Details have been elaborated on in the previous meta-analysis published by our group.[8]

Data extraction with regard to all the primary and secondary outcomes stated above was carried out independently by two authors. Multiple publications from the same group on the same cohort of patients were pooled together and considered as a single study for our meta-analysis. Details have been elaborated on in a previous meta-analysis published by our group.[8] The risk of the bias assessment was done by three authors using the risk of bias assessment tool in Review Manager (Revman) Version 5.4 software. The different types of bias looked for have been elaborated on in previous meta-analyses by our group.[8,9]

The international system of units (SI units) was used for all analyses. Continuous variable outcomes were presented as mean differences (MD). For dichotomous variables, outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI) and as hazard ratios (HR) for adverse events. RevMan 5.4 was used for the statistical analysis and generation of Forest plots in this meta-analysis. The random effect model for analysis was expressed as 95% confidence intervals (95%CI). The forest plot generated for all the outcomes was used to assess the heterogeneity. We specifically used the Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance with the I^2 test.[10] The details of heterogeneity analysis have been elaborated elsewhere.[9]

Grading of results is important as it helps us understand the quality of the results generated in a meta-analysis. Any meta-analysis can be as good as the quality of the RCTs used in the analysis. The grading/certainty of the evidence of some of the primary and major secondary outcomes in this meta-analysis was done using the Grades of Recommendation, Assessment, Development, and Evaluation approach.[11] The details have been elaborated on elsewhere.[8] Publication bias was assessed by plotting the Funnel Plot.[11,12] The details of how the Funnel plots were plotted have been elaborated elsewhere.[9] The summary of findings table was generated using the GRADE software (https://gdt.gradepro.org/app/), which highlights the grading of key outcomes of this meta-analysis.

Results

A total of 27 articles were found after the initial search [Figure 1]. Six duplicate studies were removed. Following the screening of the titles, abstracts, and full texts, we came down to three studies that were evaluated in detail for inclusion in this meta-analysis [Figure 1]. Data from two trials (112 patients) that fulfilled all criteria were analyzed in this meta-analysis.[5,6] Patient characteristics from the different RCTs in this meta-analysis have been elaborated in Table 1. Figure 2a and Figure 2b depict the risk of bias. Random sequence generation, attrition bias, reporting bias, allocation concealment bias, performance bias, and detection bias were at low risk in both studies (100%). None of the authors had competing financial interests to declare and the risk of other biases was judged to be low in both studies.

Effect of verapamil on primary and secondary outcomes

As compared to placebo, patients receiving verapamil had comparable C-peptide AUC at 3 months follow-up [MD 0.17 nmol/L (95% CI: -0.05 – 0.38); $P = 0.13$; $I^2 = 86\%$ (high heterogeneity (HH)); Figure 3a], but had a significantly higher C-peptide AUC at 1-year follow-up [MD + 0.27 nmol/L (95% CI: 0.19 – 0.35); $P < 0.01$; $I^2 = 12\%$ (low heterogeneity (LH); high certainty of evidence (HCE)); Figure 3b].

Compared to placebo, patients receiving verapamil had a comparable change in HbA1C at 3 months [MD 0.23% (95% CI: -0.43 – 0.90); $P = 0.49$; $I^2 = 88\%$ (HH); Figure 3c] and 1 year [MD 0.18% (95% CI: -0.74 – 1.10); $P = 0.70$; $I^2 = 89\%$ (HH); (moderate certainty of evidence (MCE)); Figure 3d] follow-up. Changes in SBP at 3 months [MD 1.45 mm Hg (95% CI: -1.09 – 4.00); $P = 0.26$; $I^2 = 0\%$ (LH); Figure 3e], 6 months [MD 0.98 mm Hg (95% CI: -2.41 – 4.37); $P = 0.57$; $I^2 = 29\%$ (LH)], 9 months [MD -0.56 mm Hg (95% CI: -3.57 – 2.45); $P = 0.71$; $I^2 = 0\%$ (LH)] and 1 year [MD 2 mm Hg (95% CI: -1.05 – 5.05); $P = 0.20$; $I^2 = 0\%$ (LH); Figure 3f] were comparable in patients receiving

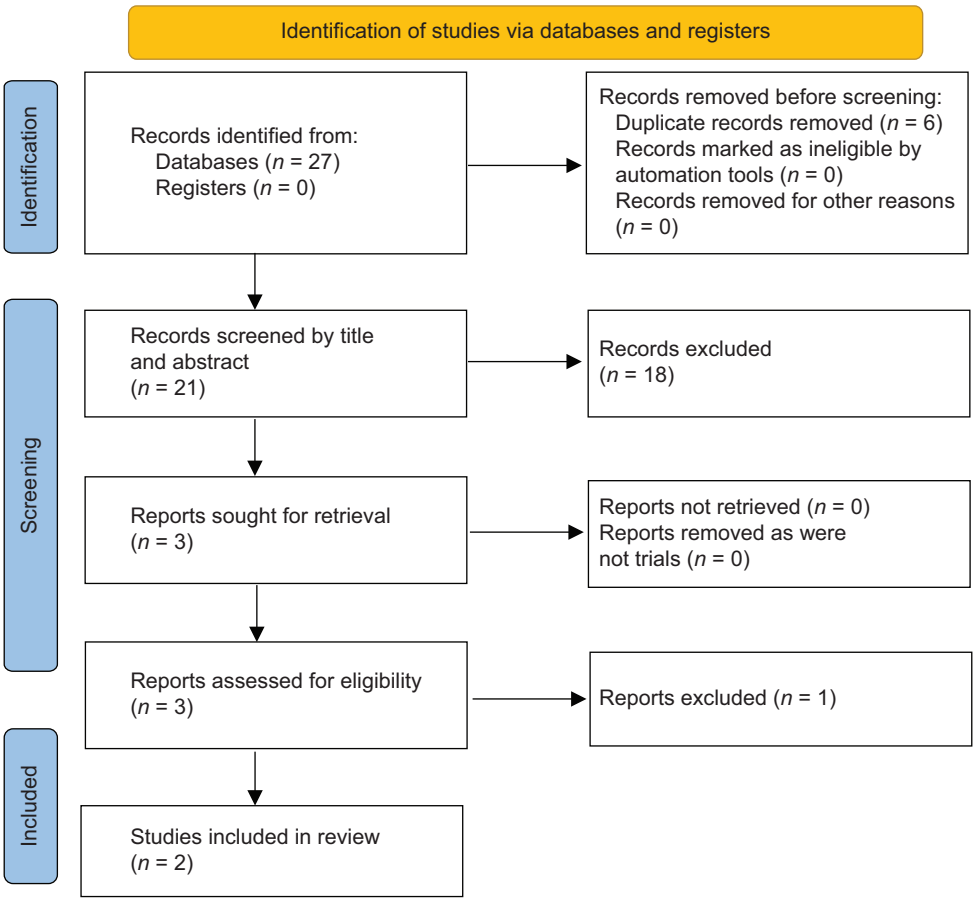

Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis. RCT: randomized controlled trial

Table 1: Patients characteristics of the different randomized controlled trials evaluated in this meta-analysis

Parameter	Ovalle *et al*.[5]		Forlenza *et al*.[6]	
	Verapamil Group (*n*=11)	Control Group (*n*=13)	Verapamil Group (*n*=47)	Control Group (*n*=41)
Age (years)	32.3±2.3	28.3±2.1	13.1±2.6	12.3±2.1
Males	55%	62%	57%	61%
T1DM duration	< 3 months	<3 months	24±5 days	25±4 days
BMI	24.4±0.8 kg/m^2	22.1±0.7 kg/m^2	73 (33-90)*	57 (32-84)*
SBP (mm Hg)	114±3	110±2	110±9	108±9
DBP (mm Hg)	74±3	71±1	64±8	63±7
HR (beats/min)	75±5	70±2	84±14	85±12
Baseline HbA1c (%)	6.6±0.4%	6.8±0.3	10.3±1.7	10.2±1.2
Fasting glucose (mmol/L)	6.4±1.0	6.8±0.3	-	-
Asian ethnicity	-	-	0%	2%
Tanner Stage (%)	-	-		
1			19%	29%
2-5			81%	71%
Dose of verapamil	Sustained-release verapamil titrated over the first 3 month from 120 mg to 360 mg		Extended release Verapamil started with 60 mg/d or 120 mg/d based on weight (1.7 mg/kg/day). The dose was escalated at 2- to 4-week intervals to a maximum of dose of 360 mg/d for participants weighing more than 50 kg	

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR : heart rate; T1DM : Type 1 diabetes mellitus; *Body mass index percentile reported as median (Interquartile range)

verapamil as compared to placebo. Changes in DBP at 3 months [MD -1.84 mm Hg (95% CI: -5.75 – 2.06); $P = 0.35$; I^2 = 64% (Moderate Heterogeneity (MH)); Figure 3g], 6 months [MD 0.47 mm Hg (95% CI: -4.43 – 5.37); $P = 0.85$;

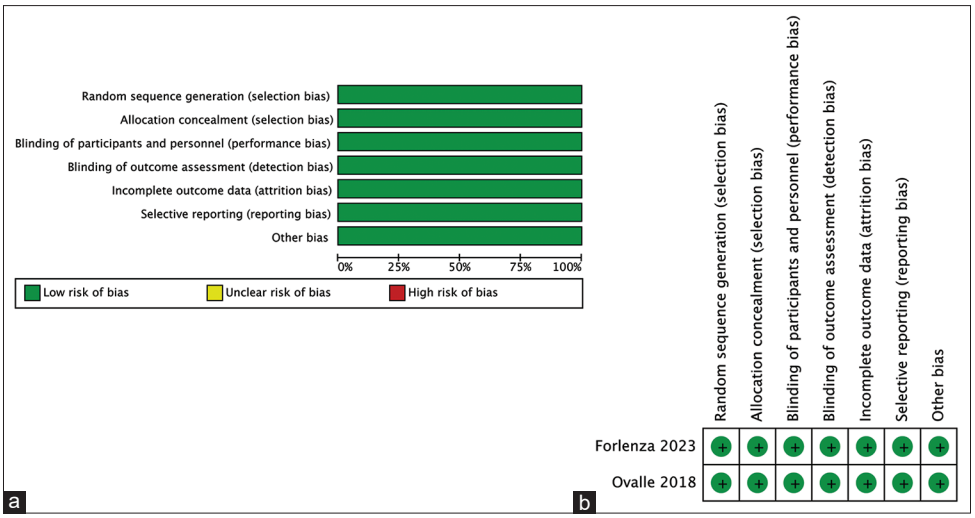

Figure 2: (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; (b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Table 2: Summary of findings of the key outcomes of this metanalysis comparing verapamil to placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (grade)
	Risk with Placebo	Risk with Verapamil			
C-peptide AUC 1 year	The mean C-peptide AUC 1 year was 0.65 nmol/L	MD 0.27 nmol/L higher (0.19 higher to 0.35 higher)	-	100 (2 RCTs)	⊕⊕⊕⊕ High
HbA1C 1 year	The mean HbA1C 1 year was 8.45%	MD 0.18% higher (0.74 lower to 1.1 higher)	-	106 (2 RCTs)	⊕⊕⊕◯ Moderate[a]
Severe Hypoglycemia	19 per 1,000	16 per 1,000 (1 to 213)	RR 0.87 (0.06 to 13.51)	112 (2 RCTs)	⊕⊕⊕⊕ High
Constipation	37 per 1,000	152 per 1,000 (37 to 507)	RR 4.11 (0.93 to 18.13)	112 (2 RCTs)	⊕⊕⊕⊕ High
Headache	148 per 1,000	71 per 1,000 (22 to 205)	RR 0.48 (0.16 to 1.43)	112 (2 RCTs)	⊕⊕⊕⊕ High
TAEs	185 per 1,000	351 per 1,000 (72 to 837)	RR 1.90 (0.52 to 6.91)	112 (2 RCTs)	⊕⊕⊕⊕ High
SAEs	93 per 1,000	130 per 1,000 (43 to 335)	OR 1.40 (0.50 to 3.93)	112 (2 RCTs)	⊕⊕⊕⊕ High

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); AUC: area under the curve; CI: confidence interval; MD: mean difference; OR: odds ratio; HbA1c: glycated hemoglobin; TAE: treatment-emergent adverse events; SAE: severe adverse events; a. Due to large variation in effect, the confidence intervals do not overlap, the *P* value for heterogeneity is <0.05, and I^2 is >60% [Figure 5]

I^2 = 77% (MH)], 9 months [MD 2 mm Hg (95% CI: -0.59 – 4.60); *P* = 0.13; I^2 = 0% (LH)] and 1 year [MD 3.08 mm Hg (95% CI: -0.84 – 6.99); *P* = 0.12; I^2 = 69% (MH); Figure 3h] were comparable in patients receiving verapamil as compared to placebo. Though heart rate (HR) at 3 months [MD -5.05 beats/minute (95% CI: -8.37 – -1.73); *P* < 0.01; I^2 = 0% (LH)] and 9 months [MD -4.23 beats/minute (95% CI: -8.12 – -0.34); *P* < 0.01; I^2 = 24% (LH)] was significantly lower in verapamil group as compared to placebo, HR at 1 year [MD 0 beats/minute (95% CI: -3.38 – 3.38); *P* = 1; I^2 = 0% (LH)] was comparable between both the groups.

Safety

The occurrence of treatment-emergent adverse events (TAEs) [Risk ratio (RR) 1.90 (95% CI: 0.52 – 6.91); *P* = 0.33; I^2 = 63% (MH); HCE; Figure 4a], severe/serious adverse events (SAEs) [RR 1.40 (95% CI: 0.50 – 3.93); *P* = 0.53; HCE], constipation [RR 4.11 (95% CI: 0.93 – 18.13); *P* = 0.06; I^2 = 0% (LH); HCE; Figure 4b], headache [RR 0.48 (95% CI: 0.16 – 1.43); *P* = 0.19; I^2 = 0% (LH); HCE; Figure 4c], severe hypoglycemia [RR 0.87 (95% CI: 0.06 – 13.51); *P* = 0.92; HCE] and increase in liver enzymes [RR 0.87 (95% CI: 0.13 – 5.92); *P* = 0.89] were comparable among patients receiving verapamil as compared to placebo.

Funnel plots were drawn to look for publication bias with regard to the key outcomes of this study and have been represented in Figure 5. The summary of findings of the key outcomes of this study is depicted in Table 2.

Discussion

In spite of extensive research spanning several decades across the globe, to date, only one medication has been approved by the USFDA for the preservation of beta cell function in people with recent onset T1DM. Teplizumab has been approved for use in people with stage-2 T1DM defined as the presence of diabetes-related autoantibodies along with biochemical but not clinical features of dysglycemia.[13] However, it must be

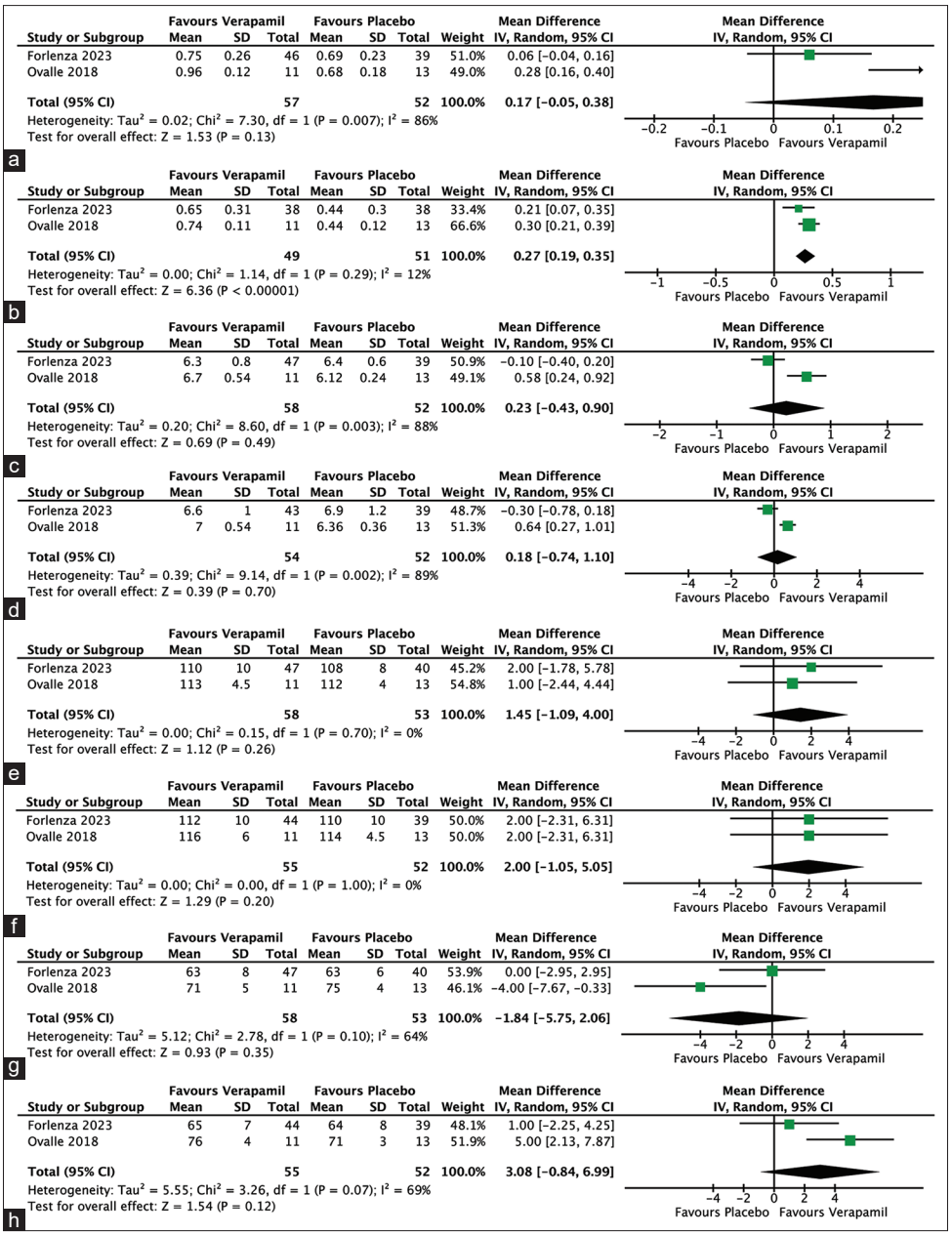

Figure 3: Forest plot highlighting the impact of verapamil as compared to placebo on (a) Area under the curve (AUC) C-peptide at 3 months; (b) AUC C-peptide at 1 year; (c) Hba1c at 3 months; (d) Hba1c at 1 year; (e): Systolic blood pressure (SBP) at 3 months; (f): SBP at 1 year; (g): Diastolic blood pressure (DBP) at 3 months; (h): DBP at 1 year

noted that teplizumab is not recommended in people with stage-3 T1DM viz. people having new onset T1DM with overt clinical features.[13] A lot of different agents have been evaluated for beta cell preservation in recent onset T1DM with largely disappointing results. Some of the major drugs already evaluated or being evaluated for beta cell preservation in T1DM include anti-thymocyte globulin, golimunmab, imatinib, baricitinib, abatacept, oral gamma-aminobutyric acid (GABA) along or in combination with glutamate decarboxylase (GAD), recombinant human glutamic acid decarboxylase 65 kDa (rhGAD65) among others.[14-26] A summary of the different agents which have been evaluated for beta cell preservation in diabetes has been elaborated in Table 3.[14-26]

TXNIP has a major role in regulating cellular redox balance.[4] TXNIP is also commonly known as thioredoxin-binding-protein-2 and vitamin D3-upregulated protein 1, highlighting the diverse role of this protein. TXNIP is normally localized in the nucleus of the cell. Under conditions of oxidative stress seen in people with diabetes, TXNIP relocates to mitochondria to interact with mitochondrial thioredoxin 2.[4] Both insulin resistance and uncontrolled hyperglycemia have been linked with overexpression of TXNIP, which in turn leads to NLRP3 inflamasome and

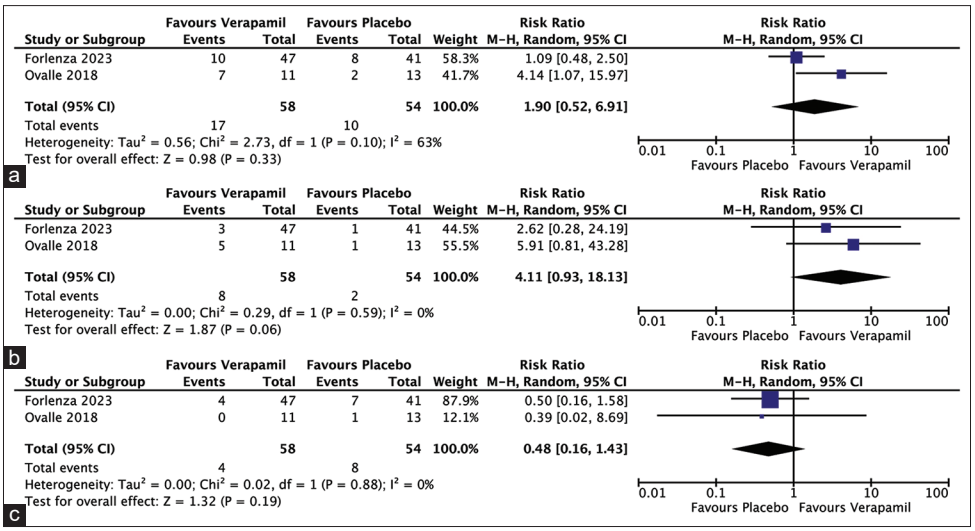

Figure 4: Forest plot highlighting the impact of verapamil as compared to placebo on (a) Treatment-emergent adverse events (TAEs); (b) Constipation (c) Headache

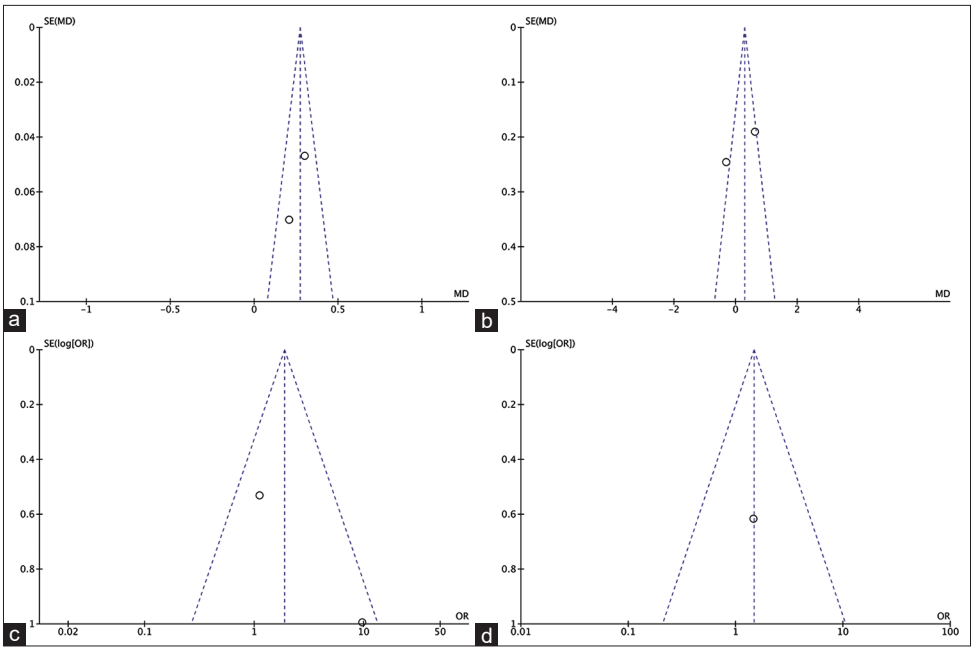

Figure 5: Funnel plot assessing the publication bias for key outcomes of this meta-analysis (a) Area under the curve (AUC) C-peptide at 12 months; (b) HbA1c at 12 months; (c): Treatment emergent adverse events; (d): severe adverse events

IL-1β activation, leading to cytokine-mediated beta-cell apoptosis/loss, along with the acceleration of development of microvascular and macrovascular complications of diabetes.[4] Hence pharmacotherapy leading to a decrease in TXNIP expression has long been a target of new drug development.[3] Metformin, dipeptidyl peptidase-4 (DPP4) inhibitor, and insulin are believed to have some role in reducing TXNIP expression.[3,4] Calcium channel blockers (CCBs), especially the L-type CCBs like verapamil were originally demonstrated to reduce TXNIP in cardiomyocytes in people with hypertension. The discovery of an L-type calcium channel in pancreatic beta cells leads to the evaluation of verapamil on TXNIP expression in pancreatic beta cells in preclinical studies, where verapamil demonstrated not only inhibition of TXNIP expression in pancreatic β-cells but also enhanced the β cell survival and function, giving rise to the concept of the role of verapamil in diabetes prevention as an anti-oxidative, anti-apoptotic and immunomodulating agent. Global T1DM proteomics has recognized Chromogranin A (CHGA) to be a T1DM autoantigen.[27] Verapamil has demonstrated also to normalize serum CHGA levels and reverse T1DM-induced elevations in circulating proinflammatory T-follicular-helper cell markers.[27]

This is the first meta-analysis to highlight the efficacy and safety of verapamil in preserving pancreatic beta cell function

Table 3: Summary of different agents being evaluated till date for beta cell preservation in diabetes

Authors (Country)	Agent; Study duration	Study details	Patient characteristics	Key Outcomes
Russel *et al*. 2023 (USA)[14]	Abatacept; 12 months	RCT; Abatacept (*n*=101); Placebo (*n*=111)	Autoantibody positive new onset T1DM	No impact on progression of glucose intolerance over 12 months; Abatacept reduced the frequency of inducible T-cell costimulatory (ICOS) + PD1 + T-follicular helper (Tfh) cells and CD4 + regulatory T cells (Tregs)
MC Vean *et al*. 2023 (USA)[15]	Intensive diabetes management (IDM) using an automated insulin delivery system; 12 months	RCT; IDM (*n*=61); standard care using continuous glucose monitor (*n*=52)	New onset T1DM (7-17 years age)	Did not affect the decline in pancreatic C-peptide secretion at 52 weeks
Rigby *et al*. 2023 (USA)[16]	Golimumab; 12 months	2 years passive follow up of T1GER (A Study of SIMPONI to Arrest β-Cell Loss in Type 1 Diabetes study	New onset T1DM (6-21 years age)	After treatment was stopped, C-peptide area under the curve (AUC) remained greater in the golimumab versus control group with lesser secline in C-peptide AUC at weeks 78 and 104 follow-up
Martin *et al*. 2022 (USA)[17]	Oral gamma aminobutyric acid (GABA) along or in combination with glutamate decarboxylase (GAD)	Oral GABA twice-daily (*n*=41), or oral GABA plus two-doses GAD-alum (*n*=25), versus placebo (*n*=31)	New onset T1DM	GABA alone or in combination with GAD-alum did nor preserve beta-cell function
Ludvigsson *et al*. 2022 (Sweden)[18]	Recombinant human glutamic acid decarboxylase 65 kDa (rhGAD65); 22 months	Intra-lymphatic injections of rhGAD65 or placebo	New onset T1DM (<6 months duration) (12-29 years age) carrying HLA DR3-DQ2 haplotype	Study ongoing; results awaited
Waibel *et al*. 2022 (Australia)[19]	Baricitinib	83 participants randomized within 100 days of diagnosis to receive either baricitinib 4 mg/day or placebo for 48 weeks	New onset T1DM (10-30 years age)	Study ongoing; results awaited
Gitelman *et al*. 2021 (USA, Australia)[20]	Imatinib	Participants were randomized to receive either 400 mg imatinib mesylate (4×100 mg film-coated tablets per day) (*n*=43) or matching placebo (*n*=21) for 26 weeks	New onset T1DM (<100 days from diagnosis) (18-45 years age); autoantibody positive	Study met its primary endpoint of adjusted mean difference in 2-h C-peptide AUC at 12 months for imatinib versus placebo treatment being 0·095 (90% CI -0·003 to 0·191; *P*=0·048, one-tailed test), which was not sustained out to 24 months
Ludvigsson *et al*. 2021 (Sweden)[21]	Combined Etanercept, GAD-alum and vitamin D treatment	Patients received Day 1-450 Vitamin D (Calciferol) 2000 U/d per os, Etanercept sc Day 1-90 0.8 mg/kg once a week and GAD-alum sc injections (20 µg, Diamyd™) Day 30 and 60	Autoantibody positive recent onset T1DM	Combination therapy with parallel treatment with GAD-alum, Etanercept and vitamin D in children and adolescents with type 1 diabetes was feasible and tolerable but had no beneficial effects on the autoimmune process or beta cell function
Keymeulen *et al*. 2021 (Belgium, UK)[22]	Anti-CD3 monoclonal antibody otelixizumab; 24 months	Placebo (*n*=6/5); otelixizumab 9 mg (*n*=9/8); otelixizumab 18 mg (*n*=8/8), otelixizumab 27 mg (*n*=7/7) completed the study	New onset T1DM (<32 days from diagnosis) (16-27 years age	A metabolic response was observed with otelixizumab 9 mg, while doses higher than 18 mg increased the risk of unwanted clinical Epstein Barr Virus (EBV) reactivation
Pozzili *et al*. 2020 (Italy, France, Germany)[23]	Albiglutide, glucagon like peptide-1 receptor agonist; 52 weeks study	once-weekly albiglutide 30 mg (up-titration to 50 mg at week 6) versus placebo	New onset T1DM	Albiglutide 30 to 50 mg weekly for 1 year had no appreciable effect on preserving residual β-cell function versus placebo.
Gitelman *et al*. 2016 (USA)[24]	Anti-thymocyte globulin (ATG)	6.5 mg/kg ATG (Thymoglobulin) (*n*=35) vs placebo (*n*=16)	New onset T1DM	Did not preserve islet function 24 months later
Haller *et al*. 2015 (USA)[25]	Low-dose anti-thymocyte globulin (ATG) and pegylated granulocyte CSF (G-CSF)	17 subjects received ATG (2.5 mg/kg intravenously) followed by pegylated G-CSF (6 mg subcutaneously every	New onset T1DM (duration of T1D >4 months and <2 years	The mean difference in mixed meal tolerance test-stimulated AUC C-peptide between treated and placebo subjects was 0.28 nmol/l/min (95% CI 0.001-0.552, *P*=0.050).

Contd...

Table 3: Contd...

Authors (Country)	Agent; Study duration	Study details	Patient characteristics	Key Outcomes
		2 weeks for 6 doses) and 8 subjects received placebo		A1c was lower in ATG/G-CSF-treated subjects at the 6-month study visit. ATG/G-CSF therapy was associated with relative preservation of Tregs.
Gitelman *et al*. 2013 (USA)[26]	Anti-thymocyte globulin (ATG)	Randomly allocating 38 to ATG and 20 to placebo	New onset T1DM	Brief course of ATG does not result in preservation of β-cell function 12 months later

RCT: randomized controlled trial; T1DM: type-1 diabetes

in people living with T1DM. Our meta-analysis highlights the encouraging data of significant improvement in C-peptide AUC after one year of therapy with verapamil in children and adults with recent onset T1DM. This meta-analysis also provides reassuring safety data on verapamil use in early T1DM. Verapamil use in such people was not associated with any significant changes in SBP, DBP, and pulse rate. Verapamil was well tolerated without any significant increase in TAEs, SAES, hypoglycemia, constipation, or headache.

An important limitation of this meta-analysis is that it has analyzed data from only 2 RCTs. Hence further studies are warranted in larger groups of patients. Also, it is important to highlight that all the current available RCTs have compared verapamil with placebo. It would be interesting to compare the outcomes of verapamil to teplizumab, but for that, we would need a separate new RCT. Also, combination therapy of verapamil with teplizumab in people with stage-2 T1DM is urgently warranted. This meta-analysis provides us with encouraging data, and similar RCTs are necessary in people with recent onset T1DM in different ethnic groups across the globe. The advantages of verapamil use are its good safety profile, good tolerability, and low cost of therapy.

To conclude, one-year of verapamil therapy in people with recent onset T1DM is associated with significant improvement in pancreatic C-peptide secretion and hence should be actively investigated in future larger and longer studies.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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