Review Article

Ranirestat Improves Electrophysiologic but not Clinical Measures of Diabetic Polyneuropathy: A Meta-Analysis

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Abstract

Ranirestat, an aldose reductase inhibitor evaluated in several randomised controlled trials (RCTs) in diabetic peripheral neuropathy (DPN). However, to date, no meta-analysis has evaluated the efficacy and safety of ranirestat in DPN. We undertook this meta-analysis to address this knowledge gap. Detailed search of electronic databases for RCTs published till December 2021 was done at Cochrane register, Medline, PubMed, Embase, clinicaltrials.gov, ctri.nic.in, global health and Google Scholar using the Boolean search strategy: ((ranirestat) OR (aldose reductase inhibitor)) AND ((diabetes) OR ("diabetes mellitus")). The primary outcome was to evaluate changes in nerve conduction velocities (NCV) of different nerves. The secondary outcomes were to evaluate alterations in amplitudes, F-wave latencies of nerves, modified Toronto Clinical Neuropathy Score (mTCNS) and adverse events. Data from 5 studies involving 1461 patients with DPN was analysed to establish the impact of ranirestat (20-40 mg/day) as compared to placebo on different electrophysiologic outcomes over a median follow-up of 52 weeks. Patients receiving ranirestat had significantly greater improvement in proximal median sensory NCV [MD 0.77 m/s (95%CI: 0.50–1.05); $P < 0.01$; $I^2 = 26\%$], distal median sensory NCV [MD 0.91 m/s (95%CI: 0.87–0.95); $P < 0.01$; $I^2 = 0\%$], median motor NCV [MD 0.63 m/s (95%CI: 0.60–0.66); $P < 0.01$; $I^2 = 0\%$], tibial motor NCV [MD 0.46 m/s (95%CI: 0.43–0.49); $P < 0.01$; $I^2 = 0\%$] and peroneal motor NCV [MD 0.80 m/s (95%CI: 0.66–0.93); $P < 0.01$; $I^2 = 0\%$]. mTCNS was not significantly different among groups. Treatment-emergent adverse events [risk ratio (RR) 0.85 (95%CI: 0.63–1.14); $P = 0.28$; $I^2 = 0\%$] and severe adverse events [RR 1.35 (95%CI: 0.86–2.11); $P = 0.20$; $I^2 = 0\%$] were comparable across study groups. In people with established DPN with long-standing diabetes, ranirestat is safe and effective in improving electrophysiologic but not clinical DPN.

Keywords: Diabetes, neuropathy, ranirestat

Introduction

Diabetic polyneuropathy (DPN) is a common microvascular complication of diabetes significantly impairing the quality of life.[1] The pathogenesis of DPN is multifactorial and involves hyperglycaemia-related advanced glycation end products (AGEs), systemic inflammation, and oxidative stress, among many others.[1] Hyperglycaemia induced increased flux through the polyol pathway, resulting in increased sorbitol formation at the neural levels, which have been implicated in its pathogenesis.[2] Studies have shown that increased neural sorbitol concentration is associated with decreased concentration of myelinated nerves, and damage to the eye lens, retina and renal glomeruli.[2] Aldose reductase inhibitors (ARIs) which inhibit the aldose reductase enzyme, resulting in decreased sorbitol formation at the cellular and tissue levels, are believed to mitigate increased sorbitol-related end-organ damage.[3] ARIs are attractive as they have the potential to modify the disease course and prevent DPN, unlike other therapies for DPN, which primarily target symptom relief (tri-cyclic antidepressants,

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anti-epileptics, selective serotonin and/or nor-adrenaline reuptake inhibitors). More than 8 different ARIs have been developed, of which epalrestat and ranirestat have been launched for clinical use.[3]

Ranirestat is an ARI which reduces sorbitol levels in nerves at doses 100-fold lower than other ARIs like zenarestat.[4] Ranirestat is one of the most extensively studied ARIs.[4] Several randomised controlled trials (RCTs) from different countries across the globe have been published that evaluate the role of ranirestat in DPN.[5] However, to date, no meta-analysis is available which has evaluated the efficacy and safety of ranirestat in managing DPN. Hence, this meta-analysis was done to establish the efficacy and safety of ranirestat in managing DPN.

Methods

The meta-analysis was done as per the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[6] The predefined protocol is registered with the international prospective register of systematic reviews (PROSPERO) having a registration number CRD42021232268. All RCTs satisfying the inclusion criteria, published till December 2021, were considered for this meta-analysis. This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA).[7] No separate ethics committee approval was required for this meta-analysis as ethical approval already exists for the individual RCTs included in this study.

The PICOS criteria were used to screen and select the studies for this meta-analysis with patients (P) being individuals with DPN; intervention (I) being the use of ranirestat over the background of standard care for DPN; control € being patients with diabetes on standard care for managing DPN but not receiving ranirestat; outcomes (O) being evaluated that impacted on electrophysiological measurements of three key nerves: median motor nerve, tibial motor nerve, and the median sensory nerve, along with changes in DPN symptomatology. Only patients with diabetes were considered for this meta-analysis. Only those RCTs which had at least 2 arms were included, with the intervention arm receiving ranirestat on the background of standard care for DPN and the non-intervention or control arm receiving placebo or any other non-ranirestat medication for DPN. Patients with DPN who were already on ARIs were excluded from this study.

The primary outcome of the meta-analysis was to evaluate the changes in nerve conduction velocities (NCVs) on electrophysiological measurements of three key nerves: the median motor nerve, the tibial motor nerve and the median sensory nerve. The secondary outcomes were to evaluate alterations in amplitudes, minimum F-wave latencies (MFWL), DPN scores like the total modified Toronto Clinical Neuropathy Score (mTCNS), neuropathy symptomatology and adverse events. Only those RCTs were included in this meta-analysis whose outcomes evaluated at least one of the primary end points or at least 2 secondary end points.

Search method for identification of studies

Detailed search of electronic databases for RCTs published till December 2021 was done at Cochrane register, Medline, PubMed, Embase (Ovid SP), clinicaltrials.gov, ctri.nic.in, global health and Google Scholar using the Boolean search strategy: ((ranirestat) OR (aldose reductase inhibitor)) AND ((diabetes) OR ("diabetes mellitus")).

Data extraction, study selection and risk of bias assessment

Data extraction was carried out independently by two authors using standard data extraction forms. The details have been elaborated on elsewhere.[8] Three authors independently assessed the risk of bias using Review Manager (Revman) version 5.3 (The Cochrane Collaboration, Oxford, UK 2014) software. We specifically looked for selection bias, performance bias, detection bias, attrition bias, reporting bias and any other bias like publication bias. The details of how the risk of bias assessment was done have already been elaborated elsewhere.[8]

Measures of treatment effect, heterogeneity assessment, grading of results and data synthesis

For continuous variables, outcomes were expressed as mean differences (MD). Conventional units were used for analysis. Dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CI). Adverse events were expressed as absolute risk differences. RevMan 5.3 was used for comparing the outcomes. Heterogeneity was assessed by studying the forest plot generated for the primary and secondary outcomes. Subsequently, heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance with the I^2 test.[7] The details have been elaborated on elsewhere.[8] Grading of the evidence related to primary and secondary outcomes was done using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach.[9] The details have been elaborated on elsewhere.[8] The presence of one or more studies outside the inverted funnel plot was taken as proof of significant publication bias.[10] A random effect model was used for the analysis of outcomes expressed as 95% confidence intervals (95%CI). Forrest plots were plotted with the left side favouring ranirestat and the right side favouring control.

Results

A total of 54 articles were found after the initial search [Figure 1]. Following the screening of the titles and abstracts, followed by full-texts, the search was reduced to 7 studies of which 5 RCTs in people with T2DM which fulfilled all criteria were analysed in this meta-analysis.[5,11-14] The studies by Bril (2004) *et al*.[15] and Bril (2006) *et al*.[14] are from the same cohort of patients. Hence, these results have been pooled together and presented under Bril (2006) *et al*.[14] Ranirestat at different doses ranging from 20-40 mg/day has been used in different

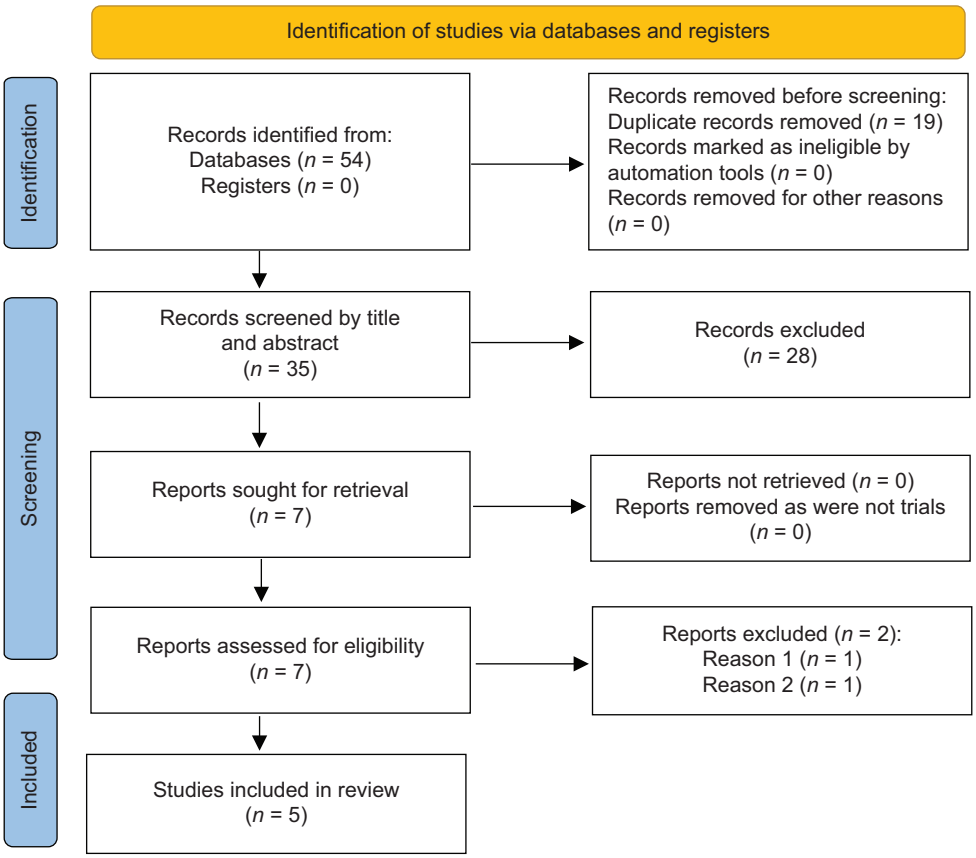

Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis Reason-1: 2 papers were from the same cohort of patients and hence were merged together for analysis as Bril 2006 *et al.*[14]; Reason-2: was a study evaluating the safety of ranirestat in hepatic disease, did not fulfil the inclusion criteria but has been discussion under the safety section of results[16]; RCT: randomised controlled trial

studies. In our meta-analysis, we considered only those patients who were receiving ranirestat 40 mg/day or 20 mg/day for the duration of the study, as it was the most common dose used across different studies. Ranirestat at a dose of 40 mg/d was used in the study by Sekiguchi *et al.,*[5] Polydefkis *et al.*[12] and Bril (2009) *et al.*[13] Ranirestat at a dose of 20 mg/d was used in the study by Satoh *et al.*[11] and Bril (2006) *et al.*[14] The duration of the study was 24 months (108 weeks), 52 weeks, 52 weeks, 26 weeks and 12 weeks in the study by Polydefkis *et al.*,[12] Sekiguchi *et al.*,[5] Bril (2009) *et al.*,[13] Satoh *et al.*[11] and Bril[2006] *et al.* respectively. The details of the included RCTs have been elaborated in Table 1.

Risk of bias in the included studies

The summaries of the risk of bias of the 5 studies included in the meta-analysis have been elaborated in Figure 2a and Figure 2b. Random sequence generation, allocation concealment, performance bias, and reporting bias were judged to be at low risk in all 5 studies (100%). Incomplete outcome data (attrition bias) was at low risk in 3 out of 5 studies (66.67%). Source of funding, especially from the pharmaceutical industry, one or more authors from pharmaceutical organisations, professional writers funded by the pharmaceutical industry and conflict of interests were looked into the "other bias" section. Another bias was at high risk in all 5 studies (100%) [Figure 2a, 2b]. Funnel plot is suggestive of the presence of most of the studies outside the plot, and hence, it is likely that significant publication bias is present [Supplementary Figure 1 and Supplementary Table 1].

Effect of ranirestat on electrophysiologic outcomes

Proximal median sensory NCV

Data from 5 studies (1182 patients) were analysed to find out the impact of ranirestat on proximal median sensory NCV. Patients receiving ranirestat had a significantly greater improvement in proximal median sensory NCV [MD 0.77 m/s (95% CI: 0.50–1.05); $P < 0.01$; $I^2 = 26\%$ (low heterogeneity); Figure 3a].

Distal median sensory NCV

Data from 3 studies (665 patients) were analysed to find out the impact of ranirestat on distal median sensory NCV. Patients receiving ranirestat had a significantly greater improvement in distal median sensory NCV [MD 0.91 m/s (95% CI: 0.87–0.95); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 3b].

Sural sensory NCV

Data from 3 studies (665 patients) were analysed to find out the impact of ranirestat on sural sensory NCV. Patients receiving ranirestat had a greater improvement in sural sensory NCV which approached statistical significance [MD 0.94 m/s (95% CI: −0.25–0.95); $P = 0.12$; $I^2 = 0\%$ (low heterogeneity); Figure 3c].

Table 1: Patient characteristics of the different RCTs evaluated in this meta-analysis

	Bril 2006[14]		Bril 2009[13]		Polydefkis 2015[12]		Satoh 2016[11]		Sekiguchi 2019[5]	
	Ranirestat Group (*n*=34)	Control Group (*n*=34)	Ranirestat Group (*n*=145)	Control Group (*n*=134)	Ranirestat Group (*n*=259)	Control Group (*n*=258)	Ranirestat Group (*n*=40)	Control Group (*n*=33)	Ranirestat Group (*n*=268)	Control Group (*n*=269)
Age (years)	59.3±13.5	60.2±10.4	54.5±9.5	56.1±8.9	0.57.3±10.0	58.2±8.9	58.9±8.7	58.2±7.5	62.1±9.1	60.9±9.0
Males	22	20	91	74	0.164	174	23	24	185	178
Diabetes duration (years)	13.7±12.0	16.1±10.5	14.1±9.0	14.6±9.0	0.11.5±7.7	12.4±9.7	15.7±7.3	15.2±7.4	15±9	14.7±8.3
DPN duration (years)	4.8±4.4	5.2±3.0	4.7±4.0	4.6±3.2	0.4.4±3.9	4.6±4.2	5.1±3.8	4.9±3.1	6.1±8.9	5.8±4.7
Baseline HbA1c (%)	8.25±1.3	8.04±1.26	8.1±1.4	8.3±1.3	7.9±1.7.	7.8±1.7	7.67±0.70	8.05±0.93	7.46±0.47	7.51±0.77
BMI	N/A	N/A	32.9±6.9	32.9±6.96	0.30.4±5.0	30.3±4.9	24.63±2.97	25.34±4.12	24.99±3.96	25.55±4.14

DPN: Diabetes peripheral neuropathy; BMI: Body mass index in kg/m^2; N/A: Not available

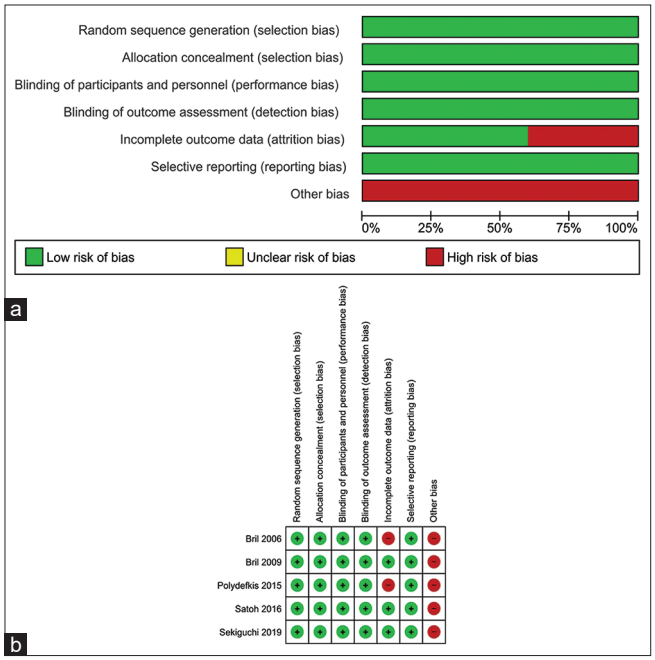

Figure 2: (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; (b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Median motor NCV

Data from 2 studies (592 patients) were analysed to find out the impact of ranirestat on median motor NCV. Patients receiving ranirestat had a significantly greater improvement in median motor NCV [MD 0.63 m/s (95% CI: 0.60–0.66); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 3d].

Tibial motor NCV

Data from 2 studies (610 patients) were analysed to find out the impact of ranirestat on tibial motor NCV. Patients receiving ranirestat had a significantly greater improvement in tibial motor NCV [MD 0.46 m/s (95% CI: 0.43–0.49); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 3e].

Peroneal motor NCV

Data from 2 studies (334 patients) were analysed to find out the impact of ranirestat on peroneal motor NCV. Patients receiving ranirestat had a significantly greater improvement in peroneal motor NCV [MD 0.80 m/s (95% CI: 0.66–0.93); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 3f].

F-wave latency

Data from 2 studies (Bril 2006 *et al.*[14] and Sekiguchi *et al.*[5]; 592 patients) were analysed to find out the impact of ranirestat on median motor nerve F-wave latency. Patients receiving ranirestat had a significantly greater improvement (reduction) in median motor nerve F-wave latency [MD − 0.28 (95% CI: −0.29 to − 0.27); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity)]. Data from 1 study (Sekiguchi *et al.*; 537 patients) was analysed to find out the impact of ranirestat on tibial motor nerve F-wave latency. Patients receiving ranirestat had a significantly greater improvement (reduction) in tibial motor nerve F-wave latency [MD − 0.18 (95% CI: −0.20 to − 0.16); $P < 0.01$; $I^2 = 0\%$].

Nerve amplitude

Data from 1 study (Satoh *et al.*[11]; 73 patients) was analysed to find the impact of ranirestat on changes in the amplitude of neural signals in different nerves. The changes in the amplitude among patients receiving ranirestat was comparable to that of controls for sural sensory nerve [MD − 0.03 µV (95% CI: −0.85–0.79); $P = 0.94$], proximal median sensory nerve [MD 0.71 µV (95% CI: −0.63–2.05); $P = 0.30$], distal median sensory nerve [MD 0.41 µV (95% CI: −1.35–2.17); $P = 0.65$] and distal tibial motor nerve [MD 0.05 µV (95% CI: −1.04–1.14); $P = 0.93$]. A significantly greater improvement in nerve amplitude with ranirestat was noted for proximal [MD 0.80 µV (95% CI: 0.13–1.47); $P = 0.02$] and distal median motor nerve [MD 0.85 µV (95% CI: 0.18–1.52); $P = 0.01$].

Effect of ranirestat on clinical outcomes:

Modified Toronto clinical neuropathy score (mTCNS) and other neuropathy clinical assessment tools

Data from 3 studies (889 patients) were analysed to find out the impact of ranirestat on mTCNS. A decrease in mTCNS

Table 2: Summary of findings of the key outcomes of this meta-analysis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Control	Risk with Ranirestat			
mTCNS (modified Toronto Clinical Neuropathy Score)	The mean mTCNS (modified Toronto Clinical Neuropathy Score) was 7.50	MD 0.2 lower (0.45 lower to 0.04 higher)	-	889 (3 RCTs)	⊕⊕⊕⊕ High
Proximal median sensory nerve conduction velocity	The mean proximal median sensory NCV was 57.10 m/s	MD 0.77 m/s higher (0.5 higher to 1.05 higher)	-	1182 (4 RCTs)	⊕⊕⊕◯ Moderatea
Distal median sensory nerve conduction velocity	The mean distal median sensory NCV was 46.54 m/s	MD 0.91 m/s higher (0.87 higher to 0.95 higher)	-	665 (3 RCTs)	⊕⊕⊕⊕ High
Sural sensory nerve conduction velocity	The mean sural sensory NCV was 44,13 m/s	MD 0.94 m/s higher (0.25 lower to 2.12 higher)	-	665 (3 RCTs)	⊕⊕⊕◯ Moderatea
Treatment-emergent adverse events (TAEs)	504 per 1,000	464 per 1,000 (390 to 537)	OR 0.85 (0.63-1.14)	1461 (5 RCTs)	⊕⊕⊕◯ Moderatea
Serious adverse events (SAEs)	54 per 1,000	71 per 1,000 (47 to 107)	OR 1.35 (0.86-2.11)	1461 (5 RCTs)	⊕⊕⊕◯ Moderatea

*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); CI: confidence interval; MD: mean difference; OR: odds ratio. GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Funnel plot is suggestive of the presence of most of the studies outside the plot, and hence, it is likely that significant publication bias is present

reflects an improvement in neuropathy symptomatology. Patients receiving ranirestat had a greater reduction in mTCNS as compared to controls but not statistically significant [MD − 0.20 (95% CI: −0.45–0.04); $P = 0.11$; $I^2 = 58\%$ (moderate heterogeneity); Figure 4a].

No significant difference in self-administered Neuropathy Total Symptom Score-6 (NTSS-6-SA) was noted among the study groups at the end of the study by Polydefkis *et al.*[12] There was no significant improvement in vibration perception threshold (VPT) with ranirestat as compared to controls in studies by Poydefkis *et al.*,[12] Bril 2009 *et al.*[13] and Bril 2006 *et al*.[14] No difference was noted in symptoms and other sensory test scores with ranirestat as compared to controls in the study by Bril 2009 *et al*.[13]

Glycated haemoglobin (HbA1c)

In the study by Sekiguchi *et al.*,[5] the mean HbA1c remained at a constant level of 7.49–7.59% in the placebo group and 7.45–7.62% in the ranirestat group throughout the study period. HbA1c did not change significantly during the course of study by Satoh *et al.*,[11] and did not have an impact on summed sensory and motor NCV on analysis of covariance (ANCOVA). HbA1c did not change significantly throughout the course of the study by Polydefkis *et al*.[12]

Tissue polyol levels

Data from 1 study (Sekiguchi *et al*.[5]; 537 patients) was analysed to find the impact of ranirestat on erythrocyte sorbitol levels. Patients receiving ranirestat had significantly lower erythrocyte sorbitol levels as compared to controls [MD -41.49 nmol/g-Hb (95% CI: −43.53 to − 39.45); $P < 0.01$]. Data from 1 study (Bril 2006 *et al.*[14]; 55 patients) was analysed to find the impact of ranirestat on sural nerve sorbitol levels (sural nerve tissue obtained through skin biopsy). Patients receiving ranirestat had significantly lower sural nerve sorbitol levels [MD − 83.50 nmol/mg % (95% CI: −114.70 to − 52.30); $P < 0.01$]. Plasma ranirestat levels were comparable in the study group as compared to controls, throughout the study, without evidence of ranirestat accumulation or autoinduction in studies by Bril 209 *et al.*[13] and Bril 2006 *et al.*[14]

Safety outcomes with ranirestat

Data from 5 studies (1461 patients) were analysed to evaluate the impact of ranirestat on the occurrence of treatment-emergent adverse events (TAEs) and severe adverse events (SAEs). The occurrence of TAEs [RR 0.85 (95% CI: 0.63–1.14); $P = 0.28$; $I^2 = 0\%$ (low heterogeneity); Figure 4b] and SAEs [RR 1.35 (95% CI: 0.86–2.11); $P = 0.20$; $I^2 = 0\%$ (low heterogeneity); Figure 4c] were not statistically different in patients receiving ranirestat as compared to controls. No adverse impact on renal and hepatic function was noted in any of the studies. Itou *et al.*[16] demonstrated that the ranirestat exposure and the plasma protein binding of ranirestat 40 mg/day drug was not substantially altered by normal, mild, or moderate hepatic impairment (protein binding 99.22%, 99.29%, and 99.00%, respectively), suggesting no dose adjustment needed for ranirestat in patients with mild or moderate hepatic impairment.[16] No significant change in blood pressure and low-density cholesterol was noted in the study by Polydefkis *et al.*[12]

In the study by Sekiguchi *et al.*,[5] one participant in the placebo group died due to acute myocardial infarction and ventricle rupture) and one participant in the ranirestat group died due to pancreatic carcinoma with metastases to the liver. Four deaths were reported in the study by Polydefkis *et al.*,[12] 2 each in the ranirestat and control group. One patient in the ranirestat

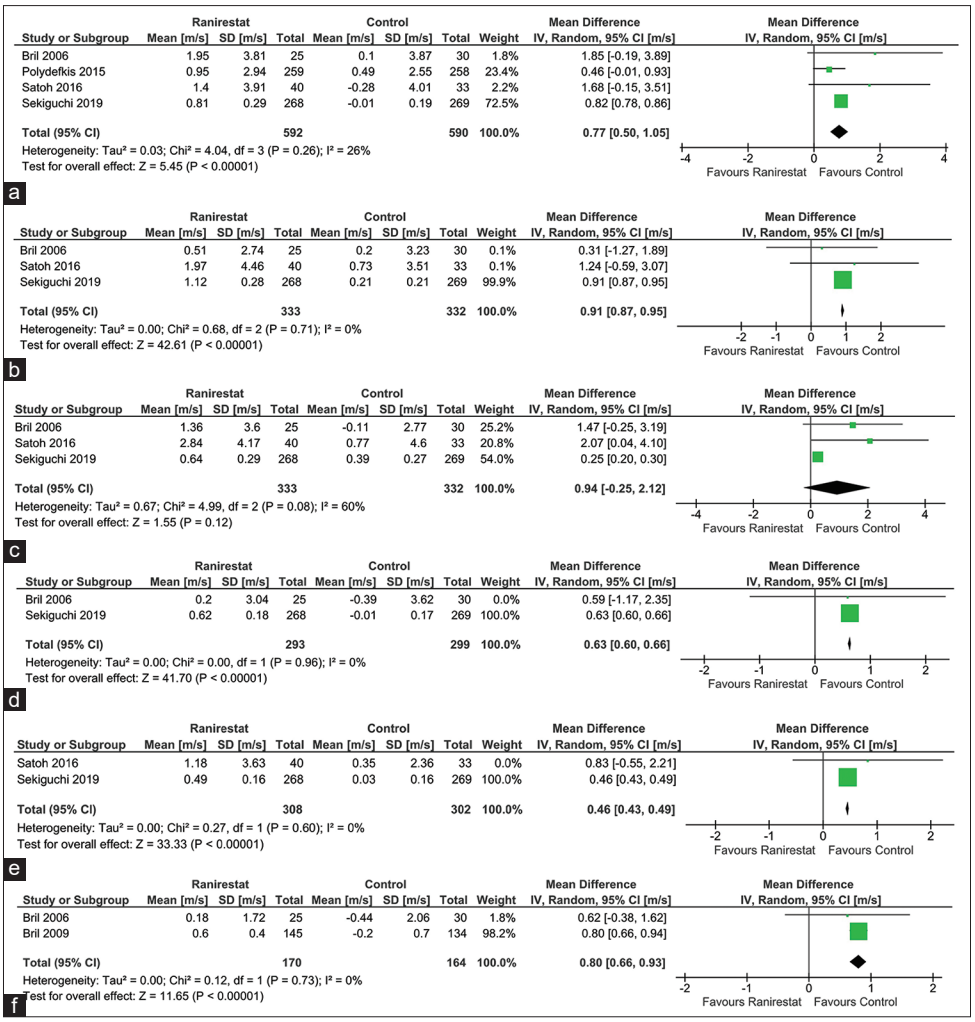

Figure 3: Forest plot evaluating the impact of ranirestat on (a) proximal median sensory NCV; (b): distal median sensory NCV; (c) sural sensory NCV; (d): median motor NC€(e) tibial motor NCV; (f): peroneal motor NCV

80 mg group died due to hypertensive heart disease considered possibly related to ranirestat.[12] No deaths were reported in the study by Satoh *et al*.,[11] Bril 2009 *et al*.[13] and Bril 2006 *et al*.[14] The summary of findings of the key outcomes of this study with the grading of the evidence has been elaborated in Table 2.

Discussion

This is the first meta-analysis to evaluate the efficacy and safety of ranirestat on different electrophysiologic and clinical aspects of DPN. This meta-analysis provides reassuring data on the safety of ranirestat. Ranirestat is well tolerated with no increase in adverse events. A specific study done on people with mild to moderate hepatic impairment documented the safety and tolerability of ranirestat in this special situation, warranting no dose adjustment. Our meta-analysis showed that ranirestat use over a median duration of 52 weeks was associated with significant improvement in NCVs of proximal and distal medial sensory nerves and median, tibial and peroneal motor nerves. However, no significant improvement was noted with regard to sural sensory NCV. An improvement in the median and tibial motor F-wave latency was also noted. A single study documented a significant reduction in sorbitol levels as the tissue level with ranirestat.

However, this electrophysiologic improvements and biochemical improvement did not translate into a meaningful significant improvement in neuropathy scores like mTCNS, pain perception scores, and VPT. This discordance needs further evaluation. It may be hypothesised that improvement in electrophysiologic parameters is apparent earlier, and it would need a longer treatment with follow-up to document meaningful changes in the clinical parameters of DPN. Also, one of the limitations of all RCTs in this meta-analysis is that the drug has been evaluated in people with a long duration of diabetes and established DPN of significant duration. It has been suggested that once DPN establishes itself, the changes are irreversible because neural tissues are not readily regenerated.[17] Inter-individual variability of tissue levels of aldose reductase among normal and people with diabetes may also determine the efficacy of ARIs.[18] It has been hypothesised that the competition of aldehyde reductases with aldose reductase for

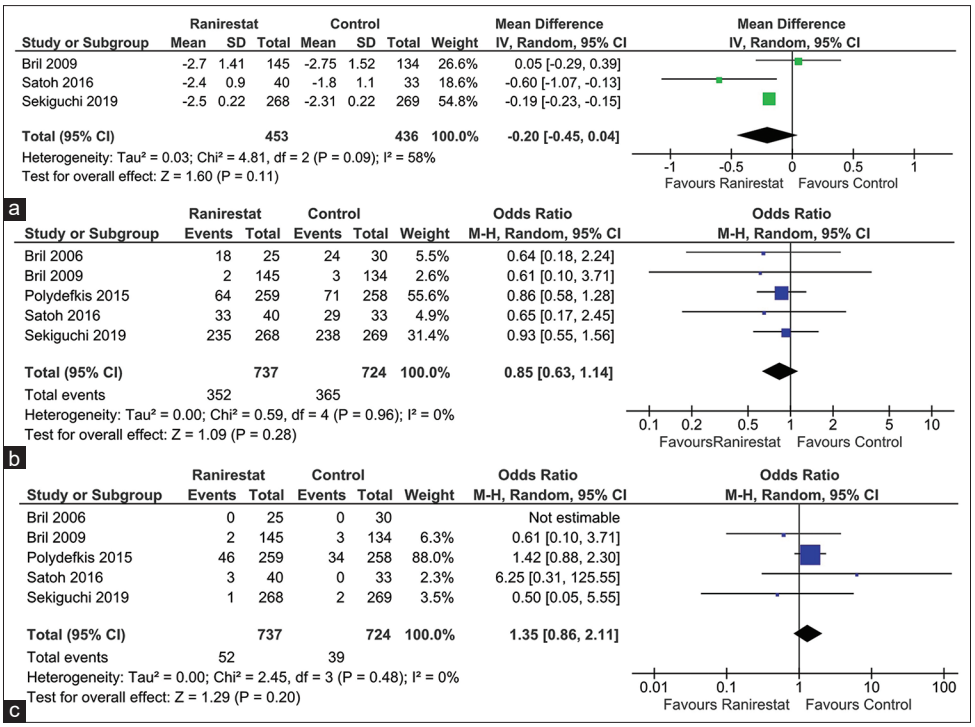

Figure 4: Forest plot evaluating the impact of ranirestat on (a) Modified Toronto Clinical Neuropathy Score (mTCNS); (b) TAEs; (c) SAEs

the inhibitors can also affect treatment outcomes, suggesting pharmacogenomic profiling of patients to determine which patients are most likely to respond to ARIs.[3] Hence, future trials with ranirestat or any other ARIs should be done in people with a relatively short duration of diabetes (less than 5 years) with good glycaemic control with mild early symptoms of DPN, to better understand the potential reversibility of clinical features of neuropathy.[3] A meta-analysis showed that lipoic acid combined with epalrestat was better than lipoic acid alone in managing DPN, improvements in motor and sensory NCVs and SNCV of different nerves.[19] Hence, multi-drug therapy of ranirestat with other agents which are known to improve neuropathy like lipoic acid is warranted. To conclude, it may be said that the current data in people with established DPN with long-standing diabetes, ranirestat is safe and effective in improving electrophysiologic but not clinical DPN.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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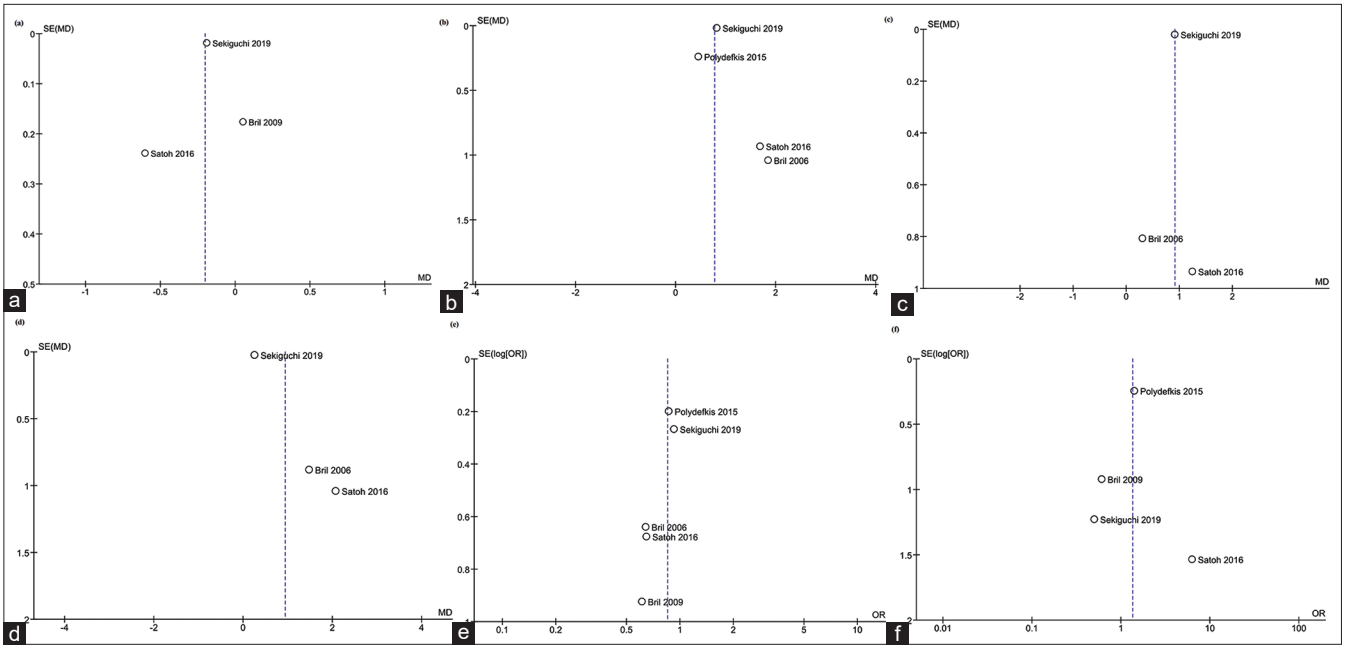
ONLINE-ONLY SUPPLEMENTARY MATERIAL:



Supplementary Figure 1: Funnel plot of all the included studies in the meta-analysis (assessing the publication bias) for (a): modified Toronto Clinical Neuropathy Score (mTCNS); (b) proximal median sensory NCV; (c): distal median sensory NCV; (d): sural sensory€V; (e): TAEs; (f): SAEsNCV: nerve conduction velocity; High publication bias is evident for proximal median sensory NCV, sural sensory NCV, TAEs and SAEs as most of the studies fall outside the funnel plot

Supplementary Table 1: Risk of bias of the different studies included in this meta-analysis

Bril 2006	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Multicentre, double-blind RCT
Allocation Concealment (Selection Bias)	Low Risk	Random Allocation Done
Blinding of Participants and Personnel (Performance Bias)	Low Risk	Double-Blinded
Blinding of Outcome Assessment (Detection Bias)	Low Risk	Double- Blinded
Incomplete Outcome Data (Attrition Bias)	High Risk	92 patients were randomised of which 82.6% of patients completed the study. Hence attrition rate was 17.4%. Attrition rate of less than 15% was considered low.
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	Dainippon Pharmaceuticals, Osaka, Japan funded the study
Bril 2009		
Random Sequence Generation (Selection Bias)	Low Risk	Multicentre, double-blind, randomised, placebo-controlled study
Allocation Concealment (Selection Bias)	Low Risk	Patients were randomised via an interactive voice-response system
Blinding Of Participants and Personnel (Performance Bias)	Low Risk	Double-Blinded
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double-Blinded
Incomplete Outcome Data (Attrition Bias)	Low Risk	549 patients were randomised of which 85.7% of patients completed the study. Hence attrition rate was 14.3%. Attrition rate of less than 15% was considered low
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	This study was funded by Dainippon Sumitomo Pharma. Two of the authors were paid employees of Dainippon Sumitomo Pharma.
Polydefkis 2015		
Random Sequence Generation (Selection Bias)	Low Risk	Double-blinded, parallel-group RCT
Allocation Concealment (Selection Bias)	Low risk	Patients were randomised via an interactive voice-response system, according to a predefined randomisation schedule stratified by site.
Blinding of Participants and Personnel (Performance Bias)	Low Risk	Double-Blinded
Blinding of Outcome Assessment (Detection Bias)	Low Risk	Double-Blinded
Incomplete Outcome Data (Attrition Bias)	High Risk	800 patients were randomised of which 633 patients completed the study. Hence attrition rate was 21%. Attrition rate of less than 15% was considered low
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	This study was funded by Eisai, Inc. During the conduct of the study, both R. J. G. and K. L. B. were full-time employees of Eisai Ltd who were sponsors of the study.
Satoh 2016		
Random Sequence Generation (Selection Bias)	Low Risk	Multicentre, double-blind, randomised, placebo-controlled study
Allocation Concealment (Selection Bias)	Low Risk	Randomisation was achieved using a computer-generated randomisation table
Blinding of Participants and Personnel (Performance Bias)	Low Risk	Double-Blinded
Blinding of Outcome Assessment (Detection Bias)	Low Risk	Double-Blinded
Incomplete Outcome Data (Attrition Bias)	Low Risk	73 patients were randomised and all of them completed the study
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	This work was supported by Sumitomo Dinippon Pharma, Co., Ltd. One of the authors was an employee of Dainippon Sumitomo Pharma.
Sekiguchi 2019		
Random Sequence Generation (Selection Bias)	Low Risk	Multicentre, placebo-controlled, randomised double-blind, parallel-group study
Allocation Concealment (Selection Bias)	Low Risk	The randomisation was generated by the independent statistician
Blinding of Participants and Personnel (Performance Bias)	Low Risk	Double-Blinded
Blinding of Outcome Assessment (Detection Bias)	Low Risk	Double-Blinded
Incomplete Outcome Data (Attrition Bias)	Low Risk	557 patients were randomised of which 492 patients completed the study and their data was analysed; the attrition rate was 11.67%. Attrition rate of less than 15% was considered low
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	The study was funded by Sumitomo Dainippon Pharma Co., Ltd. Two of the authors were full-time employees of Sumitomo Dainippon Pharma Co., Ltd.

NCV: nerve conduction velocity; High publication bias is evident for proximal median sensory NCV, sural sensory NCV, TAEs and SAEs as most of the studies fall outside the funnel plot