The impact of canagliflozin on the risk of neuropathy events

Liao, Jinlan; Kang, Amy; Xia, Chao; Young, Tamara; Di Tanna, Gian Luca; Arnott, Clare; Pollock, Carol; Krishnan, Arun V.; Agarwal, Rajiv; Bakris, George

Published in:
Diabetes and Metabolism

DOI:
10.1016/j.diabet.2022.101331

Publication date:
2022

Diabetes & Metabolism 48 (2022) 101331

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Original article

The impact of canagliflozin on the risk of neuropathy events: A post-hoc exploratory analysis of the CREDENCE trial

Jinlan Liao[a,b,1], Amy Kang[a,c,1], Chao Xia[a,d], Tamara Young[a], Gian Luca Di Tanna[a], Clare Arnott[a,e], Carol Pollock[f,g], Arun V. Krishnan[h], Rajiv Agarwal[i], George Bakris[j], David M. Charytan[k], Dick de Zeeuw[l], Hiddo J.L. Heerspink[l], Adeera Levin[m], Bruce Neal[a,n,o], David C. Wheeler[a,p], Hong Zhang[q], Bernard Zinman[r], Kenneth W. Mahaffey[s], Vlado Perkovic[q], Meg J Jardine[a,t,s], Brendan Smyth[a,u,v,*]

[a] *The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia*
[b] *Department of Nephrology, Peking University Shenzhen Hospital, Shenzhen, China*
[c] *Department of Renal Medicine, Prince of Wales Hospital, Sydney, New South Wales, Australia*
[d] *Department of Radiology and Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China*
[e] *Department of Cardiology, Royal Prince Alfred Hospital, Sydney Medical School, Sydney, New South Wales, Australia*
[f] *Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia*
[g] *Royal North Shore Hospital, Sydney, New South Wales, Australia*
[h] *Prince of Wales Clinical School, University of New South Wales, Australia*
[i] *Indiana University School of Medicine and VA Medical Centre, Indianapolis, IN, USA*
[j] *Department of Medicine, University of Chicago Medicine, Chicago, IL, USA*
[k] *Nephrology Division, New York University Langone Medical Centre, New York University School of Medicine, New York, NY, USA*
[l] *Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands*
[m] *Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada*
[n] *The Charles Perkins Centre, University of Sydney, Sydney, New South Wales, Australia*
[o] *Imperial College London, London, United Kingdom*
[p] *Department of Renal Medicine, University College London Medical School, London, United Kingdom*
[q] *Renal Division of Peking University First Hospital, Beijing, China*
[r] *Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada*
[s] *Department of Medicine, Stanford Centre for Clinical Research, Stanford University School of Medicine, Stanford, CA, USA*
[t] *Concord Repatriation General Hospital, Sydney, New South Wales, Australia*
[u] *NHMRC Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia*
[v] *Department of Renal Medicine, St George Hospital, Sydney, New South Wales, Australia*

ARTICLE INFO

Article History:
Received 3 November 2021
Revised 29 December 2021
Accepted 8 February 2022
Available online 13 February 2022

Keywords:
Adverse event
Diabetic kidney disease
Diabetic neuropathy
Randomized controlled trial
Sodium Glucose Co-transporter Inhibitors

ABSTRACT

Aim: Canagliflozin reduces the risk, and progression, of diabetic kidney disease. We hypothesized that it may improve the microvascular complication of neuropathy.
Methods: The CREDENCE trial randomized participants with type 2 diabetes and kidney disease to canagliflozin 100 mg daily or placebo. Neuropathy events were defined post-hoc as any reported adverse event consistent with a peripheral or autonomic neuropathy event. The effect of canagliflozin and predictors of neuropathy events were estimated using Cox regression analysis. In sensitivity analyses the endpoint was restricted to sensorimotor polyneuropathy, diabetic neuropathy, and non-autonomic neuropathy events.
Results: Almost half (48.8%) of the 4401 participants had a diagnosis of neuropathy at baseline. Over a median of 2.45 years of follow up, 657 people experienced a neuropathy event (63.2 per 1000 patient-years). Independent factors associated with higher risk of experiencing neuropathy events were non-white race, younger age, higher glycated haemoglobin and lower estimated glomerular filtration rate. The incidence of neuropathy events was similar in people randomized to canagliflozin and placebo (334/2202 vs. 323/2199; HR 1.04, 95% CI 0.89 to 1.21, $P = 0.66$). Canagliflozin had no impact on sensorimotor polyneuropathy (HR 0.93, 95% CI 0.69 to 1.25, $P = 0.63$), diabetic neuropathy (HR 0.91, 95% CI 0.68 to 1.22, $P = 0.52$), or non-autonomic

See Appendix in supplementary material associated with this article on line.

* Corresponding author at: NHMRC Clinical Trials Centre, University of Sydney, Medical Foundation Building, 92-94 Parramatta Road, Camperdown NSW 2050, Australia.
E-mail address: brendan.smyth@sydney.edu.au (B. Smyth).

[1] Co-principal authors

https://doi.org/10.1016/j.diabet.2022.101331

neuropathy (HR 1.03, 95% CI 0.87 to 1.21, $P = 0.77$). The lack of effect on neuropathy events was consistent in subgroup analyses.
Conclusion: Canagliflozin did not affect the risk of neuropathy events in the CREDENCE trial. Future large randomized studies with prespecified neuropathy endpoints are required to determine the impact of sodium glucose cotransporter 2 inhibitors on diabetic neuropathy.

Introduction

Neuropathy affects up to half of all people with type 2 diabetes mellitus (T2DM) [1]. It most commonly presents with distal pain and sensory loss from sensorimotor polyneuropathy, followed by postural hypotension or erectile dysfunction from autonomic neuropathy, however, other nerve pathologies such as carpal tunnel syndrome, medication toxicity and inflammatory neuropathies are also more common in people with T2DM [2]. The high prevalence of non-diabetic neuropathy in T2DM may be due to a higher burden of comorbidity and medication use, immunomodulatory effects of hyperglycaemia, or the interplay of neuropathic insults [3]. People with both T2DM and chronic kidney disease (CKD) experience accelerated nerve injury, perhaps due to the combination of hyperglycaemia, hyperkalaemia, uraemic toxins, and atherosclerotic vasculopathy [4]. The symptoms of neuropathy, namely pain, paraesthesia and postural hypotension reduce quality of life and increase the risk of foot ulcers, falls and fractures [2, 5]. Neuropathies, especially diabetic neuropathy, may not be reversible and prevention is crucial.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of cardiovascular disease [6] and slow progression of CKD [7], however their impact on neuropathy is not well understood. Animal models suggest that SGLT2 inhibitors may be neuroprotective [8–10], through glucose-lowering or glucose-independent mechanisms such as shifting metabolism from glucose to fat oxidation, anti-inflammatory effects, and reducing oxidative stress [11, 12], and a small randomized study found evidence of improvement in cardiac autonomic function when empagliflozin was administered following acute myocardial infarction [13]. To explore the hypothesis that SGLT2 inhibitors may reduce the incidence or progression of peripheral neuropathy, we conducted an exploratory analysis of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial to determine if treatment with canagliflozin resulted in fewer neuropathy events in those with T2DM and diabetic kidney disease.

Methods

The CREDENCE trial was a multicentre, randomized, double-blind, placebo-controlled trial designed to assess the effects of the SGLT2 inhibitor canagliflozin on renal outcomes in patients with T2DM with diabetic kidney disease (estimated glomerular filtration rate (GFR) of 30 to ⟨ 90 ml/min/1.73m^2 and urine albumin to creatinine ratio of ⟩ 300 to 5000 mg/g)[14, 15]. The trial randomized 4401 participants from 690 sites in 34 countries in a 1:1 ratio to receive either canagliflozin 100 mg daily orally or placebo.

Neuropathy adverse events

The primary endpoint for this analysis was the first occurrence of an adverse event (AE) related to neuropathy in all trial participants (with or without neuropathy at baseline). In the CREDENCE trial, all AEs (including serious AEs) occurring after randomization were assigned a single Medical Dictionary for Regulatory Activities (MedDRA) code from pre-specified lists by site investigators. Two clinicians blinded to treatment allocation (JL and CX) independently categorized MedDRA terms indicative of a neuropathy (of any cause) according to the terms used in the Toronto Classification prior to the analyses being performed [2]. This analysis was post-hoc and AEs were categorized following data-lock. Reviewers were aware of the primary trial results but were blinded to treatment allocation relating to AEs or the participants experiencing them.

The MedDRA terms used to define neuropathy AEs are listed in the Table S1 (see supplementary materials associated with this article on line). The adverse events identified in this fashion were considered to be surrogate indicators of the presence or severity of neuropathy. The resulting list of terms defined 'neuropathy AE' for the primary analysis. Subsets (or clusters) of terms within this list were selected a priori to define more specific endpoints as events consistent with a) 'diabetic neuropathy', b) 'sensorimotor polyneuropathy', or c) 'autonomic neuropathy'. These definitions were used for sensitivity analysis. Discrepancies were resolved by review by a third clinician (AK).

Statistical analysis

Continuous data are presented as the mean ± SD or median (interquartile limits) as appropriate. Categorical variables are expressed as numbers and percentages. All analyses were conducted according to intention-to-treat principles. For the primary analysis and comparison of baseline characteristics, a two-sided P-value of < 0.05 was considered statistically significant. However, we also chose to quantify the risk from multiple testing in the multivariable model and in the subgroup analyses using adjusted two-sided P-value thresholds calculated according to the Holm-Bonferroni correction [16]. Given the exploratory nature of this analysis, a family-wise error rate of 0.1 was chosen (i.e. an overall 10% chance of a false positive) and applied separately to the multivariable analysis and to the subgroup analyses (as a whole). We have chosen to present unadjusted p-values and, where relevant, to indicate where a significant result did not also meet adjusted significance thresholds.

Prediction model construction

Potential risk factors for neuropathy events were pre-selected on the basis of known associations with neuropathy and biological plausibility [17]. Baseline sociodemographic factors were age, sex and race. Baseline clinical factors were history of neuropathy, history of retinopathy, history of cardiovascular disease (coronary artery disease, cerebrovascular disease, or peripheral vascular disease), duration of diabetes, body mass index (BMI), systolic blood pressure (SBP), glycated haemoglobin (HbA1c), urine albumin to creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) measured by the Chronic Kidney Disease Epidemiology Collaboration formula, serum triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and baseline use of the following medications: metformin, sulphonylureas, glucagon-like peptide-1 (GLP-1) receptor agonist, insulin, statin, antithrombotic agent. The effect of these variables was examined by fitting a multivariable Cox model (stratified by eGFR at baseline) assessing time to neuropathy AE and a predefined set of possible risk factors (as listed above). Continuous variables were not categorized. Cholesterol was removed from consideration owing to a strong association with LDL-C. The proportional hazard assumption was checked by visual assessment of the log cumulative-hazard functions and by Kolmogorov-type Supremum test. As there was evidence

of a time dependant hazard ratio for age, an interaction term between age and follow-up time was included in the final model. In a post-hoc analysis, the relationship between continuous parameters identified as associated with neuropathy was further explored within the multivariable model by treating the parameter of interest as a restricted cubic spline, with knots at the 10th, 50th and 90th centile. The hazard ratio, adjusted for covariates, for neuropathy events by baseline parameter was plotted over the central 90% of the distribution (i.e. from the 5th centile to 95th centile).

Effect of canagliflozin on neuropathy

The primary outcome and pre-specified sensitivity analyses ('diabetic neuropathy events', 'sensorimotor polyneuropathy events', and 'neuropathy events excluding autonomic neuropathy events' (Table S1; see supplementary materials associated with this article on line) were performed using a Cox proportional-hazards model stratified by eGFR at baseline. The sensitivity analysis of 'neuropathy events excluding autonomic neuropathy events' was chosen as some autonomic symptoms, such as orthostatic hypotension, may be indistinguishable from symptoms of hypovolemia, a potential side effect of canagliflozin. Pre-specified subgroup analyses were undertaken by age, sex, race, history of neuropathy, history of retinopathy, duration of diabetes, and baseline parameters: body mass index (BMI), SBP, HbA1c, UACR, and eGFR. Subgroup analyses were performed to assess the heterogeneity of treatment effects by tests for the interaction between canagliflozin and the subgroup in stratified Cox proportional-hazards models. Statistical analyses were performed using SAS Enterprise Guide 7.15 (SAS Inc, Cary, NC) and Stata/IC 15.1 (StataCorp, College Station, TX).

Results

Baseline characteristics and neuropathy events

Of 4401 participants, the mean age was 63.0 ± 9.2 years, mean duration of diabetes was 15.8 ± 8.6 years, mean HbA1c was 8.3 ± 1.3%, and 2147 (48.8%) had a diagnosis of neuropathy at baseline (Table 1). Those with neuropathy at baseline were more likely to be female, white race, with a longer duration of diabetes, higher cholesterol and UACR; and were more likely to have co-morbid heart failure, retinopathy, or cardiovascular or peripheral vascular disease. Over a median of 2.62 years (range 0.02 to 4.53) of follow-up, 657 participants experienced at least one neuropathy AE (63.2 per 1000 patient-years) (Table 2; Table S2: see supplementary materials associated with this article on line). The most common MedDRA terms for neuropathy events were (in order of frequency) diabetic neuropathy, pain in extremity, diabetic foot, postural dizziness, orthostatic hypotension and peripheral neuropathy, which collectively accounted for 63% of analysed neuropathy AEs (Table S3; see supplementary materials associated with this article on line).

Primary outcome, sensitivity analyses and subgroup analyses

Rates of neuropathy events were similar in people randomized to canagliflozin and placebo (334/2202 in the canagliflozin arm, 323/2199 in the placebo arm; HR 1.03, 95% CI 0.89 to 1.21, P = 0.66) (Table 2, Fig. 1). The results were similar for the pre-specified sensitivity analyses, with no difference in AE related to non-autonomic neuropathy (279/2202 versus 271/2199, HR 1.03, 95% CI 0.87 to 1.21, P = 0.77), sensorimotor polyneuropathy (84/2202 versus 90/2199, HR 0.93, 95% CI 0.69 to 1.25, P = 0.63), or diabetic neuropathy (84/2202 versus 92/2199, HR 0.91, 95% CI 0.68 to 1.22, P = 0.52). After adjustment for multiple comparisons, the effect of canagliflozin on neuropathy events was similar across all tested subgroups, including those with and without neuropathy at baseline (Fig. 2; Table S4: see supplementary materials associated with this article on line).

Predictors of neuropathy events

Factors associated with a higher risk of neuropathy events in multivariable analysis were Black, Asian, or other non-white race, younger age, higher glycated haemoglobin or lower eGFR (Table 3). Weak associations between neuropathy events and baseline use of insulin or statin, and serum potassium did not meet significance thresholds adjusted for multiple comparisons (Table S5; see supplementary materials associated with this article on line). The relationship

Table 1
Demographic and clinical characteristics of participants with or without neuropathy at baseline.

Characteristic	No known neuropathy at baseline	Prevalent neuropathy	*P*-value	All participants
	(*N* = 2254)	(*N* = 2147)		(*N* = 4401)
Age– yr.	63.1 ± 9.4	63.0 ± 9.0	0.65	63.0 ± 9.2
Female sex–no. (%)	694 (30.8)	800(37.3)	< 0.0001	1494 (33.9)
Race or ethnic group–no. (%)			0.0002	
White	1447 (64.2)	1484 (69.1)		2931 (66.6)
Black	104 (4.6)	120 (5.6)		224 (5.1)
Asian	500 (22.2)	377 (17.6)		877 (19.9)
Other	203 (9.0)	166 (7.7)		369 (8.4)
Current smoker–no. (%)	322 (14.3)	317 (14.8)	0.65	639 (14.5)
Hypertension–no. (%)	2172 (96.4)	2088 (97.3)	0.094	4260 (96.8)
Heart Failure–no. (%)	221 (9.8)	431 (20.1)	< 0.0001	652 (14.8)
Duration of diabetes–yr.	15.1 ± 8.7	16.5 ± 8.5	< 0.0001	15.8 ± 8.6
Cardiovascular–no. (%)	946 (42.0)	1274 (59.3)	< 0.0001	2220 (50.4)
Amputation–no. (%)	60 (2.7)	174 (8.1)	< 0.0001	234 (5.3)
Peripheral vascular disease–no. (%)	343 (15.2)	703 (32.7)	< 0.0001	1046 (23.8)
Retinopathy–no. (%)	681 (30.2)	1201 (55.9)	< 0.0001	1882 (42.8)
Body-mass index	31.4 ± 6.2	31.3 ± 6.1	0.65	31.3 ± 6.2
Blood pressure–mmHg				
Systolic	139.8 ± 15.7	140.2 ± 15.5	0.44	140.0 ± 15.6
Diastolic	78.3 ± 9.4	78.3 ± 9.3	0.82	78.3 ± 9.4
Glycated haemoglobin–%	8.2 ± 1.3	8.3 ± 1.3	0.057	8.3 ± 1.3
Total Cholesterol(mmol/L)	4.6 ± 1.2	4.8 ± 1.4	< 0.0001	4.7 ± 1.3
Triglycerides (mmol/L)	2.2 ± 1.5	2.3 ± 1.8	0.33	2.2 ± 1.6
HDL-C(mmol/L)	1.1 ± 0.3	1.2 ± 0.4	0.14	1.1 ± 0.3
LDL-C(mmol/L)	2.4 ± 1.0	2.6 ± 1.1	< 0.0001	2.5 ± 1.1
Estimated GFR – ml/min/1.73m^2	56.2 ± 18.3	56.2 ± 18.2	0.94	56.2 ± 18.2
Median urinary albumin-to-creatinine ratio – mg/g (IQL)	877 (449–1722)	964 (483–1971)	0.0007	927 (463–1833)

Table 2
Primary outcome and sensitivity analyses.

	Canagliflozin *no. of participants with event/total no. of participants*	Placebo *no. of participants with event/total no. of participants*	Canagliflozin *event rate/1000 patient years*	Placebo *event rate/1000 patient years*	Hazard Ratio HR (95% CI)	*P* value
Neuropathy events						
All neuropathy events	334/2202	323/2199	64.1	62.3	1.03(0.89–1.21)	0.66
Sensorimotor polyneuropathy events	84/2202	90/2199	14.9	16.1	0.93(0.69–1.25)	0.63
Diabetic neuropathy events	84/2202	92/2199	14.9	16.5	0.91(0.68–1.22)	0.52
Neuropathy events excluding autonomic neuropathy events	279/2202	271/2199	52.5	51.3	1.03(0.87–1.21)	0.77

between risk of neuropathy, baseline HbA1c, and baseline eGFR is presented in Figure S1; see supplementary materials associated with this article on line.

Discussion

This exploratory study is the first to examine the effect of an SGLT2 inhibitor on neuropathy events in a randomized cohort to our knowledge and found no effect on the risk of neuropathy events, including in a range of important subgroups. Multivariable analysis showed non-white race, younger age, lower baseline eGFR and higher glycated haemoglobin to be independently associated with neuropathy events. The lack of observed effect of SGLT2 inhibitors on neuropathy is in contrast to their clear benefit on renal and cardiovascular outcomes and suggests that other treatment approaches may be required to improve neuropathy risk.

Current treatment guidelines for T2DM are based on studies that have focused on macrovascular outcomes with – until recently – few studies focusing primarily on microvascular outcomes [18]. Despite the high prevalence and disabling nature of neuropathy in T2DM, treatments capable of altering its natural history are lacking [19]. A meta-analysis of key studies on the intensity of glycaemic control suggests that, in contrast to albuminuria progression, more intensive glucose control does not reduce the incidence of neuropathy [20]. There has been little attention paid to neuropathy outcomes in recent trials of novel glucose lowering agents [21]. The TECOS study of sitagliptin vs. placebo reported an incidence of new diabetic neuropathy of 4.1% and 3.8%, respectively (suggesting no impact of sitagliptin, although formal statistical analysis was not provided) [22]; a rate similar to the 4.0% seen in the present study. Only two small randomized studies have examined the effect of GLP-1RA on neuropathy in humans, both finding no evidence of a beneficial effect on symptoms or signs of neuropathy [23, 24]. Overall, the limited evidence available is not encouraging and neuropathy remains the only micro- or macrovascular complication of diabetes for which there is no evidence-based disease-modifying treatment.

In contrast to the clinical studies, pre-clinical studies suggest that SGLT2 inhibitors may be neuroprotective, with a reduction in sensory nerve hypersensitivity [9], preservation of motor nerve conduction velocity[8] and reduction in sympathetic nervous system activity [25, 26]. This disconnect highlights the growing understanding of diabetic neuropathy as a complex disease resulting from multiple interacting causal pathways which may be challenging to replicate in pre-clinical studies. While hyperglycaemia is a risk factor for the development of neuropathy in both type 1 and type 2 DM, it is clearly one factor amongst many, particularly in T2DM, where (in contrast to type 1 DM) improved glycaemic control has not been shown to improve neuropathy outcomes [20]. This, in itself, supplies one possible explanation for the lack of efficacy of SGLT2 inhibitors in the present study. However, the between-group difference in glycaemic control was modest (mean glycated haemoglobin being lower in the canagliflozin arm by 0.25%), thus providing little scope for the assessment of the relationship between improved glycaemic control and neuropathy. In addition to glycaemic control, observational studies in both type 1 and type 2 DM have highlighted the potential importance of vascular risk factors, including higher BMI, hypertension, history of cardiovascular disease, smoking and triglyceride level, as independent risk factors for the development of neuropathy [27, 28].

The present study identified the expected associations between lower eGFR and higher glycated haemoglobin, and neuropathy events. Younger age was associated with a higher risk. Cohort studies have demonstrated a similar incidence of neuropathy in younger and older people with T2DM, and that neuropathy is common at diagnosis; new onset retinopathy has been found to associate with younger

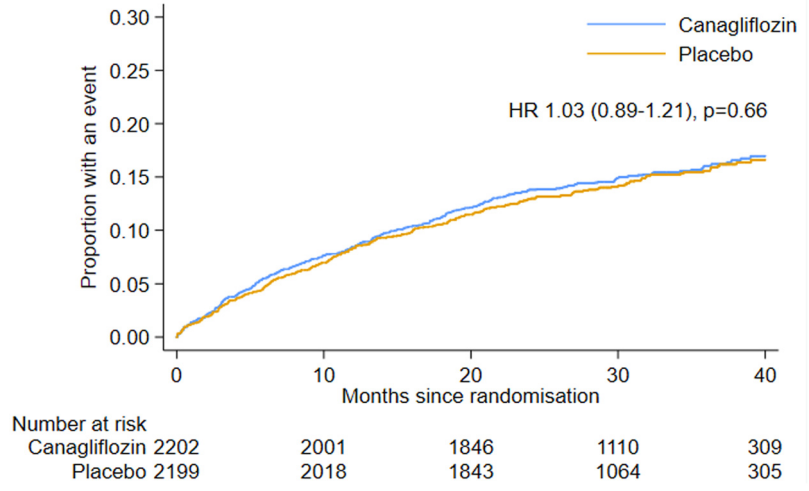

Fig. 1. Time to first neuropathy events
Kaplan-Meier curve for neuropathy adverse events. Hazard ratio from Cox-regression.

Subgroup	Canagliflozin n/N	Placebo n/N	Canagliflozin events/1000 person-years	Placebo events/1000 person-years	Hazard ratio (95% CI)	Interaction P value
All participants	334/2202	323/2199	64.1	62.3	1.03 (0.89-1.21)	NA
Age						
<65 yr	177/1193	177/1151	63.6	66.4	0.96 (0.78-1.18)	0.32
≥65 yr	157/1009	146/1048	64.8	57.8	1.12 (0.90-1.41)	
Sex						
Male	217/1440	214/1467	63.1	61.3	1.03 (0.85-1.25)	0.99
Female	117/762	109/732	66.2	64.1	1.03 (0.79-1.33)	
Race						
White	203/1487	167/1444	55.8	47.2	1.19 (0.97-1.46)	0.34
Black or African American	22/112	25/112	82.6	97.2	0.87 (0.49-1.54)	
Asian	71/425	83/452	75.1	83.2	0.92 (0.67-1.26)	
Other	38/178	48/191	107.0	120.8	0.86 (0.56-1.32)	
History of Neuropathy						
Yes	176/1077	160/1070	70.4	64.1	1.11 (0.89-1.37)	0.42
No	158/1125	163/1129	58.3	60.5	0.97 (0.78-1.21)	
History of Retinopathy						
Yes	153/935	144/947	70.1	65.2	1.08 (0.86-1.36)	0.64
No	181/1267	179/1252	59.8	60.1	1.00 (0.82-1.23)	
Duration of diabetes						
<10 years	68/563	65/550	50.4	50.1	1.02 (0.72-1.43)	0.88
≥10 years	266/1639	258/1649	69.0	66.3	1.04 (0.88-1.24)	
Baseline BMI						
<30 kg/m2	155/998	149/1028	67.8	62.7	1.08 (0.86-1.35)	0.50
≥30 kg/m2	177/1198	174/1168	60.7	62.0	0.98 (0.79-1.21)	
Baseline SBP						
<140mmhg	166/1105	155/1077	63.1	61.7	1.04 (0.84-1.30)	0.99
≥140mmhg	168/1097	168/1122	65.3	62.8	1.03 (0.83-1.28)	
Baseline glycated hemoglobin						
<8%	156/1027	127/1029	63.6	50.8	1.25 (0.99-1.58)	0.03*
≥8%	178/1174	196/1169	64.6	73.0	0.90 (0.73-1.10)	
eGFR						
30 to <45ml/min/1.73m2	121/678	110/687	77.6	69.6	1.12 (0.87-1.45)	0.55
45 to <60ml/min/1.73m2	106/630	100/636	71.7	66.0	1.09 (0.83-1.43)	
≥60ml/min/1.73m2	107/893	113/876	49.4	54.0	0.92 (0.71-1.20)	
Baseline UACR						
≤1000mg/g	184/1185	176/1163	64.4	63.4	1.02 (0.83-1.25)	0.89
>1000mg/g	150/1017	147/1036	63.8	60.9	1.04 (0.83-1.31)	
Baseline Triglycerides						
<1.7mmol/L	143/942	129/1012	65.0	54.1	1.19 (0.94-1.52)	0.10
≥1.7mmol/L	191/1260	194/1187	63.6	69.2	0.93 (0.76-1.13)	
Medication						
Baseline use of Insulin						
Yes	247/1452	235/1432	73.7	70.8	1.04 (0.87-1.25)	0.85
No	87/750	88/767	46.9	47.0	1.01 (0.75-1.36)	
Baseline use of Statin						
Yes	259/1538	240/1498	70.9	67.8	1.05 (0.88-1.25)	0.62
No	75/664	83/701	48.2	50.4	0.96 (0.70-1.31)	

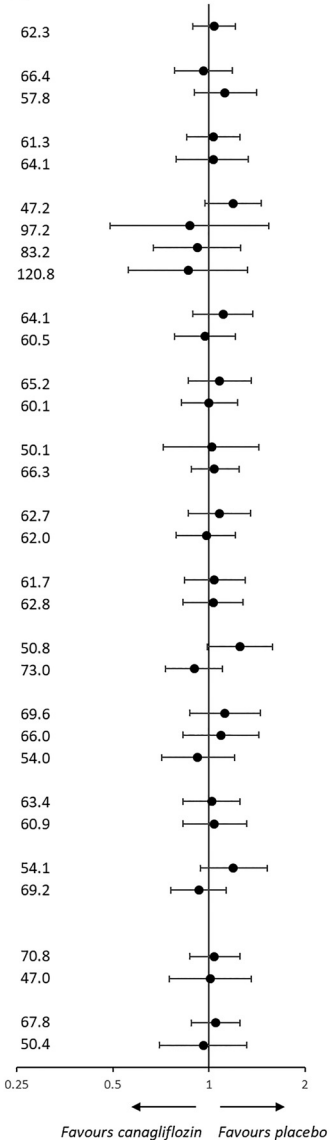

Fig. 2. Subgroup analysis of effect of canagliflozin on neuropathy

P-values are for interaction between treatment group and subgroup in Cox-proportional hazards analysis of time to neuropathy event. BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio. * indicates p-values that did not remain statistically significant after adjustment for multiple testing (Table S4; see supplementary materials associated with this article on line).

age [29]. This mirrors previously described phenotypic differences between younger and older people with T2DM, reflected in varying incidence for cardiovascular and kidney disease versus neuropathic and retinal complications [30]. We also found that white participants had a higher prevalence of neuropathy at baseline, yet participants of non-white ethnicity were at higher risk of neuropathy events during the trial, independent of other risk factors for neuropathy. The relative prevalence of diabetic (or other) peripheral neuropathy amongst different racial or ethnic groups has not been well described. A cross-sectional study of 266 participants in the United Kingdom found a lower prevalence of diabetic neuropathy in South Asians compared to whites [31], while a larger cross-sectional UK study of 15,692 participants found lower rates of neuropathy in South Asians compared to white Caucasians but a higher prevalence of neuropathic pain [32]. However, two studies from the United States have not found differences in the prevalence of neuropathy between white, black, and Hispanic Americans [33, 34]. The reasons for the higher risks in non-white participants in the present study are unclear, but may reflect racial inequities in the access to diabetes care and subsequent effects on glycaemic control and kidney and cardiovascular outcomes [35].

Interestingly, a baseline history of neuropathy was not associated with an increased risk for a neuropathy event in this study and the rates of neuropathy events were similar in those with and without such a baseline history. The baseline diagnosis was derived from medical history provided to the investigator, rather than by dedicated clinical or neurophysiological assessment, and the accuracy of routine physician assessment of a history of peripheral neuropathy is questionable, with evidence that only one third of patients with a mild-moderate neuropathy are correctly identified as so by their physician [36]. This inaccuracy may be compounded by differential access to care and diagnosis between racial groups and countries, which may contribute to the discrepancy between the higher prevalence of a history of neuropathy at baseline in white participants and the observed increased risk of neuropathy events in non-white participants seen in this study. Nevertheless, in the absence of dedicated neurological assessment we are unable to determine to what extent

Table 3
Multivariable model of risk of first occurrence of neuropathy event.

Variable	Hazard ratio(95% confidence interval)	*P*-value
Age (per 5 years)	0.87 (0.81 to 0.93)	< 0.001
Sex (ref=Male)	1.03 (0.87 to 1.23)	0.712
Race (ref=White)		
Asian	1.45 (1.18 to 1.79)	< 0.001
Black	1.59 (1.16 to 2.17)	0.004
Other	1.96 (1.53 to 2.51)	< 0.001
History of Neuropathy	1.12 (0.95 to 1.31)	0.185
History of Retinopathy	1.03 (0.87 to 1.21)	0.764
Systolic blood pressure (per 5 mmHg)	1.003 (0.978 to 1.028)	0.836
Glycated haemoglobin (%)	1.10 (1.03 to 1.17)	0.002
Body mass index (kg/m^2)	1.003 (0.990 to 1.017)	0.635
Duration of diabetes (years)	1.007 (0.998 to 1.017)	0.144
Smoker	1.16 (0.94 to 1.44)	0.175
History of cardiovascular disease	1.04 (0.88 to 1.24)	0.641
Urine albumin-to-creatinine ratio (per 10 mg/mmol)	0.994 (0.989 to 1.000)	0.054
Low density lipoprotein-cholesterol (mmol/l)	0.97 (0.89 to 1.05)	0.424
High density lipoprotein-cholesterol (mmol/l)	0.85 (0.66 to 1.11)	0.227
Triglycerides (mmol/l)	0.998 (0.948 to 1.050)	0.932
Estimated glomerular filtration rate (ml/min/1.73m^2)	0.986 (0.979 to 0.994)	< 0.001
Insulin use	1.26 (1.02 to 1.57)	0.034*
Glucagon-like peptide-1 agonist use	1.13 (0.79 to 1.60)	0.505
Metformin use	1.12 (0.94 to 1.33)	0.216
Sulphonylurea use	0.99 (0.81 to 1.21)	0.897
Statin use	1.28 (1.06 to 1.56)	0.011*
Anti-thrombotic use	1.003 (0.843 to 1.194)	0.971
Potassium (mmol/l)	0.85 (0.73 to 0.99)	0.036*

Multivariable Cox-regression model of predictors of first neuropathy event. The model was stratified by baseline eGFR group and included an age by time interaction to maintain proportional hazards. Randomized allocation was not included in the model.

* indicates p-values that did not remain significant after adjustment for multiple testing (see Supplementary Table 4).

misclassification at baseline history or in the attribution of AE to neuropathy may have affected to our findings.

The apparent lack of effect of an SGLT2 inhibitor on neuropathy, in addition to a lack of effect of retinopathy [37, 38], reflects the growing awareness of the heterogeneous pathophysiological pathways contributing to 'microvascular' disease in those with diabetes, such that the goals of treatment are not simply glycaemic control. Indeed, in contrast to T1DM, meta-analysis of a number of large scale randomized studies in people with T2DM, has shown intensive glycaemic control has only a modest effect on neurophysiological parameters and no significant effect on clinical neuropathy [39]. This stands in contrast to nephropathy and retinopathy, where intensive glycaemic control does appear to have a modest impact [39]. The primary results of the CREDENCE study emphasize the independence of microvascular disease and glycaemic control, with robust and early reductions in nephropathy with SGLT2 inhibition despite an average difference in glycated haemoglobin of only 0.25% [15]. Likewise, despite reduction in nephropathy events, SLGT2 inhibitors do not appear to affect the incidence of diabetic retinopathy, and semaglutide (a glucagon-like peptide-1 receptor agonist) may increase the risk [37, 40, 41]. Fundamentally, the divergence in efficacy of the various glucose-lowering agents on neuropathy, retinopathy and nephropathy challenges the practice of grouping these complications together under the label of 'microvascular disease'. Animal studies show important differences in the pattern of glucose metabolism in the retina, kidney and nerve, along with distinct pathophysiological mechanisms, including lipid metabolism and mitochondrial function, mediating damage in those with T2DM [42]. This results in distinct natural histories and emphasizes the need to pursue novel therapies targeting these separate pathways.

The strengths of this study include its multi-centre randomized design, large size with diverse countries and racial groups, and the blinded assessment of adverse events. The primary limitation of this study is the reliance on adverse events coded per MedDRA rather than the gold standard of a dedicated assessment of neuropathy by standardized clinical and/or neurophysiological criteria [2], although given the significant cost and burden for participants, such assessments may be difficult to implement in a large randomized trial [43]. Administrative codes can reliably detect severe neuropathy in epidemiological research [44] and adverse events related to neuropathy have been used as a neuropathy endpoint in other clinical trials [45]. Recognizing that neuropathy in diabetes is heterogenous, we used a broad definition of neuropathy in this analysis. However, it is plausible that SGLT2 inhibitors have a specific effect on a subtype of neuropathy, which our analysis would have less power to detect. Other limitations include that this was a post-hoc analysis and the study was terminated early at a median of 2.6 years for overall efficacy for the primary endpoint, which may well be too early to detect a difference in neuropathy events, especially without dedicated neurological testing.

In conclusion, this post-hoc exploratory analysis of the CREDENCE randomized trial suggests that canagliflozin does not affect the risk of neuropathy events in patients with type 2 diabetes and albuminuric kidney disease. Non-white race, younger age, lower baseline eGFR and higher glycated haemoglobin were independently associated with neuropathy events. The findings need to be replicated in other studies and could reflect insufficient duration of treatment for a benefit to be observed but do suggest a need for dedicated studies, using well-validated neurological endpoints, of treatments to prevent or slow the progression of diabetic neuropathy. Such an endeavour could be aided by a better understanding of the distinct pathophysiology that drives neuropathy independently of other diabetic complications.

Trial registration: ClinicalTrials.gov number, NCT02065791

Acknowledgements

Author contributions

Design and oversight of the CREDENCE study was provided by VP, MJ, CP, RA, GB, DMC, DdZ, HJLH, AL, BN, DCW, HZ, BZ, KWM. MJ, BS and CA conceptualized the present study. Adverse event terminology was categorized by JL, AK and CX. The analysis was designed by BS and AK, with expert review and revision provided by GLDT. Statistical analysis was performed by JL, AK, TY and BS. Figures were produced by AK and BS. The manuscript was drafted by JL, AK, TY and BS and interpretation of the analysis provided by CA, AVK, RA, GB, DMC, DdZ, BN, DCW, BZ, KWM, VP and MJ. The manuscript was revised by BS with critical review from CA, CP, AVK, RA, GB, DMC, DdZ, HJLH, BN, DCW, BZ, AL, KWM, VP and MJ. All authors had full access to the data on request and JL, AK and BS verified all the data in the study. All authors reviewed the manuscript and have agreed to publication of the final version.

Funding

The CREDENCE study was sponsored by Janssen Research and Development, and was conducted collaboratively by the sponsor, an academic-led steering committee, and an academic research organization, George Clinical. This post hoc analysis of the CREDENCE trial was not specifically funded. The funders were not involved in the design, analysis, reporting, or decision to submit this manuscript for publication. JL was supported by grants from the San-Ming Project of Medicine, Shenzhen (SZSM201812097) and the Medical Science

and Technology Research Foundation of Guangdong Province (B2019025). AK is supported by an NHMRC Postgraduate Scholarship (1150349) via the University of New South Wales, an Australian Government Research Training Program Fee Offset and has received a George Institute Scholarship. TY was supported by a University Postgraduate Award via University of New South Wales. CX was supported by a scholarship from the China Scholarship Council. DMC reports personal fees from Janssen, during the conduct of the study. We thank the participants in this trial and thank the study investigators, who are listed in the Supplementary Appendix to the primary CREDENCE study publication.

Data sharing

Data from this study is available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu/). This includes deidentified individual participant data, data definition specification, annotated case report form, protocol with amendments and primary statistical analysis plan.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.diabet.2022.101331.

References

[1] Pop-Busui R, Lu J, Lopes N, Jones TL, BARI 2D Investigators. Prevalence of diabetic peripheral neuropathy and relation to glycemic control therapies at baseline in the BARI 2D cohort. J Peripher Nerv Syst 2009;14:1–13.
[2] Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40:136–54.
[3] Sharma KR, Cross J, Farronay O, Ayyar DR, Shebert RT, Bradley WG. Demyelinating neuropathy in diabetes mellitus. Arch Neurol 2002;59:758765.
[4] Krishnan AV, Kiernan MC. Neurological complications of chronic kidney disease. Nat Rev Neurol 2009;5:542–51.
[5] Brown SJ, Handsaker JC, Bowling FL, Boulton AJM, Reeves ND. Diabetic peripheral neuropathy compromises balance during daily activities. Diabetes Care 2015;38:1116–22.
[6] Arnott C, Li Q, Kang A, Neuen BL, Bompoint S, Lam CSP, Rodgers A, et al. Sodium-glucose cotransporter 2 inhibition for the prevention of cardiovascular events in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. J Am Heart Assoc 2020;9:e014908.
[7] Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;7:845–54.
[8] Takakura S, Toyoshi T, Hayashizaki Y, Takasu T. Effect of ipragliflozin, an SGLT2 inhibitor, on progression of diabetic microvascular complications in spontaneously diabetic Torii fatty rats. Life Sci 2016;147:125–31.
[9] Lee KA, Jin HY, Lee NY, Kim YJ, Park TS. Effect of empagliflozin, a selective sodium-glucose cotransporter 2 inhibitor, on kidney and peripheral nerves in streptozotocin-induced diabetic rats. Diabetes Metab J 2018;42:338–42.
[10] Abdelsameea AA, Kabil SL. Mitigation of cisplatin-induced peripheral neuropathy by canagliflozin in rats. Naunyn Schmiedebergs Arch Pharmacol 2018;391:945–52.
[11] Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, et al. Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes 2016;65:1190–5.
[12] Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nat Rev Endocrinol 2012;8:495–502.
[13] Shimizu W, Kubota Y, Hoshika Y, Mozawa K, Tara S, Tokita Y, et al. Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial. Cardiovasc Diabetol 2020;19:148.
[14] Jardine MJ, Mahaffey KW, Neal B, Agarwal R, Bakris GL, Brenner BM, et al. The Canagliflozin and renal endpoints in diabetes with established nephropathy clinical evaluation (CREDENCE) study rationale, design, and baseline characteristics. Am J Nephrol 2017;46:462–72.
[15] Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–306.
[16] Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979;6:65–70.
[17] Heinze G, Wallisch C, Dunkler D. Variable selection – A review and recommendations for the practicing statistician. Biom J 2018;60:431–49.
[18] American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Suppl 1):S111–24.
[19] Chalk C, Benstead TJ, Moore F. Aldose reductase inhibitors for the treatment of diabetic polyneuropathy. Cochrane Database Syst Rev 2007;2007(4):Cd004572.
[20] Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431–7.
[21] El Mouhayyar C, Riachy R, Khalil AB, Eid A, Azar S. SGLT2 Inhibitors, GLP-1 agonists, and DPP-4 inhibitors in diabetes and microvascular complications: a review. Int J Endocrinol 2020;2020:1762164.
[22] Green JB, Bethel A, Armstrong PW, Buse JB, Engel SS, Garg JG, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–42.
[23] Jaiswal M, Martin CL, Brown MB, Callaghan B, Albers JW, eFeldman EL, et al. Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study. J Diabetes Complications 2015;29:1287–94.
[24] Ponirakis G, Abdul-Ghani MA, Jayyousi A, Almuhannadi H, Petropoulos IN, Khan A, et al. Effect of treatment with exenatide and pioglitazone or basal-bolus insulin on diabetic neuropathy: a substudy of the Qatar Study. BMJ Open Diabetes Res Care 2020;8(1):e001420.
[25] Scheen AJ. Effect of SGLT2 inhibitors on the sympathetic nervous system and blood pressure. Curr Cardiol Rep 2019;21:70.
[26] Dimova R, Tankova T. Does SGLT2 inhibition affect sympathetic nerve activity in type 2 diabetes? Horm Metab Res 2021;53:75–84.
[27] Tesfaye S, Chaturvedi N, Eaton SEM, Ward JD, Manes C, Ionescu-Tirgoviste C, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med 2005;352:341–50.
[28] van der Velde J, Koster A, Strotmeyer ES, Mess WH, Hilkman D, Reulen JPH, et al. Cardiometabolic risk factors as determinants of peripheral nerve function: the Maastricht Study. Diabetologia 2020;63:1648–58.
[29] An J, Nichols GA, Qian L, Munis MA, Harrison TN, Li Z, et al. Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident type 2 diabetes. BMJ Open Diabetes Res Care 2021;9:e001847.
[30] Kolb H, Schneider B, Heinemann L, Heise T, Lodwig V, Tshiananga JKT, et al. Type 2 diabetes phenotype and progression is significantly different if diagnosed before versus after 65 years of age. J Diabetes Sci Technol 2008;2:82–90.
[31] Tahrani AA, Altaf GA, Piya MK, Barnett AH. Peripheral and autonomic neuropathy in South Asians and White Caucasians with type 2 diabetes mellitus: possible explanations for epidemiological differences. J Diabetes Res 2017;2017:1273789.
[32] Abbott CA, Malik RA, van Ross ERE, Kulkarni J, Boulton AJM. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011;34:2220–4.
[33] Wendel CS, Shah JH, Duckworth WC, Hoffman RM, Mohler JM, Murata GH. Racial and ethnic disparities in the control of cardiovascular disease risk factors in Southwest American veterans with type 2 diabetes: the Diabetes Outcomes in Veterans Study. BMC Health Serv Res 2006;6:58.
[34] Mather KJ, Behu I, Baker C, Cohen RM, Crandall JP, deSouza C, et al. Prevalence of microvascular and macrovascular disease in the Glycemia reduction approaches in diabetes - a comparative effectiveness (GRADE) Study cohort. Diabetes Res Clin Pract 2020;165:108235.
[35] Campbell JA, Wlaker RJ, Smalls BL, Egede LE. Glucose control in diabetes: the impact of racial differences on monitoring and outcomes. Endocrine 2012;42:471–82.
[36] Herman WH, Kennedy L. Underdiagnosis of peripheral neuropathy in type 2 diabetes. Diabetes Care 2005;28:1480–1.
[37] Li C, Zhou Z, Neuen BL, Yu J, Huang Y, Young T, Li J, et al. Sodium-glucose co-transporter-2 inhibition and ocular outcomes in patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2021;23:252–7.
[38] Inzucchi SE, Wanner C, Hehnke U, Zweiner I, Kaspers S, Clark D, et al. Retinopathy outcomes with empagliflozin versus placebo in the EMPA-REG OUTCOME Trial. Diabetes Care 2019;42:e53–5.
[39] Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431–7.
[40] Trujillo J. Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes. J Clin Pharm Ther 2020;45(Suppl 1):43–60.
[41] Vilsbøll T, Bain SC, Leiter LA, Lingvay I, Matthews D, Simo R, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab 2018;20:889–97.
[42] Eid S, Sas KM, Abcouwer SF, Feldman EL, Garner TW, Pennathur S, et al. New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. Diabetologia 2019;62:1539–49.
[43] Salvotelli L, Stoico V, Perrone F, Cacciatori V, Negri C, Brangani C, et al. Prevalence of neuropathy in type 2 diabetic patients and its association with other diabetes

complications: the Verona Diabetic Foot Screening Program. J Diabetes Compl 2015;29:1066–70.
[44] Christensen DH, Knudsen ST, Nicolaisen SK, Andersen H, Callaghan BC, Finnerup NB, et al. Can diabetic polyneuropathy and foot ulcers in patients with type 2 diabetes be accurately identified based on ICD-10 hospital diagnoses and drug prescriptions? Clin Epidemiol 2019;11:311–21.
[45] Goldstein D, vn Hoff DD, Moore M, Greeno E, Tortora G, Ramanathan RK, et al. Development of peripheral neuropathy and its association with survival during treatment with nab-paclitaxel plus gemcitabine for patients with metastatic adenocarcinoma of the pancreas: a subset analysis from a randomised phase III trial (MPACT). Eur J Cancer 2016;52:85–91.