

# Efficacy of epalrestat plus $\alpha$ -lipoic acid combination therapy *versus* monotherapy in patients with diabetic peripheral neuropathy: a meta-analysis of 20 randomized controlled trials

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## Abstract

**OBJECTIVE:** To evaluate the efficacy of  $\alpha$ -lipoic acid (ALA) plus epalrestat combination therapy in the treatment of diabetic peripheral neuropathy (DPN).

**DATA SOURCES:** The electronic databases of PubMed, Medline, Embase, the Cochrane Library, the Chinese National Knowledge Infrastructure, the Wanfang Database and the Chinese Biomedical Database were used to retrieve relevant studies without language restrictions. The search was conducted from the inception of each database to 7 October 2016. The key terms were (diabetic peripheral neuropathy or diabetic neuropathy or DPN) AND ( $\alpha$ -lipoic acid or lipoic acid or thioctic acid) AND epalrestat.

**DATA SELECTION:** All of the eligible studies met the following inclusion criteria: (1) Randomized controlled trials that compared efficacy and safety of epalrestat plus ALA combination therapy *versus* epalrestat or ALA monotherapy in patients with DPN. (2) The minimum duration of treatment was 2 weeks. (3) The DPN patients were diagnosed using the World Health Organization standardized type 2 diabetes mellitus and DPN criteria. (4) Studies contained at least one measure that could reflect the efficacy of the drug and nerve conduction velocities. Studies in which the control group used epalrestat or ALA combined with other drugs were excluded. Statistical analyses were performed using STATA software for meta-analysis.

**OUTCOME MEASURES:** The primary outcomes were the therapeutic efficacy, median motor nerve conduction velocity (MNCV), median sensory nerve conduction velocity (SNCV), peroneal MNCV and peroneal SNCV.

**RESULTS:** Twenty studies with 1894 DPN patients were included, including 864 patients in the ALA plus epalrestat group, 473 in the ALA group and 557 in the epalrestat group. The efficacy of ALA plus epalrestat combination therapy was superior to ALA and epalrestat monotherapies ( $RR = 1.29$ , 95%  $CI: 1.21-1.38$ ;  $RR = 1.43$ , 95%  $CI: 1.34-1.54$ , respectively). ALA plus epalrestat combination therapy also significantly improved median MNCV ( $WMD = 5.41$ , 95%  $CI: 2.07-8.75$ ), median SNCV ( $WMD = 5.87$ , 95%  $CI: 1.52-10.22$ ), peroneal MNCV ( $WMD = 5.59$ , 95%  $CI: 2.70-8.47$ ) and peroneal SNCV ( $WMD = 4.57$ , 95%  $CI: 2.46-6.68$ ).

**CONCLUSION:** ALA plus epalrestat combination therapy was superior to ALA and epalrestat monotherapies for clinical efficacy and nerve conduction velocities in patients with DPN.

**Key Words:** nerve regeneration; antioxidant; aldose reductase inhibitor; diabetic complication; diabetes; combination therapy; nerve conduction velocity; nerve electrophysiology; peripheral nerve injury; neural regeneration

## Introduction

Diabetic peripheral neuropathy (DPN) is a common microvascular complication of diabetes, and approximately 60% to 70% of people with diabetes have different forms of neuropathy (Tesfaye, 2011; Alam et al., 2017). A recent epidemiological survey showed that 30–40% of diabetic patients experienced DPN. Ninety percent of these patients suffered sensory neuropathy, the main clinical symptoms of which are distal limb sensory abnormalities, hypoesthesia or anesthesia (Boulton et al., 2004; Ogbera et al., 2015). Half of

patients with DPN are asymptomatic, so the disease is often neglected, leading to ulceration and serious infections that, in some cases, results in amputation; the quality of life is significantly lower when the disease becomes severe (Won and Park, 2016). DPN is not only an important cause of disability and death in diabetic patients, but also promotes other complications of diabetes. Therefore, prevention and treatment of DPN are of great clinical significance, but effective prevention and treatment measures are still lacking. The pathogenesis of DPN is complicated and involves diverse

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mechanisms (Zhang et al., 2007). Although strict control of glucose is still the most important approach for the treatment of DPN, several studies have suggested oxidative stress as a mechanism of DPN and that antioxidant treatment can significantly improve the long-term quality of life of patients with DPN and effectively prevent the progression of DPN (Obrosova et al., 2002; Yang et al., 2015).

$\alpha$ -Lipoic acid (ALA), a powerful antioxidant, inhibits oxidative stress by reducing the formation of free radicals (Packer, 1998). ALA can improve the clinical symptoms of DPN and enhance nerve conduction velocity (NCV) (Gu et al., 2010). Epalrestat is a specific inhibitor of aldose reductase. Activation of the polyol pathway leads to the production of large amounts of free radicals, resulting in enhanced oxidative stress. Epalrestat reduces oxidative stress by blocking the polyol pathway (Li et al., 2016). Epalrestat is mainly used to treat diabetic neuropathy and it is effective for DPN and autonomic neuropathy. It also has a therapeutic effect on diabetic macroangiopathy and diabetic nephropathy. The efficacy of ALA plus epalrestat combination therapy in patients with DPN compared with ALA or epalrestat monotherapy has been evaluated by many researchers from mainland China. We conducted a meta-analysis of relevant randomized controlled trials to comprehensively understand the efficacy of ALA and epalrestat combination therapy for DPN. We evaluated primary outcomes, including therapeutic efficacy, median motor nerve conduction velocity (MNCV), median sensory nerve conduction velocity (SNCV), peroneal MNCV and peroneal SNCV. In addition, adverse events were recorded as secondary outcomes.

## Data and Methods

### Search strategy

The electronic databases of PubMed, Medline, Embase, the Cochrane Library, the Chinese National Knowledge Infrastructure, the Wanfang Database and the Chinese Biomedical Database were used to retrieve relevant studies without language restrictions. We combined MeSH and free terms to identify all relevant articles. The search terms were (diabetic peripheral neuropathy, diabetic neuropathies or DPN) AND (alpha-lipoic acid, thioctic acid or lipoic acid) AND epalrestat. The search was conducted from the inception of each database to 7 October 2016.

### Study selection

All of the eligible studies in this meta-analysis met the following inclusion criteria: (a) Randomized controlled trials that compared efficacy and safety of epalrestat plus ALA combination therapy versus epalrestat or ALA monotherapy in patients with DPN. (b) The minimum duration of treatment was 2 weeks. (c) Patients with DPN were diagnosed using the World Health Organization standardized type 2 diabetes mellitus and DPN criteria. (d) The studies contained at least one measure that could reflect the efficacy of the drug and nerve conduction velocities (NCVs).

The exclusion criteria were as follows: The control group used epalrestat or ALA combined with other drugs.

### Data extraction and quality assessment

Studies were reviewed in detail if they met the inclusion and exclusion criteria when we screened the titles and abstracts. The following information was extracted by two independent investigators (Ming Zhao and Jia-Yi Chen): the first author's name, sample size of the intervention and control groups, baseline characteristics (age, the number of males and females, the duration of diabetes and DPN), duration of treatment, daily dose of epalrestat and ALA, and primary outcomes including therapeutic efficacy, median MNCV, median SNCV, peroneal MNCV and peroneal SNCV. In addition, adverse events were recorded as secondary outcomes. Discrepancy was resolved by consensus or adjudication by a third investigator.

The methodological quality of included studies was assessed using the parameters proposed by Jadad et al. (1996). Four items, random sequence generation, allocation concealment, double blinding and withdrawals and dropouts, were evaluated, and the score ranged from 0 to 2 for each item. Studies scoring 4–7 points were regarded as high quality, while 0–3 points indicated low quality (Moher et al., 1998).

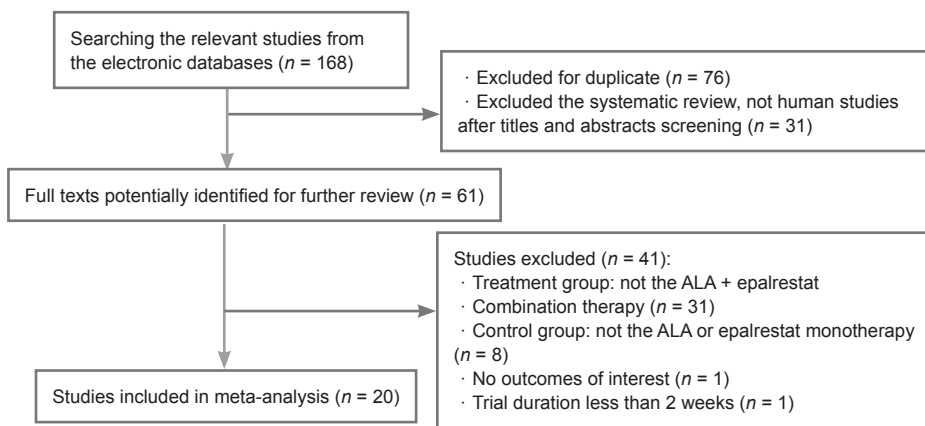
### Outcome measures

In our meta-analysis, the primary outcomes were therapeutic efficacy (valid or invalid), median MNCV, median SNCV, peroneal MNCV and peroneal SNCV. Adverse events were recorded as secondary outcomes.

### Statistical analysis

Meta-analysis was performed using STATA, version 12.0 (Stata corporation, College Station, TX, USA). The efficacy and NCV data were dichotomous and continuous, respectively, and they were expressed as relative risk (RR) and weighted mean difference (WMD) with 95% confidence intervals (CIs), respectively. Heterogeneity was evaluated using Cochran's Q test with  $P < 0.1$  considered statistically significant. The  $I^2$  statistic was also used to assess the magnitude of heterogeneity across studies. Values of  $I^2$  less than 25%, 50% and 75% represented low, medium and high heterogeneity, respectively. If  $P > 0.1$ , indicating no significant heterogeneity, a fixed effect model was selected; otherwise, a random effect model was applied (Higgins et al., 2003).

To explore the source of heterogeneity, subgroup analysis was conducted based on sample size, study duration or study quality. Sensitivity analysis was performed to evaluate the stability of results using different statistical models (fixed effect model vs. random effect model) or different effect measures (relative risk vs. odds ratio). Moreover, funnel plots and Begg's and Egger's tests were used to assess publication bias, with a  $P$  value  $\leq 0.1$  considered statistically significant (Begg and Mazumdar, 1994; Egger et al., 1997). We also undertook the nonparametric "trim and fill" procedure to further assess the possible effect of publication bias in our meta-analysis. The possibility of hypothetical "missing" studies (negative or unpublished studies) was considered; the "trim and fill" method was used to impute their RRs and



**Figure 1** Flow chart of the study selection process. ALA:  $\alpha$ -Lipoic acid.

recalculate a pooled RR that incorporated the hypothetical missing studies as though they actually existed (Duval and Tweedie, 2000).

## Results

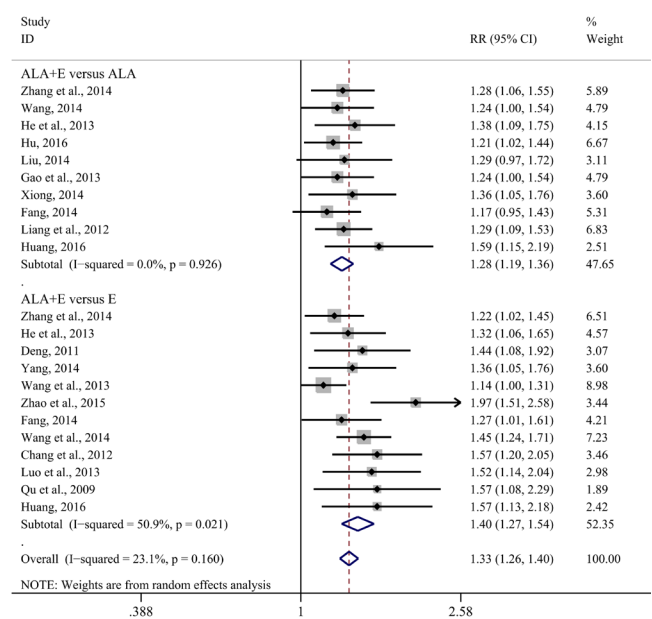
### Study description

We identified 168 relevant studies from the electronic databases, but only 20 met the inclusion and exclusion criteria for selection (Qu and Zeng, 2009; Deng, 2011; Chang and Zhang, 2012; Liang et al., 2012; Gao et al., 2013; He et al., 2013; Luo et al., 2013; Wang et al., 2013; Fang, 2014; Liu, 2014; Wang, 2014; Wang and Chen, 2014; Xiong, 2014; Yang, 2014; Zhang et al., 2014; Yan, 2015; Zhao et al., 2015; Hu et al., 2016; Huang, 2016; Liu, 2016).

Among 41 studies that were excluded after being reviewed in detail, 31 were removed because the treatment group did not receive epalrestat plus ALA combination therapy; eight studies were removed because the control group did not receive epalrestat or ALA monotherapy; one did not report the outcomes of the efficacy of drugs or NCVs and one had a trial duration of less than 2 weeks.

The control groups of studies identified in PubMed, Medline, Embase, and the Cochrane Library were almost all placebo or blank controls, which did not satisfy the inclusion criteria; therefore, the studies included in this meta-analysis were all from mainland China. The study selection process is shown in **Figure 1**.

A total of 1894 DPN patients were included in this meta-analysis, with 864 in the ALA plus epalrestat group, 473 in the ALA group and 557 in the epalrestat group. The treatment duration among studies ranged from 14 to 84 days. The daily dose of ALA was 300, 450 or 600 mg administered *via* intravenous infusion, and the dose of epalrestat was 150 mg through oral administration. Four studies did not report the age of patients (He et al., 2013; Fang, 2014; Zhang et al., 2014; Yan, 2015). In addition, eight studies did not report the duration of diabetes (Deng, 2011; He et al., 2013; Fang, 2014; Liu, 2014, 2016; Zhang et al., 2014; Yan, 2015; Hu et al., 2016) and eleven studies did not report the duration of DPN (Qu and Zeng, 2009; Chang and Zhang, 2012; Liang et al., 2012; Gao et al., 2013; He et al., 2013; Luo et al., 2013; Fang, 2014; Liu, 2014; Yang, 2014; Yan, 2015; Liu, 2016). **Tables 1** and **2** show the characteristics of the included stud-

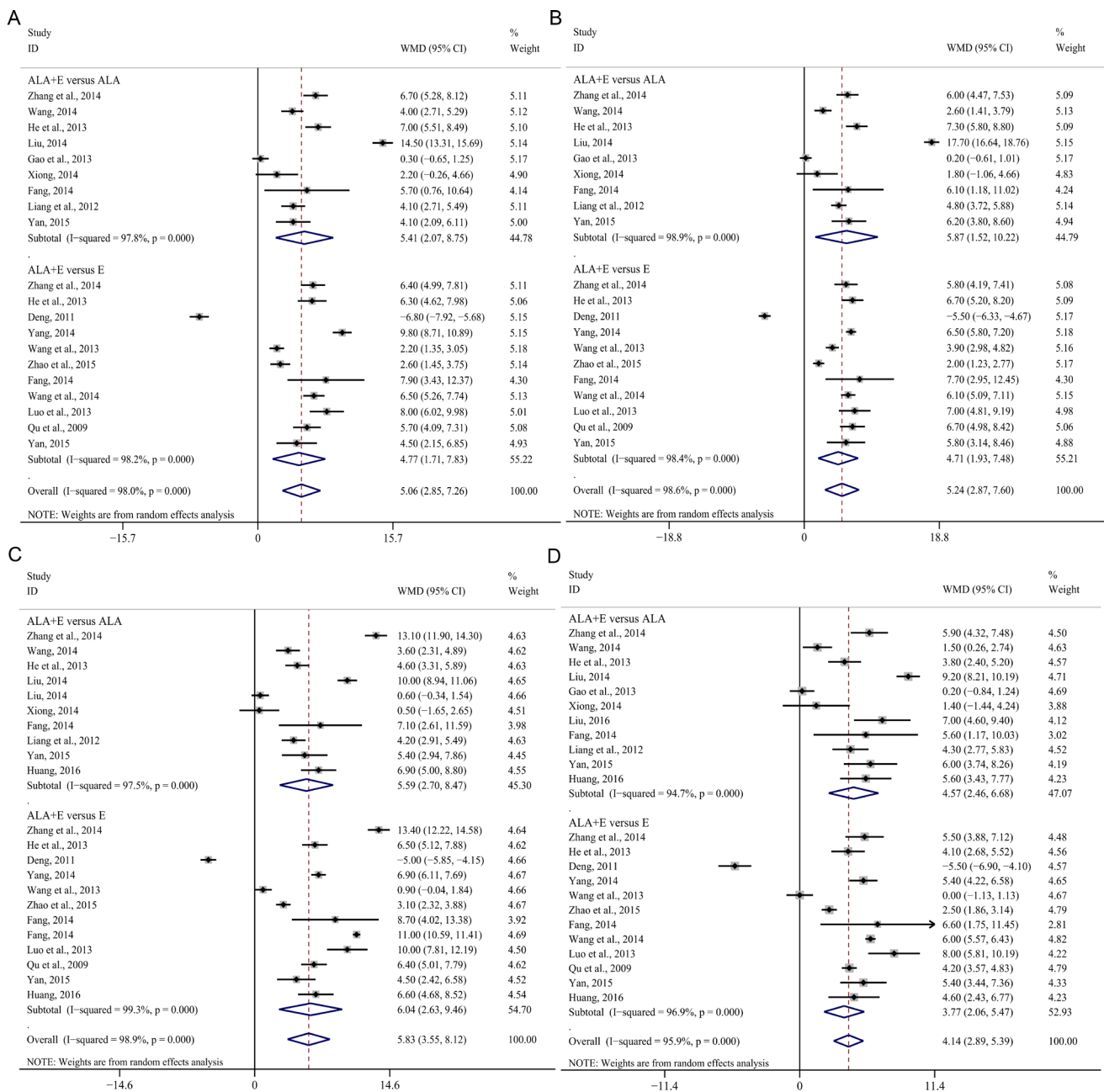


**Figure 2** Comparison of efficacy of ALA plus epalrestat combination therapy and monotherapies for diabetic peripheral neuropathy. ALA:  $\alpha$ -Lipoic acid; E: epalrestat; RR: relative risk; CI: confidence interval.

ies. The quality assessment of the 20 studies is summarized in **Table 3**; most studies had a quality score less than 4, and only two studies had a score of 4 (Liu, 2014; Wang, 2014).

### Efficacy

Analysis of 18 studies with 1754 DPN patients indicated that the efficacy of ALA plus epalrestat combination therapy was remarkably better than that of epalrestat or ALA monotherapy (Qu and Zeng, 2009; Deng, 2011; Chang and Zhang, 2012; Liang et al., 2012; Gao et al., 2013; He et al., 2013; Luo et al., 2013; Wang et al., 2013; Fang, 2014; Liu, 2014; Wang, 2014; Wang and Chen, 2014; Xiong, 2014; Yang, 2014; Zhang et al., 2014; Zhao et al., 2015; Hu et al., 2016; Huang, 2016). A fixed effect model was applied because the heterogeneity among studies was insignificant ( $I^2 = 23.1%$ ,  $P = 0.160$ ). The efficacy of ALA plus epalrestat combination therapy was better than that of ALA alone (RR = 1.28, 95% CI: 1.19–1.36,  $P < 0.001$ ), and also better than that of epalrestat alone (RR = 1.40, 95% CI: 1.27–1.54,  $P < 0.001$ ) (**Figure 2**).



**Figure 3 Comparison of efficacies of ALA, epalrestat, and their combination in nerve conduction velocities for diabetic peripheral neuropathy. (A) Median MNCV; (B) median SNCV; (C) peroneal MNCV; (D) peroneal SNCV. ALA:  $\alpha$ -Lipoic acid; E: epalrestat; WMD: weighted mean difference; CI: confidence interval; MNCV: motor nerve conduction velocity; SNCV: sensory nerve conduction velocity.**

**Median MNCV**

Sixteen studies with 1555 DPN patients measured median MNCV (Qu and Zeng, 2009; Deng, 2011; Liang et al., 2012; Gao et al., 2013; He et al., 2013; Luo et al., 2013; Wang et al., 2013; Fang, 2014; Liu, 2014; Wang, 2014; Wang and Chen, 2014; Xiong, 2014; Yang, 2014; Zhang et al., 2014; Yan, 2015; Zhao et al., 2015). Significant heterogeneity between studies was observed ( $I^2 = 98.0\%$ ,  $P < 0.001$ ), so the random effect model was applied. Median MNCV in the ALA plus epalrestat group was significantly higher than that in the ALA group ( $WMD = 5.41$ , 95%  $CI: 2.07-8.75$ ,  $P = 0.002$ ), and also higher than that in the epalrestat group ( $WMD = 4.77$ , 95%

$CI: 1.71-7.83$ ,  $P = 0.002$ ) (Figure 3A).

**Median SNCV**

Sixteen studies with 1555 DPN patients measured median SNCV (Qu and Zeng, 2009; Deng, 2011; Liang et al., 2012; Gao et al., 2013; He et al., 2013; Luo et al., 2013; Wang et al., 2013; Fang, 2014; Liu, 2014; Wang, 2014; Wang and Chen, 2014; Xiong, 2014; Yang, 2014; Zhang et al., 2014; Yan, 2015; Zhao et al., 2015). Heterogeneity was statistically significant among the studies ( $I^2 = 98.6\%$ ,  $P < 0.001$ ), so the random effect model was applied. Median MNCV in the ALA plus epalrestat group was significantly higher than that in the ALA

**Table 1 Characteristics of included studies in the meta-analysis of ALA plus epalrestat combination therapy versus ALA monotherapy in patients with DPN**

| Study               | Sample size [(ALA+E)/ALA] | Age (year) | Male/female | Treatment regimen per day |             |              | Study duration (day) | Type of diabetes | Diabetes duration (year) | DPN duration (year) | Outcomes                      |
|---------------------|---------------------------|------------|-------------|---------------------------|-------------|--------------|----------------------|------------------|--------------------------|---------------------|-------------------------------|
|                     |                           |            |             | ALA+E                     |             |              |                      |                  |                          |                     |                               |
|                     |                           |            |             | ALA                       | E           | ALA          |                      |                  |                          |                     |                               |
| Zhang et al. (2014) | 55/55                     | NA         | NA          | 450 mg ivgtt              | 150 mg p.o. | 450 mg ivgtt | 21                   | Type 2           | NA                       | 9.3                 | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Wang (2014)         | 40/40                     | 57.3       | 46/34       | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 42                   | Type 2           | 10                       | 1.5                 | E, mMNCV, mSNCV, pMNCV, pSNCV |
| He et al. (2013)    | 36/35                     | NA         | NA          | 300 mg ivgtt              | 150 mg p.o. | 300 mg ivgtt | 28                   | Type 2           | NA                       | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Hu et al. (2016)    | 42/42                     | 60.7       | 45/39       | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 21                   | Type 2           | NA                       | 11.7                | E                             |
| Liu (2014)          | 24/24                     | 56         | 29/19       | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 28                   | Type 2           | NA                       | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Gao et al. (2013)   | 40/40                     | 53.3       | 41/39       | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 14                   | Type 2           | 6.75                     | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Xiong (2014)        | 45/45                     | 40–70      | 63/27       | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 28                   | Type 2           | 0.5–12                   | 2 months–3 years    | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Liu (2016)          | 34/34                     | 52.1       | 39/29       | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 30                   | Type 2           | NA                       | NA                  | pSNCV                         |
| Fang (2014)         | 30/30                     | NA         | NA          | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 14                   | Type 2           | NA                       | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Liang et al. (2012) | 75/75                     | 57.5       | 70/80       | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 21                   | Type 2           | 9.35                     | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Yan (2015)          | 24/24                     | NA         | NA          | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 21                   | Type 2           | NA                       | NA                  | mMNCV, mSNCV, pMNCV, pSNCV    |
| Huang (2016)        | 29/29                     | 54.7       | 35/23       | 600 mg ivgtt              | 150 mg p.o. | 600 mg ivgtt | 21                   | Type 2           | 11.35                    | 5.8                 | E, pMNCV, pSNCV               |

ALA:  $\alpha$ -Lipoic acid; DPN: diabetic peripheral neuropathy; E: epalrestat; ivgtt: intravenous infusion; p.o.: per os; mMNCV: median motor nerve conduction velocity; mSNCV: median sensory nerve conduction velocity; pMNCV: peroneal motor nerve conduction velocity; pSNCV: peroneal sensory nerve conduction velocity; NA: not available.

**Table 2 Characteristics of included studies in the meta-analysis of ALA plus epalrestat combination therapy versus epalrestat monotherapy in patients with DPN**

| Study               | Sample size [(ALA+E)/E] | Age (year) | Male/female | Treatment regimen per day |             |             | Study duration (day) | Type of diabetes | Diabetes duration (year) | DPN duration (year) | Outcomes                      |
|---------------------|-------------------------|------------|-------------|---------------------------|-------------|-------------|----------------------|------------------|--------------------------|---------------------|-------------------------------|
|                     |                         |            |             | ALA+E                     |             |             |                      |                  |                          |                     |                               |
|                     |                         |            |             | ALA                       | E           | E           |                      |                  |                          |                     |                               |
| Zhang et al. (2014) | 55/55                   | NA         | NA          | 450 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 21                   | Type 2           | NA                       | 9.30                | E, mMNCV, mSNCV, pMNCV, pSNCV |
| He et al. (2013)    | 36/35                   | NA         | NA          | 300 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 28                   | Type 2           | NA                       | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Deng (2011)         | 43/43                   | 56.5       | 50/36       | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 28                   | Type 2           | NA                       | 8.30                | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Yang (2014)         | 45/45                   | 56.5       | 47/43       | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 28                   | Type 2           | 8.30                     | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Wang et al. (2013)  | 41/41                   | 58.7       | 53/29       | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 21                   | Type 2           | 8.90                     | 5.20                | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Zhao et al. (2015)  | 66/60                   | 54.2       | 58/68       | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 84                   | Type 2           | 4.00                     | 2.35                | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Fang (2014)         | 30/30                   | NA         | NA          | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 14                   | Type 2           | NA                       | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Wang et al. (2014)  | 80/80                   | 56         | 100/60      | 300 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 21                   | Type 2           | 4.00                     | 10 months–2 years   | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Chang et al. (2012) | 50/50                   | 58.3       | 54/46       | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 28                   | Type 2           | 10.00                    | NA                  | E                             |
| Luo et al. (2013)   | 40/40                   | 57         | 48/32       | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 14                   | Type 2           | 15.70                    | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Qu et al. (2009)    | 25/25                   | 58.6       | 27/23       | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 28                   | Type 2           | 10.00                    | NA                  | E, mMNCV, mSNCV, pMNCV, pSNCV |
| Yan (2015)          | 24/24                   | NA         | NA          | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 21                   | Type 2           | NA                       | NA                  | mMNCV, mSNCV, pMNCV, pSNCV    |
| Huang (2016)        | 29/29                   | 54.5       | 34/24       | 600 mg ivgtt              | 150 mg p.o. | 150 mg p.o. | 21                   | Type 2           | 11.40                    | 5.95                | E, pMNCV, pSNCV               |

ALA:  $\alpha$ -Lipoic acid; DPN: diabetic peripheral neuropathy; E: epalrestat; ivgtt: intravenous infusion; p.o.: per os; mMNCV: median motor nerve conduction velocity; mSNCV: median sensory nerve conduction velocity; pMNCV: peroneal motor nerve conduction velocity; pSNCV: peroneal sensory nerve conduction velocity; NA: not available.

**Table 3 Quality assessment of the studies included in the meta-analysis**

| Study               | Random sequence generation | Allocation concealment | Double blinding | Withdrawals and dropouts | Total score |
|---------------------|----------------------------|------------------------|-----------------|--------------------------|-------------|
| Zhang et al. (2014) | 1                          | 1                      | 0               | 1                        | 3           |
| Wang (2014)         | 2                          | 1                      | 0               | 1                        | 4           |
| He et al. (2013)    | 1                          | 1                      | 0               | 1                        | 3           |
| Hu et al. (2016)    | 1                          | 1                      | 0               | 1                        | 3           |
| Liu (2014)          | 2                          | 1                      | 0               | 1                        | 4           |
| Gao et al. (2013)   | 1                          | 1                      | 0               | 1                        | 3           |
| Xiong (2014)        | 1                          | 1                      | 0               | 1                        | 3           |
| Liu (2016)          | 1                          | 1                      | 0               | 1                        | 3           |
| Fang (2014)         | 1                          | 1                      | 0               | 1                        | 3           |
| Liang et al. (2012) | 1                          | 1                      | 0               | 1                        | 3           |
| Yan (2015)          | 1                          | 1                      | 0               | 1                        | 3           |
| Huang (2016)        | 1                          | 1                      | 0               | 1                        | 3           |
| Deng (2011)         | 1                          | 1                      | 0               | 1                        | 3           |
| Yang (2014)         | 1                          | 1                      | 0               | 1                        | 3           |
| Wang et al. (2013)  | 1                          | 1                      | 0               | 1                        | 3           |
| Zhao et al. (2015)  | 1                          | 1                      | 0               | 1                        | 3           |
| Wang et al. (2014)  | 1                          | 1                      | 0               | 1                        | 3           |
| Chang et al. (2012) | 1                          | 1                      | 0               | 1                        | 3           |
| Luo et al. (2013)   | 1                          | 1                      | 0               | 1                        | 3           |
| Qu et al. (2009)    | 1                          | 1                      | 0               | 1                        | 3           |

group ( $WMD = 5.87$ , 95%  $CI: 1.52-10.22$ ,  $P = 0.008$ ), and also higher than that in the epalrestat group ( $WMD = 4.71$ , 95%  $CI: 1.93-7.48$ ,  $P = 0.001$ ) (Figure 3B).

**Peroneal MNCV**

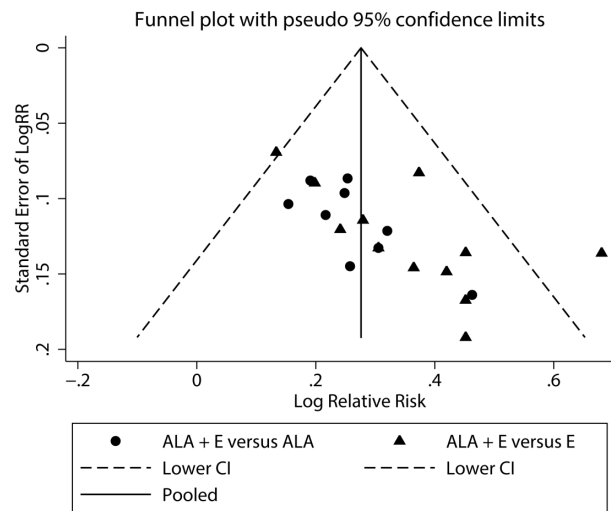
Seventeen studies with 1642 DPN patients measured peroneal MNCV (Qu and Zeng, 2009; Deng, 2011; Liang et al., 2012; Gao et al., 2013; He et al., 2013; Luo et al., 2013; Wang et al., 2013; Fang, 2014; Liu, 2014; Wang, 2014; Wang and Chen, 2014; Xiong, 2014; Yang, 2014; Zhang et al., 2014; Yan, 2015; Zhao et al., 2015; Huang, 2016). Heterogeneity was statistically significant among the studies ( $I^2 = 98.9\%$ ,  $P = 0.000$ ). Peroneal MNCV in the ALA plus epalrestat group was significantly higher than that in the ALA group ( $WMD = 5.59$ , 95%  $CI: 2.70-8.47$ ,  $P < 0.001$ ), and also higher than that in the epalrestat group ( $WMD = 6.05$ , 95%  $CI: 2.63-9.46$ ,  $P < 0.001$ ) (Figure 3C).

**Peroneal SNCV**

Eighteen studies with 1710 DPN patients measured peroneal SNCV (Qu and Zeng, 2009; Deng, 2011; Liang et al., 2012; Gao et al., 2013; He et al., 2013; Luo et al., 2013; Wang et al., 2013; Fang, 2014; Liu, 2014; Wang, 2014; Wang and Chen, 2014; Xiong, 2014; Yang, 2014; Zhang et al., 2014; Yan, 2015; Zhao et al., 2015; Huang, 2016; Liu, 2016). Heterogeneity was statistically significant among the studies ( $I^2 = 95.9\%$ ,  $P < 0.001$ ). Peroneal SNCV in the ALA plus epalrestat group was significantly higher than that in the ALA group ( $WMD = 4.57$ , 95%  $CI: 2.46-6.68$ ,  $P < 0.001$ ), and also higher than that in the epalrestat group ( $WMD = 3.77$ , 95%  $CI: 2.06-5.47$ ,  $P < 0.001$ ) (Figure 3D).

**Subgroup analysis**

To explore the source of heterogeneity among the studies,



**Figure 4 Funnel plot of publication bias in the analysis of efficacy of ALA plus epalrestat combination therapy versus ALA or epalrestat monotherapy in patients with diabetic peripheral neuropathy.** ALA:  $\alpha$ -Lipoic acid; E: epalrestat.

subgroup analyses based on sample size and trial duration were performed. The results are shown in Tables 4 and 5. In some cases, for instance, the sample size was less than 100 or the trial duration was more than 28 days, NCVs were not always higher in the ALA plus epalrestat treatment group compared with the ALA or epalrestat group, because we found that some confidence intervals for RR contain 1. This indicated no significant difference between the ALA plus epalrestat group and the ALA or epalrestat groups. In addition, significant heterogeneities regarding NCV outcomes still existed in every subgroup.

**Safety**

There were no serious adverse events during the treatments. Only a few mild adverse events were observed, such as nausea (Xiong, 2014; Zhao et al., 2015; Hu et al., 2016) and stomach upset (Liang et al., 2012; Gao et al., 2013) in the combination therapy group, pain at the injection site (Fang, 2014; Xiong, 2014) in the ALA therapy group, and dizziness (Liang et al., 2012) in the epalrestat group. However, the studies did not report these events in detail, so no further analysis was performed.

**Sensitivity analysis and publication bias**

Sensitivity analysis was performed to evaluate the stability of results among studies. The results of sensitivity analysis of efficacy of ALA plus epalrestat combination therapy versus ALA or epalrestat monotherapy using an alternative statistical method (random effect model:  $RR = 1.28$ , 95%  $CI: 1.19-1.37$ ;  $RR = 1.40$ , 95%  $CI: 1.27-1.54$ , respectively) or effect measure ( $OR = 4.22$ , 95%  $CI: 2.84-6.28$ ;  $OR = 5.76$ , 95%  $CI: 2.08-15.97$ , respectively) did not change the pooled effects.

Finally, publication bias was assessed by funnel plots (Figure 4), and the asymmetry of the funnel plot was evaluated by Begg's and Egger's tests. Results for Begg's ( $P = 0.128$  and

**Table 4 Subgroup analysis for outcomes with ALA plus epalrestat combination therapy versus ALA monotherapy in patients with DPN**

| Variables         | Efficacy         |                    | Median MNCV       |                    | Median SNCV        |                    | Peroneal MNCV      |                    | Peroneal SNCV    |                    |
|-------------------|------------------|--------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|------------------|--------------------|
|                   | RR (95% CI)      | I <sup>2</sup> (%) | RR (95% CI)       | I <sup>2</sup> (%) | RR (95% CI)        | I <sup>2</sup> (%) | RR (95% CI)        | I <sup>2</sup> (%) | RR (95% CI)      | I <sup>2</sup> (%) |
| Sample size       |                  |                    |                   |                    |                    |                    |                    |                    |                  |                    |
| Less than 100     | 1.29 (1.19–1.41) | 0                  | 5.41 (0.96–9.86)  | 98.3               | 6.00 (0.06–11.94)  | 99.2               | 4.78 (1.97–7.59)   | 96.4               | 4.45 (1.84–7.06) | 95.7               |
| 100 or more       | 1.29 (1.13–1.46) | 0                  | 5.39 (2.85–7.94)  | 84.8               | 5.27 (4.12–6.42)   | 36.4               | 8.65 (–0.07–17.38) | 99.0               | 5.09 (3.52–6.66) | 50.9               |
| Trial duration    |                  |                    |                   |                    |                    |                    |                    |                    |                  |                    |
| Less than 28 days | 1.28 (1.18–1.39) | 0                  | 4.03 (1.21–6.85)  | 93.5               | 4.49 (1.52–7.45)   | 94.9               | 6.20 (1.62–10.78)  | 98.1               | 4.48 (2.00–6.96) | 91.2               |
| 28 days or more   | 1.32 (1.16–1.49) | 0                  | 6.97 (1.30–12.64) | 98.3               | 7.39 (–0.84–15.61) | 99.2               | 5.59 (2.70–8.47)   | 96.9               | 4.62 (1.08–8.17) | 96.3               |

ALA:  $\alpha$ -Lipoic acid; DPN: diabetic peripheral neuropathy; E: epalrestat; mMNCV: median motor nerve conduction velocity; mSNCV: median sensory nerve conduction velocity; pMNCV: peroneal motor nerve conduction velocity; pSNCV: peroneal sensory nerve conduction velocity; RR: relative risk; CI: confidence interval.

**Table 5 Subgroup analysis for outcomes with ALA plus epalrestat combination therapy versus epalrestat monotherapy in patients with DPN**

| Variables         | Efficacy         |                    | Median MNCV       |                    | Median SNCV       |                    | Peroneal MNCV     |                    | Peroneal SNCV     |                    |
|-------------------|------------------|--------------------|-------------------|--------------------|-------------------|--------------------|-------------------|--------------------|-------------------|--------------------|
|                   | RR (95% CI)      | I <sup>2</sup> (%) | RR (95% CI)       | I <sup>2</sup> (%) | RR (95% CI)       | I <sup>2</sup> (%) | RR (95% CI)       | I <sup>2</sup> (%) | RR (95% CI)       | I <sup>2</sup> (%) |
| Sample size       |                  |                    |                   |                    |                   |                    |                   |                    |                   |                    |
| Less than 100     | 1.37 (1.25–1.50) | 22.8               | 4.64 (1.71–7.83)  | 98.6               | 4.77 (0.74–8.81)  | 98.8               | 4.97 (1.33–8.61)  | 98.6               | 3.51 (1.02–6.00)  | 96.5               |
| 100 or more       | 1.52 (1.37–1.68) | 70.0               | 5.15 (2.52–7.80)  | 92.3               | 4.60 (1.60–7.59)  | 95.7               | 9.16 (3.51–14.81) | 99.4               | 4.64 (2.02–7.27)  | 97.5               |
| Trial duration    |                  |                    |                   |                    |                   |                    |                   |                    |                   |                    |
| Less than 28 days | 1.34 (1.24–1.46) | 46.3               | 5.75 (3.51–7.98)  | 91.6               | 5.68 (4.48–6.87)  | 66.9               | 7.86 (3.90–11.82) | 98.7               | 5.03 (2.79–7.26)  | 94.1               |
| 28 days or more   | 1.55 (1.38–1.73) | 21.5               | 3.51 (–2.70–9.73) | 99.1               | 3.26 (–1.72–8.23) | 99.3               | 6.05 (2.63–9.46)  | 99.2               | 2.17 (–0.60–4.93) | 97.7               |

ALA:  $\alpha$ -Lipoic acid; DPN: diabetic peripheral neuropathy; E: epalrestat; mMNCV: median motor nerve conduction velocity; mSNCV: median sensory nerve conduction velocity; pMNCV: peroneal motor nerve conduction velocity; pSNCV: peroneal sensory nerve conduction velocity; RR: relative risk; CI: confidence interval.

0.064) and Egger's tests ( $P = 0.035$  and  $0.015$ ) for ALA plus epalrestat combination therapy versus ALA or epalrestat monotherapy, respectively, and the fact that the funnel plot was asymmetrical on visual inspection, indicated the possibility of publication bias. Because of this, we conducted a sensitivity analysis using the trim and fill method, which was based on the assumption that the funnel plot asymmetry was caused by publication bias. We used the iterative method to estimate the missing studies. After adding some studies, we re-calculated the pooled RR and 95% CI; if the change was not statistically significant, publication bias had little effect on the results and the results were stable. The results showed that the efficacy of ALA plus epalrestat combination therapy was still higher than ALA or epalrestat monotherapy (RR = 1.25, 95% CI: 1.18–1.36; RR = 1.28, 95% CI: 1.21–1.36, respectively).

## Discussion

The prevalence of diabetes has increased rapidly in the past decades, and the number of diabetic patients is estimated to approach 642 million worldwide in 2040 (Zhao et al., 2016). In the life-time of a diabetic patient, the possibility of DPN occurrence is more than 60%, and 36% of patients with DPN suffer from severe and refractory pain (Mehra et al., 2014). The pathogenesis of DPN is a result of multiple factors that are not fully understood. The mechanisms by which high blood glucose leads to DPN include mitochondrial dysfunction, oxidative stress, polyol pathway activation, microvascular dysfunction and altered protein kinase C activity

(Caballero et al., 1999; Yagihashi et al., 2007). High blood glucose acts as an initiating factor, generating a large number of reactive oxygen species through the mitochondrial transmission chain, consuming free radical scavengers, and leading to weakened antioxidant ability in nerve tissue (Calcutt et al., 2008). Catanaro et al. (2013) found bradykinin B1 receptor (BKB1-R) over-expression in the sciatic nerve of streptozotocin-induced diabetic rats. They also found that the BKB1-R antagonist, R-954, inhibited oxidative stress, promoted the recovery of Na (+)/K (+)-ATPase and to some extent alleviated diabetic neuropathy. It is generally believed that DPN results from interactions among multiple factors; therefore, DPN treatment should not only focus on lowering the level of blood glucose, but should also take a multi-directional comprehensive approach, including protection of microcirculation.

ALA, as an antioxidant, can directly eliminate free radicals, inhibit peroxidation, increase blood flow in neurocutaneous vessels, raise the reduced glutathione content of peripheral nerves, and improve microcirculation in patients with DPN (Nickander et al., 1996; Haak et al., 2000). Several large-scale randomized controlled trials have shown that ALA is an efficient medication in treating DPN, leading to significant improvement of patients' symptoms, subjective sensation and, therefore, better quality of life (Ziegler et al., 1995, 1999, 2006; Ametov et al., 2003).

Epalrestat is a noncompetitive and reversible inhibitor of aldose reductase, which is the rate-limiting enzyme in the polyol pathway. Epalrestat is important for protection

against oxidative injuries and is therefore used for the treatment of DPN (Sato et al., 2013). Epalrestat is easily absorbed into neural tissues and inhibits aldose reductase with few adverse effects (Yama et al., 2016). In a long-term clinical trial conducted by Hotta et al. (2006), patients with DPN were treated with epalrestat for over three years, and epalrestat effectively delayed the progression of DPN and ameliorated the associated clinical symptoms of this disease.

In our meta-analysis, 20 trials with 1894 DPN patients were included to assess the efficacy and safety of the combination therapy of ALA plus epalrestat in comparison with the monotherapies. The results demonstrated that ALA plus epalrestat combination therapy had a better efficacy and led to higher NCVs than ALA or epalrestat monotherapy. Moreover, no serious adverse events were observed during any of these treatments. However, in subgroup analysis based on sample size or trial duration, no statistical significance was found between ALA plus epalrestat combination therapy and either monotherapy regarding NCVs. The reason for this may be that the sample size was small and that the methodological quality was poor in the included studies.

To the best of our knowledge, this meta-analysis is the first to evaluate the efficacy of ALA plus epalrestat combination therapy in DPN patients. We conducted this meta-analysis using rigorous search and statistical analysis methods to ensure accuracy of the results. However, several potential limitations of our meta-analysis should be fully recognized. First, most studies did not report the blinding of participants and personnel or the concealment of randomization allocation, resulting in low-quality scores for these studies. Second, the sample sizes were small and patient withdrawal or dropout was not described. Third, the studies included were all published, which may cause potential bias because data without statistical significance may have not been published.

In conclusion, the results of this meta-analysis show that compared with ALA or epalrestat monotherapy, the ALA plus epalrestat combination therapy dramatically improves the clinical efficacy and accelerates nerve conduction. However, additional large-scale randomized controlled trials still need to be conducted to confirm these findings.

**Author contributions:** LL and SZB designed the study. JYC and YDC conducted the experiments. MZ and YDC obtained the data. MZ and JYC analyzed the data. MZ drafted the paper. YBZ and SZB made critical revisions to the paper. All authors approved the final version of the paper.

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