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Original Article

Endothelin-receptor antagonists for diabetic nephropathy: A meta-analysis

WENMING YUAN,[1] YI LI,[2] JI WANG,[3] JING LI,[3] SHENJU GOU[1] and PING FU[1]

[1]Renal Division, Department of Medicine, [3]Division of Evidence-Based Medicine and Clinical Epidemiology, West China Hospital of Sichuan University, Chengdu, Sichuan, China, and [2]Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI, USA

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Correspondence:
Professor Ping Fu, Renal Division, Department of Medicine, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China.
Email: fupinghx@163.com

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ABSTRACT:

Aim: **Endothelin-receptor antagonists may be a novel therapeutic strategy for diabetic nephropathy, but their use remains controversial. This meta-analysis seeks to evaluate the effectiveness and safety of endothelin-receptor antagonists for patients with diabetic nephropathy.**

Methods: **Literature reviews of the PubMed, EMBASE and CENTRAL databases were conducted to identify randomized controlled trials (RCTs) comparing endothelin-receptor antagonist treatment with placebo in patients with diabetic nephropathy. Quality assessment was performed by using the Cochrane Handbook's tools for assessing risk of bias; meta-analysis was conducted by RevMan 5.3.**

Resutls: **Five RCTs (n = 2034 patients) were included for analysis. Compared with placebo, endothelin-receptor antagonists showed significant benefits for lowering albuminuria (five trials, n = 2034 patients; SMD 0.66 95% confidence interval (CI) 0.56 to 0.76), but there was no significant difference in the risk of death (two trials, n = 1674 patients; RR 1.49 95% CI 0.81 to 2.76). In addition, risk of cardiovascular events and other serious adverse events were significantly higher in the endothelin-receptor antagonists group than the placebo group (four trials, n = 1956 patients; RR 1.45 95% CI 1.07 to 1.97; five trials, n = 2034 patients; RR 1.32 95% CI 1.10 to 1.58).**

Conclusion: **Endothelin-receptor antagonists can reduce albuminuria in patients with diabetic nephropathy, although use resulted in more serious adverse events compared with placebo. There is a potential need for further RCTs, which has larger sample size and longer duration.**

Diabetic nephropathy is a leading cause of end stage renal disease in many countries. Despite attempts at rigorous control of hyperglycaemia and hypertension, some patients with diabetic nephropathy still experience cardiovascular or renal events.[1] Many clinical studies have confirmed that renin angiotensin system (RAS) inhibitors (angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB)) can reduce albuminuria in patients with diabetic nephropathy, and delay progression of chronic kidney disease. These agents can cause hyperkalaemia and creatinine elevation, making their use in patients with decreased kidney function.[2,3] Despite this potential risk, endothelin-receptor (ER) antagonists have been used as a novel treatment option for patients with diabetic nephropathy.[4]

Endothelins are proteins that are produced by many cells and contribute to hypertension. Endothelin-1 is an isoform of endothelins that can activate both endothelin A receptor (ET_AR) and endothelin B receptor (ET_BR). It has been confirmed that the levels of circulating and renal endothelin-1 are elevated in patients with diabetes and in preclinical models. The activation of glomerular ET_AR can promote the proliferation of podocyte and mesangial cells, leading to albuminuria and renal dysfunction.[5–7] Previous clinical trials have revealed that ER antagonists can reduce albuminuria in patients with diabetic nephropathy, regardless of the involvement of ET_AR.[8,9] This suggests that ER antagonists may be a novel and beneficial drug for diabetic nephropathy.[10] However, Mann et al. (2010) reported an early termination of a trial of ER antagonists that was prompted by

safety concerns with avosentan, including hypervolaemia, congestive heart failure, hypotension and anaemia.[9] Therefore, potential morbidity risks must be considered. In view of scarcity of systematic research in the area, we seek to fill a gap in the literature through meta-analysis of the effectiveness and safety of endothelin-receptor antagonists for patients with diabetic nephropathy.

METHODS

Data sources and searches

We conducted a literature review of Pubmed (January 1966 to December 2014), EMBASE (1980 to December 2014), CENTRAL (searched December 2014). Specified search terms included 'endothelin-receptor antagonists', 'atrasentan', 'avosentan', 'diabetic' and 'random'. These searches were followed by manual review of the identified trial publications.

Trials selection

The initial sample included all randomized controlled trials (RCTs), in which patients with diabetic nephropathy received endothelin-receptor antagonists. The first period of randomized cross-over studies were also considered for inclusion.

Eligible trials included: (i) patients 18 years of age or older; with (ii) a diabetes diagnosis of a minimum of 4 weeks; (iii) a measured estimated glomerular filtration rate (eGFR) > 20 mL/min per 1.73 m^2 or serum creatinine <3 mg/dL; and (iv) microalbuminuria or macroalbuminuria (urinary albumin-to-creatinine ratio (UACR) >3 mg/mmol or UAER > 0.2 mg/min).

Individuals were excluded if they had received a diagnosis of an immune-related renal diseases, such as minimal change disease, IgA nephropathy, membranous nephropathy, focal segmental glomerular sclerosis, and lupus nephritis. Patients of all racial, ethnicity, and nationality groups were included.

Eligible trials included intervention comparisons of atrasentan versus placebo, avosentan versus placebo, and bosentan versus placebo. Clinical outcomes included primary (all-cause mortality, cardiovascular events), and secondary measures (albuminuria (changes of urine albumin-to-creatinine ratio (UACR) or urinary albumin excretion rate (UAER)) and estimated glomerular filtration rate (eGFR). Safety outcomes assessed included adverse events, systolic (SBP) and diastolic (DBP) blood pressure, peripheral oedema, and anaemia.

Data extraction and risk of bias assessment

Two authors independently abstracted data using a standard data extraction form. If an individual study was represented in more than one publication, the data were combined.[11] Discrepancies in data extraction were discussed by the group and resolved by Ping Fu, the project director.

Data extraction variables included patient characteristics, interventions, outcome measures, and treatment periods. The assessment of risk of bias included the examination of sequence generation, allocation concealment, blinding, incomplete outcomes, selective reporting, and other biases.

Measure of treatment effect

For binary outcomes (e.g. mortality, cardiovascular events, adverse events), the results of intervention were expressed as risk ratio (RR) with 95% confidence intervals (CI). For continuous outcomes (e.g. changes of UACR, eGFR, SBP, and DBP), the results were expressed as mean difference (MD) with 95% CIs. When different scales had been applied, the SMD was used. Presence and extent of heterogeneity among studies was analyzed by using a χ^2 test and I^2 statistic. Homogeneity is indicated by *P*-value >0.1 or $I^2 < 50\%$, making a fixed-effect model appropriate. Measured probability less than 0.1 or $I^2 > 50\%$ may represent substantial heterogeneity. Where indicated by the type of trial interventions, subgroup analyses were conducted to explore any identified heterogeneity. A random-effect model was used to incorporate unobservable heterogeneity across studies, a common approach in meta-analysis. Of the five included trials, four assessed at least two different doses of ER antagonists groups. For each trial we collapsed all treatment doses of ER antagonists groups into a single group for comparison with placebo. Combined data were analyzed by Revman 5.3.[12]

RESULTS

Result of searches

Of the 647 potentially eligible trials identified by electronic searching, five RCTs ($n = 2034$ patients) met inclusion criteria; screening processes and results are presented in Fig. 1.[8–10,13,14] The characteristic of five included trials were shown in Table 1.

Risk of bias in included trials

All five included trials exhibited low risk of bias with respect to sequence generation, allocation concealment, blinding, incomplete outcome and selective reporting. Two of these trials contained other potential bias.[14] The Mann 2010 trial discontinued after a median follow-up of 4 months because patients experienced adverse events of hypervolaemia and congestive heart failure.[9] The Wenzel 2009 trial included three authors who

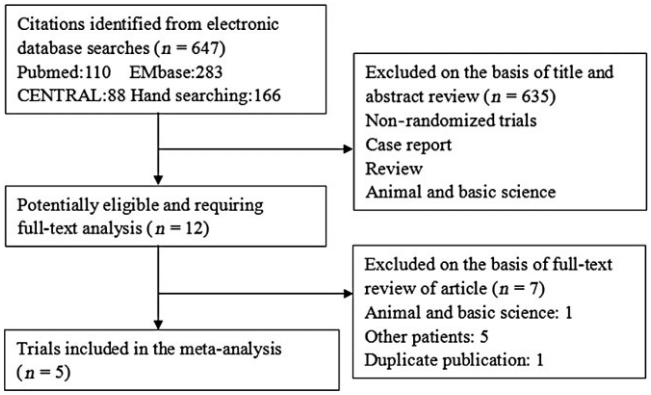

Fig. 1 Flow diagram of search and selection.

Table 1 Characteristics of included trials

Study ID	Study type	No. patients	Type of patients	Interventions	Outcomes	Treatment period
Kohan *et al*. 2011[8]	RCT	89	Diabetic nephropathy eGFR > 20 mL/min per 1.73 m^2 UACR of 100–3000 mg/g Mean age of 64 years Duration of diabetes >1 year	Atrasentan 0.25 mg/day (*n* = 22) Atrasentan 0.75 mg/day (*n* = 22) Atrasentan 1.75 mg/day (*n* = 22) Placebo (*n* = 23)	1. UACR 2. CV events† 3. Adverse events	8 weeks
Mann *et al*. 2010[9]	RCT	1392	Diabetic nephropathy Scr of 1.3 to 3.0 mg/dL UACR ≥ 309 mg/g Mean age of 61 years Duration of diabetes >3 years	Avosentan 25 mg/day (*n* = 455) Avosentan 50 mg/day (*n* = 478) Placebo (*n* = 459)	1. Death 2. CV events† 3. eGFR 4. UACR 5. Adverse events	4 to 16 months
Rafnsson *et al*. 2012[13]	RCT	56	Diabetes and microalbuminuria Scr < 3.0 mg/dL UACR > 3 mg/mmol mean age of 62 years Duration of diabetes >2 years	Bosentan 250 mg/day (*n* = 28)‡ Placebo (*n* = 28)	1. UACR 2. Scr 3. Adverse events	4 weeks
Wenzel *et al*. 2009[14]	RCT	286	Diabetic nephropathy Scr <3.0 mg/dL UAER of 0.2 to 5.6 mg/min Mean age of 59 years Duration of diabetes >4 weeks	Avosentan 5 mg/day (*n* = 59) Avosentan 10 mg/day (*n* = 57) Avosentan 25 mg/day (*n* = 60) Avosentan 50 mg/day (*n* = 53) Placebo (*n* = 57)	1. Death 2. CV events† 3. UAER 4. eGFR 5. Adverse events	12 weeks
Zeeuw *et al*. 2014[10]	RCT	211	Diabetic nephropathy eGFR of 30–75 mL/min per 1.73 m^2 UACR > 300–3500 mg/g Mean age of 65 years Duration of diabetes >1 year	Atrasentan 0.75 mg/day (*n* = 78) Atrasentan 1.25 mg/day (*n* = 83) Placebo (*n* = 50)	1. UACR 2. CV events† 3. eGFR 4. Adverse events	12 weeks

†CV, cardiovascular. ‡Bosentan at 62.5 mg twice daily for 2 weeks and increased to 125 mg twice daily for 2 weeks.

received benefits from a related pharmaceutical company, indicating a potential conflict of interest. The author R.R.W. had received consultant fees from SPEEDEL Pharma AG. The other two authors T.L. and S.K. had been used by and hold stock in SPEEDEL Pharma AG.[14] Of the five included trials, four trials were registered with the ClinicalTrials.gov database.[8–10,13] Details of the risk of bias are shown in Table 2.

Results of meta-analysis

Primary outcomes

All-cause mortality. Two trials reported the all-cause mortality of patients with diabetic nephropathy.[9,14] Of the 1674 patients, a total of 55 patient deaths occurred (3.6% (*n* = 42/1162) in the treatment group, 2.5% (*n* = 13/512) in the placebo group). In the Mann 2010 and the Wenzel 2009, the rates of deaths were 3.6% and 1.7%, respectively.[9,14] There was no statistically significant difference in the risk of death among patients treated with ER antagonists as compared to placebo (two trials, *n* = 1674 patients; RR 1.49 95% CI 0.81 to 2.76, see Fig. 2a). There was no statistical evidence of heterogeneity ($I^2 = 0\%$, $P = 0.20$). In the subgroup analysis, there was also no significant difference in patient death for individual types and doses of ER antagonists groups as compared with the placebo group.

Cardiovascular events. Four trials reported the rate of cardiovascular events. There were defined as coronary artery disease, nonfatal acute myocardial infarction, stroke or congestive heart failure.[8–10,14] A total of 194 cardiovascular events occurred in 1956 patients (9.9%; 10.7% (*n* = 146/1367) in the treatment group, 8.1% (*n* = 48/589) in the placebo group). The meta-analysis indicated that risk of cardiovascular events was statistically significant higher in treatment group than placebo group (four trials, *n* = 1956 patients; RR 1.45 95% CI 1.07 to 1.97, see Fig. 2b). There was no statistical evidence of heterogeneity ($I^2 = 0\%$, $P = 0.88$). This result was dominated by the Mann 2010 trial that contributed 95.5% weight to the summary estimate. Mann 2010 trial reported a higher risk of cardiovascular events in treatment group than the placebo group but the other three trials reported no significant difference.[8–10,14]

Secondary outcomes

Albuminuria. To assess the albuminuria in patients with diabetic nephropathy, all five trials reported the changes of UACR or UAER from baseline to each final observation. Four trials used UACR[8–10,13] and one trial used UAER.[14] We chose SMD as a summary statistic in the meta-analysis because different scales had been applied. There was a statistically

Table 2 Risk of bias in included trials

Study ID	Sequence generation	Allocation concealment	Blinding	Incomplete outcome	Selective reporting	Other bias
Kohan 2011[4]	Compute randomization (low risk)	Central allocation (low risk)	Double-blind (low risk)	6/66 patients discontinued from intervention group; 2/23 patients discontinued from control group (low risk)	It is clear that the published reports include all expected outcomes. (low risk)	None NCT00920764 (low risk)
Mann *et al*. 2010[9]	Compute randomization (low risk)	Central allocation (low risk)	Double-blind (low risk)	176/933 patients withdrew from intervention group; 53/459 patients withdrew from control group (low risk)	It is clear that the published reports include all expected outcomes. (low risk)	The trial was terminated early NCT00120328 (high risk)
Rafnsson *et al*. 2012[13]	Compute randomization (low risk)	Sealed envelopes (low risk)	Double-blind (low risk)	3/28 patients discontinued from intervention group; 2/28 patients discontinued from control group (low risk)	It is clear that the published reports include all expected outcomes. (low risk)	None NCT01357109 (low risk)
Wenzel *et al*. 2009[14]	Randomization using permuted blocks of five (low risk)	Central allocation (low risk)	Double-blind (low risk)	32/229 patients withdrew from intervention group; 2/57 patients withdrew from control group (low risk)	It is clear that the published reports include all expected outcomes (low risk)	Some authors have received fees or hold stock from Pharma companies (high risk)
Zeeuw *et al*. 2014[10]	Compute randomization (low risk)	Central allocation (low risk)	Double-blind (low risk)	26/161 patients discontinued from intervention group; 2/50 patients discontinued from control group (low risk)	It is clear that the published reports include all expected outcomes. (low risk)	None NCT01356849 NCT01424319 (low risk)

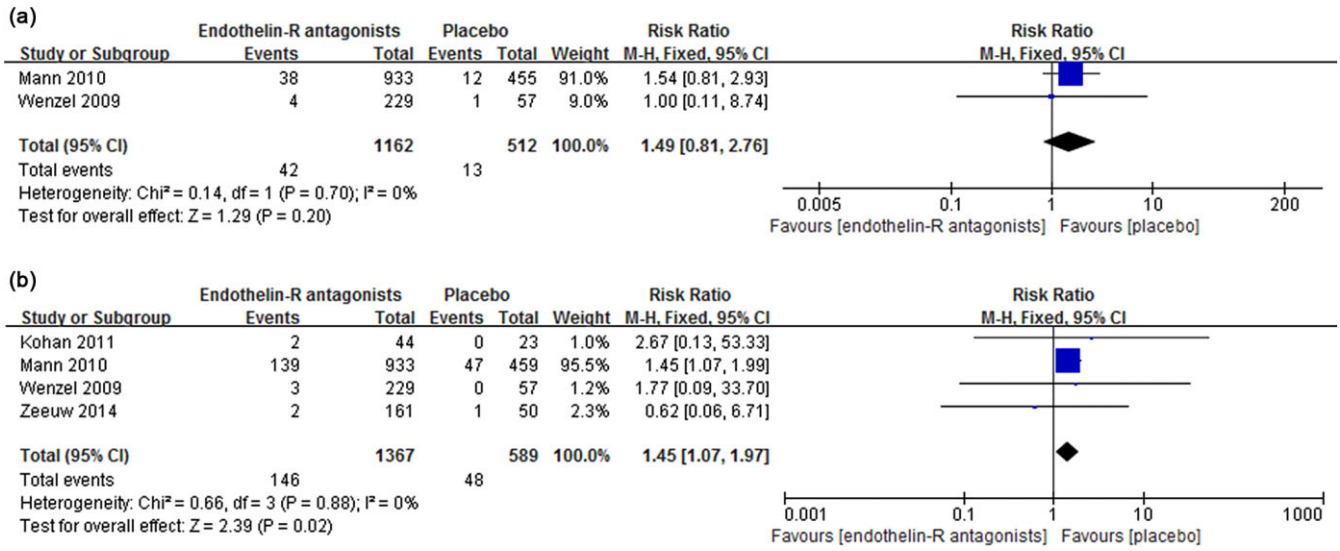

Fig. 2 (a) Endothelin-receptor antagonists versus placebo on mortality. (b) Endothelin-receptor antagonists versus placebo on cardiovascular events.

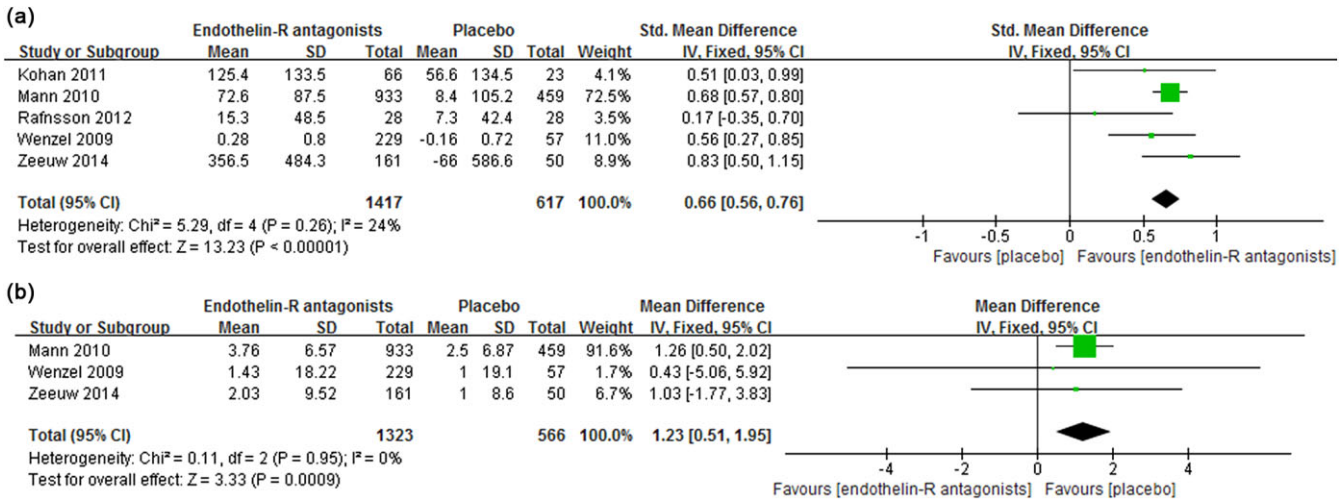

Fig. 3 (a) Endothelin-receptor antagonists versus placebo on changes of albuminuria. (b) Endothelin-receptor antagonists versus placebo on changes of estimated glomerular filtration rate (eGFR).

significant difference in lowering albuminuria among patients treated with ER antagonists compared with placebo (5 trials, $n = 2034$ patients; SMD 0.66 95% CI 0.56 to 0.76, see Fig. 3a). There was no statistical evidence of heterogeneity ($I^2 = 24\%$, $P = 0.26$). In the subgroup analysis, as compared to placebo groups there were significant reductions of albuminuria in patients receiving total daily doses of atrasentan 0.75 mg, atrasentan 1.25 mg, atrasentan 1.75 mg, avosentan 5 mg, avosentan 10 mg, avosentan 25 mg and avosentan 50 mg, respectively, but no significant differences for those prescribed atrasentan 0.25 mg and bosentan 250 mg.

Furthermore, two trials reported the number of patients who achieved 40% or greater reductions in UACR.[8,10] The results of meta-analysis also showed no statistically significant difference in lowering albuminuria in the treatment group compared with the placebo group (two trials, $n = 300$ patients, RR 4.16 95% CI 2.01 to 8.61).

eGFR. Three trials reported the changes of eGFR from baseline to each final observation.[8,10] The meta-analysis showed that eGFR significantly increased among patients treated with ER antagonists compared with placebo (three trials, $n = 1889$ patients, MD 1.23 95% CI 0.51 to 1.95, see Fig. 3b). In the subgroup analysis, there were statistically significant increases in eGFR in patients receiving total daily doses of avosentan 25 mg and avosentan 50 mg, but no differences for patients prescribed atrasentan 0.75 mg, atrasentan

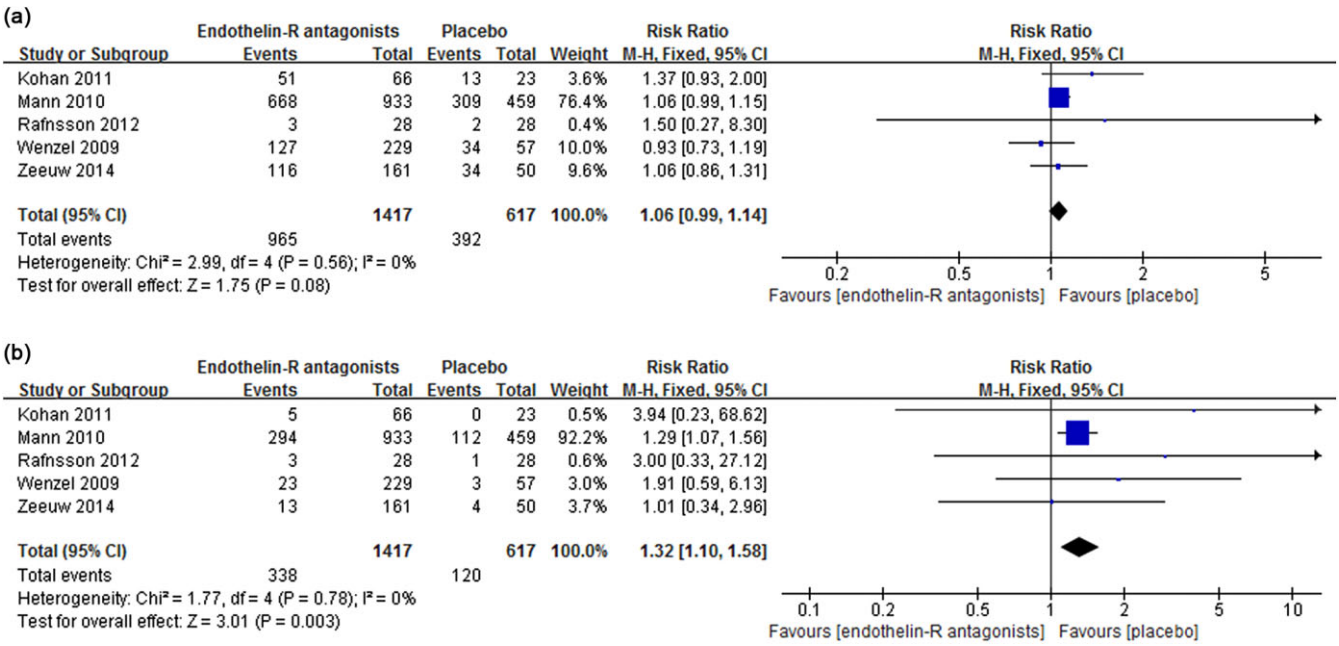

Fig. 4 (a) Endothelin-receptor antagonists versus placebo on adverse events. (b) Endothelin-receptor antagonists versus placebo on serious adverse events.

1.25 mg, avosentan 5 mg and avosentan 10 mg when compared with the placebo group.

Safety outcomes

Adverse events. All five trials reported adverse events with ER antagonists, including oedema, hypervolaemia, hypotension, anaemia, and dyspnea.[8–10,13,14] Almost 67% of all patients ($n = 1357$) reported at least one adverse event, 68.1% of the treatment group ($n = 965$) and 63.5% of the placebo group ($n = 392$). The majority of these adverse events were mild or moderate in severity and were considered unrelated to treatment. Treatment groups experienced a higher rate of adverse events as compared to placebo, but not significantly so (five trials, $n = 2034$ patients; RR 1.06 95% CI 0.99 to 1.14, see Fig. 4a).

There was no statistical evidence of heterogeneity ($I^2 = 0\%$, $P = 0.56$). The serious adverse events occurred more often with the use of ER antagonists and a total of 22.5%, or $n = 458/2034$ patients had at least one serious adverse event in 2034 patients (23.9% ($n = 338/1417$) in the treatment group, 19.4% ($n = 120/617$) in the placebo group). The meta-analysis showed that the risk of serious adverse events was statistically significantly higher in treatment groups than placebo groups (five trials, $n = 2034$ patients; RR 1.32 95% CI 1.10 to 1.58, see Fig. 4b). There was also no statistical evidence of heterogeneity ($I^2 = 0\%$, $P = 0.81$).

Blood pressure. All five trials reported the changes of SBP and DBP.[8–10,13,14] There were statistically significant reductions of SBP and DBP in the treatment group as compared with the placebo (five trials, $n = 2034$ patients; SBP, MD 3.88 95% CI 2.40 to 5.36; DBP, MD 2.65 95% CI 1.01 to 4.30).

Peripheral oedema. All the five trials reported the peripheral oedema events.[8–10,13,14] There were no statistically significant differences in treatment groups as compared with placebo (five trials, $n = 2034$ patients; RR 1.11 95% CI 0.90 to 1.36).

Anaemia. Four trials reported the changes in haemoglobin from baseline to each final observation.[8,10,13,14] There was a statistically significant reduction of haemoglobin for patients in treatment groups compared with placebo groups (four trials, $n = 642$ patients. MD 0.69, 95% CI 0.51 to 0.87).

Two trials reported the rate of anaemia and a total of 143 anaemia events occurred in 1678 patients (8.5%; 10.8% ($n = 125/1162$) in the treatment group, 3.5% ($n = 18/516$) in the placebo group).[9,14] There was a significant increase of risk of anaemia for treatment group patients compared with placebo groups (two trials, $n = 1678$ patients. RR 3.22 95% CI 1.99 to 5.20).

DISCUSSION

Summary of main result

Endothelin-receptor antagonists have been proven to effectively lower albuminuria in diabetic rat models.[15] This

meta-analysis further revealed that ER antagonists were beneficial in lowering albuminuria among patients with diabetic nephropathy. However, compared with placebo, ER antagonists resulted in more serious adverse events and higher risks of cardiovascular events, hypotension and anaemia.

Applicability of evidence

Patient age and types of endothelin-receptor antagonists are factors associated with higher risks of cardiovascular and adverse events as evidenced in this meta-analysis. Most patients with diabetic nephropathy were older than 60 years and were likely to endure hypotension and oedema. Some studies had proven that hypotension and oedema may lead to cardiovascular endpoints.[16,17] The differential inhibition effect of endothelins may also contribute to heart failures, as the inhibition effect of ET_BR may lead to fluid and salt retention, partially mediated via the epithelial sodium transporter in tubular cells,[18] resulting in congestive heart failure. There was no head-to-head clinical trial of selective ET_A vs. $ET_{A/B}$ antagonists in patients with diabetic nephropathy. Further RCTs will need to compare the effectiveness of ET_AR with $ET_{A/B}R$ antagonists.

Quality of evidence

Four trials in the meta-analysis had relatively small sample sizes;[8,10,13,14] hence there is a likelihood that the results of meta-analysis were largely driven by a single trial with the largest sample size, which is the Mann 2011 trial. However, this trial was terminated prematurely after a median follow-up of 4 months because of the significant safety concerns related to cardiovascular events.[9]

Limitation of this meta-analysis

Four trials assessed more than two doses of endothelin-receptor antagonists, when compared with a common placebo group.[8–10,14] This precludes a direct meta-analysis of pairwise comparisons; a unit-of-analysis error would arise if the placebo group was included more than twice in the same meta-analysis. We conducted the meta-analysis from the recommend method in the Cochrane handbook, after combining all ER antagonists groups into a single treatment.[11]

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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