ORIGINAL RESEARCH

Clinical Adverse Effects of Endothelin Receptor Antagonists: Insights From the Meta-Analysis of 4894 Patients From 24 Randomized Double-Blind Placebo-Controlled Clinical Trials

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***Background*—**Evidence of the clinical safety of endothelin receptor antagonists (ERAs) is limited and derived mainly from individual trials; therefore, we conducted a meta-analysis.

***Methods and Results*—**After systematic searches of the Medline, Embase, and Cochrane Library databases and the ClinicalTrials.gov website, randomized controlled trials with patients receiving ERAs (bosentan, macitentan, or ambrisentan) in at least 1 treatment group were included. All reported adverse events of ERAs were evaluated. Summary relative risks and 95% CIs were calculated using random- or fixed-effects models according to between-study heterogeneity. In total, 24 randomized trials including 4894 patients met the inclusion criteria. Meta-analysis showed that the incidence of abnormal liver function (7.91% versus 2.84%; risk ratio [RR] 2.38, 95% CI 1.36–4.18), peripheral edema (14.36% versus 9.68%; RR 1.44, 95% CI 1.20–1.74), and anemia (6.23% versus 2.44%; RR 2.69, 95% CI 1.78–4.07) was significantly higher in the ERA group compared with placebo. In comparisons of individual ERAs with placebo, bosentan (RR 3.78, 95% CI 2.42–5.91) but not macitentan (RR 1.17, 95% CI 0.42–3.31) significantly increased the risk of abnormal liver function, whereas ambrisentan (RR 0.06, 95% CI 0.01–0.45) significantly decreased that risk. Bosentan (RR 1.47, 95% CI 1.06–2.03) and ambrisentan (RR 2.02, 95% CI 1.40–2.91) but not macitentan (RR 1.08, 95% CI 0.81–1.46) significantly increased the risk of peripheral edema. Bosentan (RR 3.09, 95% CI 1.52–6.30) and macitentan (RR 2.63, 95% CI 1.54–4.47) but not ambrisentan (RR 1.30, 95% CI 0.20–8.48) significantly increased the risk of anemia. ERAs were not found to increase other reported adverse events compared with placebo.

***Conclusions*—**The present meta-analysis showed that the main adverse effects of treatment with ERAs were hepatic transaminitis (bosentan), peripheral edema (bosentan and ambrisentan), and anemia (bosentan and macitentan). **(*J Am Heart Assoc*. 2016;5: e003896 doi: 10.1161/JAHA.116.003896)**

Key Words: adverse drug event • endothelin • endothelin receptor antagonists • meta-analysis

Within 3 years of cloning of the 2 mammalian endothelin receptors, orally active endothelin receptor antagonists (ERAs) were tested in humans in the early 1990s, and the first clinical trial of ERA therapy for treating human disease was published in 1995. Four nonpeptide ERAs—bosentan, sitaxsentan, macitentan, and ambrisentan—that are either mixed endothelin ETA/ETB receptor antagonists or that display ETA selectivity have been developed for clinical use primarily in pulmonary arterial hypertension (PAH), a progressive disease without a cure.[1–3] To date, a number of published randomized double-blind placebo-controlled clinical trials have suggested that ERAs significantly improve exercise

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Accompanying Figures S1 through S5 are available at http://jaha.ahajournals.org/content/5/11/e003896/DC1/embed/inline-supplementary-material-1.pdf

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capacity, symptoms, cardiopulmonary hemodynamic variables, and slow clinical worsening.[4–8] Along with their widespread clinical use, the adverse effects of ERAs, such as elevation of liver transaminases, peripheral edema, anemia, and gastrointestinal reaction, were gradually reported.[4–8] Sitaxsentan, as the first selective ETA antagonist, has been authorized in the European Union since 2006 for the treatment of PAH and has been marketed in 16 European Union member states. Nevertheless, several reports of fatal liver injury with the use of sitaxsentan in PAH patients pushed Pfizer to withdraw the commercial drug from the market worldwide in 2010.[9] Bosentan, ambrisentan, and macitentan are the current ERAs, thus it is necessary to assess their safety in clinical patients.

Studies designed to address the clinical safety of ERAs are currently lacking, and the limited evidence is related to reported adverse events in clinical trials of ERAs. Most of these trials included relatively small samples, and each study individually had only a small number of adverse events. To enhance precision by combining the results of individual studies and producing a single major effect, we conducted a systematic review and meta-analysis of the adverse effects of ERAs.

Methods

Data Sources and Searches

We conducted this review according to the methods recommended by the Cochrane Collaboration and documented the process and results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews.[10,11] A systematic English-language search of the Medline, Embase, and Cochrane Library electronic databases and the ClinicalTrials.gov website was conducted to identify all potential eligible trials (up to October 2015). Key terms used for the systematic search were "endothelin receptor antagonists or bosentan or ambrisentan or macitentan" and "clinical trial or controlled clinical trial or randomized controlled trial." References of all pertinent articles were further scrutinized to ensure that all relevant studies were identified.

Study Selection

The following inclusion criteria for study selection were used: double-blind randomized controlled trials; human participants; patients with any types of disease; studies consisting of at least 1 group receiving bosentan, ambrisentan, or macitentan therapy; studies including only adults (aged >18 years); and studies reporting relevant adverse events for ERAs and placebo groups separately. For multiple publications of 1 randomized controlled trial, we included the publication most relevant to our inclusion criteria in terms of detailed reporting of adverse events.

Data Extraction and Quality Evaluation

Two reviewers (A.W. and Z.G.) examined the electronic searches and obtained full reports of all citations that were likely to meet the selection criteria. Adverse events that were not reported in the publications were further extracted from the registry and results database (ClinicalTrials.gov). Disagreements were resolved by consensus after discussion. The data extracted from each study contained the name of the first author, study design, study duration, study population characteristics (age, sex, and number of patients), treatment groups, comparison groups, duration of follow-up, and all reported adverse events. In addition, the GRADE approach was used to rate the quality of the included studies.[12] To assess the methodological quality of randomized trials, we determined how the randomization sequence was generated, how allocation was concealed, whether there were important imbalances at baseline, which groups were blinded (patients, caregivers, data collectors, outcome assessors, data analysts), what the rate of loss to follow-up was (in the intervention and control arms), whether the analyses were by intention to treat, and how studies dealt with missing outcome data. For each study, we also assessed how the population was selected, the duration and route of medication administration, the adequacy of study follow-up, and the funding source.

Assessment of Bias

We used the criteria described in the Cochrane Handbook of Systematic Reviews 5.1.0 to assess trial-level risk of bias in the included studies.[10] Two reviewers independently assessed studies for risk of bias. Any discrepancies were resolved by discussion and consensus. A graph of the risk of bias and a summary were generated. Funnel plots were generated to assess for publication bias.

Data Analysis

Statistical analyses were performed using RevMan 5.3 software (Nordic Cochrane Centre, The Cochrane Collaboration). Individual studies and meta-analysis estimates were derived and presented in forest plots.[13] Results are reported as risk ratios (RRs) with 95% CIs. Heterogeneity, defined as variation beyond chance, was evaluated through the I^2 test that measures the percentage of total variation between studies.[14] For each meta-analysis, the fixed-effects analysis was performed; however, when I^2 was >50%, high

heterogeneity was assumed, and the random-effects model was performed. $P<0.05$ indicated a statistically significant difference.

Subgroup and Sensitivity Analyses

Subgroup analyses were performed by dosage of bosentan (125, 250, and 500 mg twice daily), ambrisentan (2.5, 5.0, and 10.0 mg once daily), and macitentan (3.0 and 10.0 mg once daily). Another subanalysis of ERAs versus placebo was performed according to disease type (PAH and other diseases). In addition, we conducted sensitivity analyses using relative risk and different continuity correction factors to determine whether these choices of analysis methods affected the conclusions.

Results

Study Evaluation

Figure 1 shows the flow diagram of the selection process to determine eligible studies. A total of 1345 studies were searched using the aforementioned retrieval methods, and 24 studies meeting the inclusion criteria were ultimately screened. In total, 4894 patients were included, consisting of 3084 patients in the medication group and 1810 patients in the placebo group. The characteristics of the 24 included studies are outlined in Table 1. All data included in the meta-analysis were from randomized placebo-controlled clinical trials, and the participants, clinicians, and assessors were blinded. All but 1 trial (ASSET-1)[26] had low risk of attrition bias. On this basis, we considered the quality of the evidence to be high. A summary of the risks of bias in the included studies is shown in Figure 2.

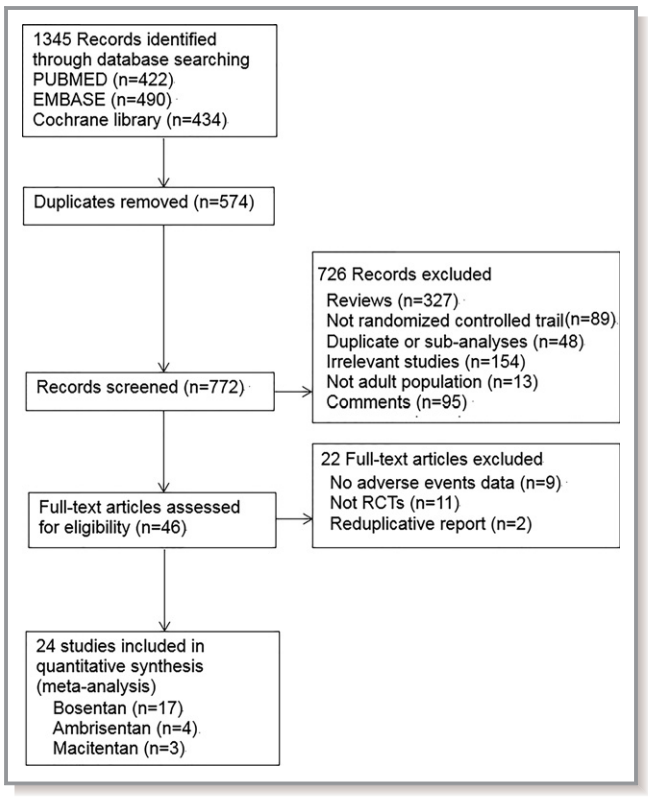

Figure 1. Flow diagram for the selection of eligible randomized controlled trials. RCT indicates randomized controlled trial.

Safety Analysis

All adverse events in the 24 trials were collected, and their absolute and relative frequencies in the treatment groups and the placebo groups were analyzed. The following adverse events were included for comparative analysis of tolerability and safety: blood and lymphatic system disorders (thrombocytopenia and anemia), cardiovascular disorders (cardiac failure, hypotension, and palpitation), gastrointestinal disorders (abdominal pain, gastroesophageal reflux disease, diarrhea, constipation, vomiting, and nausea), general disorders (peripheral edema, chest pain, fatigue, cough, and flushing), hepatobiliary disorders (abnormal liver function), infections (sinusitis, nasopharyngitis, respiratory tract infection, infected skin ulcer, pneumonia, and bronchitis), musculoskeletal and connective tissue disorders (pain in extremity, back pain, leg pain, myalgia, and arthralgia), nervous system disorders (headache, dizziness, and syncope), and respiratory disorders (dyspnea, hypoxemia, and respiratory failure). RRs with their corresponding 95% CIs are presented in Table 2, and heterogeneity analysis was carried out for each of the 34 adverse events selected. The most significant results of the data from meta-analyses are discussed next.

For abnormal liver function, defined as aspartate or alanine aminotransferase >3 times the upper limit of normal or treatment withdrawal due to elevated liver enzymes (Figure 3), the data showed a significantly higher risk with ERAs than placebo (7.91% versus 2.84%; RR 2.38, 95% CI 1.36–4.18, $P=0.002$). Further analyses comparing the 3 ERAs with placebo found that bosentan showed a significantly higher risk of abnormal liver function compared with placebo (12.30% versus 2.47%; RR 3.78, 95% CI 2.42–5.91, $P<0.0001$), whereas ambrisentan (0% versus 2.71%; RR 0.06, 95% CI 0.01–0.45, $P=0.007$) and macitentan (4.61% versus 3.95%; RR 1.17, 95% CI 0.42–3.31, $P=0.76$) did not show an increased risk compared with placebo.

The data showed a significantly higher risk of peripheral edema with ERAs compared with placebo (14.36% versus 9.68%; RR 1.44, 95% CI 1.20–1.74, $P=0.0001$) (Figure 4). Further analyses comparing the 3 ERAs with placebo found that both bosentan (10.3% versus 7.1%; RR 1.47, 95% CI

Table 1. Characteristics of Included Studies

Source	Design	Duration (Weeks)	Disease	Trial Group		Control Group	
				Treatment	n	Treatment	n
Krum et al, 1998[15]	RCT	4	Hypertension	Bosentan 100 mg/500 mg/ 1000 mg QD; 1000 mg BID	194	Placebo	99
Channick et al, 2001[16]	RCT	12	PAH	Bosentan 125 mg BID	21	Placebo	11
Rubin et al, 2002 (BREATHE-1)[5]	RCT	16	PAH	Bosentan 125 mg/250 mg BID	144	Placebo	69
Humbert et al, 2004 (BREATHE-2)[6]	RCT	16	PAH	Bosentan 125 mg BID	22	Placebo	11
Korn et al, 2004 (RAPIDS-1)[17]	RCT	16	SSc	Bosentan 125 mg BID	79	Placebo	43
Packer et al, 2005 (REACH-1)[18]	RCT	26	CHF	Bosentan 500 mg BID	244	Placebo	126
Galie et al, 2006 (BREATHE-5)[19]	RCT	16	PAH	Bosentan 125 mg BID	37	Placebo	17
Galie et al, 2008 (EARLY)[20]	RCT	24	PAH	Bosentan 125 mg BID	93	Placebo	92
Jaïs et al 2008 (BENEFIT)[21]	RCT	16	PAH	Bosentan 125 mg BID	77	Placebo	80
King et al, 2008 (BUILD-1)[22]	RCT	48	IPF	Bosentan 125 mg BID	74	Placebo	84
Stolz et al, 2008[23]	RCT	12	COPD	Bosentan 125 mg BID	20	Placebo	10
Seibold et al, 2010[24]	RCT	48	SSc	Bosentan 125 mg BID	71	Placebo	81
Kefford et al, 2010[25]	RCT	96	Metastatic melanoma	Bosentan 500 mg BID plus dacarbazine 1000 mg/m^2 every 3 weeks	38	Placebo plus dacarbazine 1000 mg/m^2 every 3 weeks	38
Barst et al, 2010 (ASSET-1, 2)[26]	RCT	16	PAH	Bosentan 125 mg BID	11	Placebo	15
Matucci-Cerinic et al, 2011 (RAPIDS-2)[27]	RCT	2	SSc	Bosentan 125 mg BID	96	Placebo	90
King et al, 2011 (BUILD-3)[28]	RCT	48	IPF	Bosentan 125 mg BID	406	Placebo	209
Corte et al, 2014 (BPHIT)[29]	RCT	16	PAH	Bosentan 125 mg BID	40	Placebo	20
Galie et al, 2008 (ARIES-1)[4]	RCT	12	PAH	Ambrisentan 5 mg/10 mg QD	134	Placebo	67
Galie et al, 2008 (ARIES-2)[4]	RCT	12	PAH	Ambrisentan 2.5 mg/5 mg QD	127	Placebo	65
Raghu et al, 2013 (ARTEMIS-IPF)[30]	RCT	48	IPF	Ambrisentan 10 mg QD	329	Placebo	163
ARTEMIS-PH[31]	RCT	56	PAH	Ambrisentan 10 mg QD	15	Placebo	25
Raghu et al, 2013 (MUSIC)[32]	RCT	52	IPF	Macitentan 10 mg QD	119	Placebo	59
Pulido et al, 2013 (SERAPHIN)[33]	RCT	26	PAH	Macitentan 3 mg/10 mg QD	492	Placebo	249
DUAL-1[34]	RCT	16	SSc	Macitentan 3 mg/10 mg QD	191	Placebo	97

CHF indicates chronic heart failure; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; PAH, pulmonary arterial hypertension; RCT, randomized controlled trial; SSc, systemic sclerosis.

1.06–2.03, P=0.02) and ambrisentan (20.8% versus 10.3%; RR 2.02, 95% CI 1.40–2.91, P=0.0002) showed a significantly higher risk of peripheral edema compared with placebo, whereas macitentan (14.7% versus 13.5%; RR 1.08; 95% CI 0.81–1.46, P=0.59) did not show an increased risk.

For anemia, defined as the absolute value of hemoglobin <120 g/L in women and <130 g/L in men[35] (Figure 5), the data showed a significantly higher risk with ERAs compared with placebo (6.23% versus 2.44%; RR 2.69, 95% CI 1.78–4.07, P<0.0001). Further analyses showed that bosentan (4.72% versus 2.01%; RR 3.09, 95% CI 1.52–6.30, P=0.002) and macitentan (9.98% versus 3.7%; RR 2.63, 95% CI 1.54–4.47, P=0.0004) showed a significantly higher risk compared with placebo, whereas ambrisentan did not show an increased risk of anemia (0.85% versus 0.56%; RR 1.30, 95% CI 0.20–8.48, P=0.78).

As shown in Figure S1, the data showed a significantly lower risk of cough with ERAs compared with placebo (11.67% versus 16.42%; RR 0.73, 95% CI 0.61–0.88, P=0.0009). Bosentan (12.61% versus 17.50%; RR 0.76, 95% CI 0.59–0.97, P=0.03) and macitentan (10.31% versus 16.56%; RR 0.62, 95% CI 0.44–0.87, P=0.005) showed a significantly lower risk of cough compared with placebo, whereas no significantly different of cough incidence was observed between ambrisentan and placebo groups (11.58% versus 12.92%; RR 0.90, 95% CI 0.56–1.45, P=0.66).

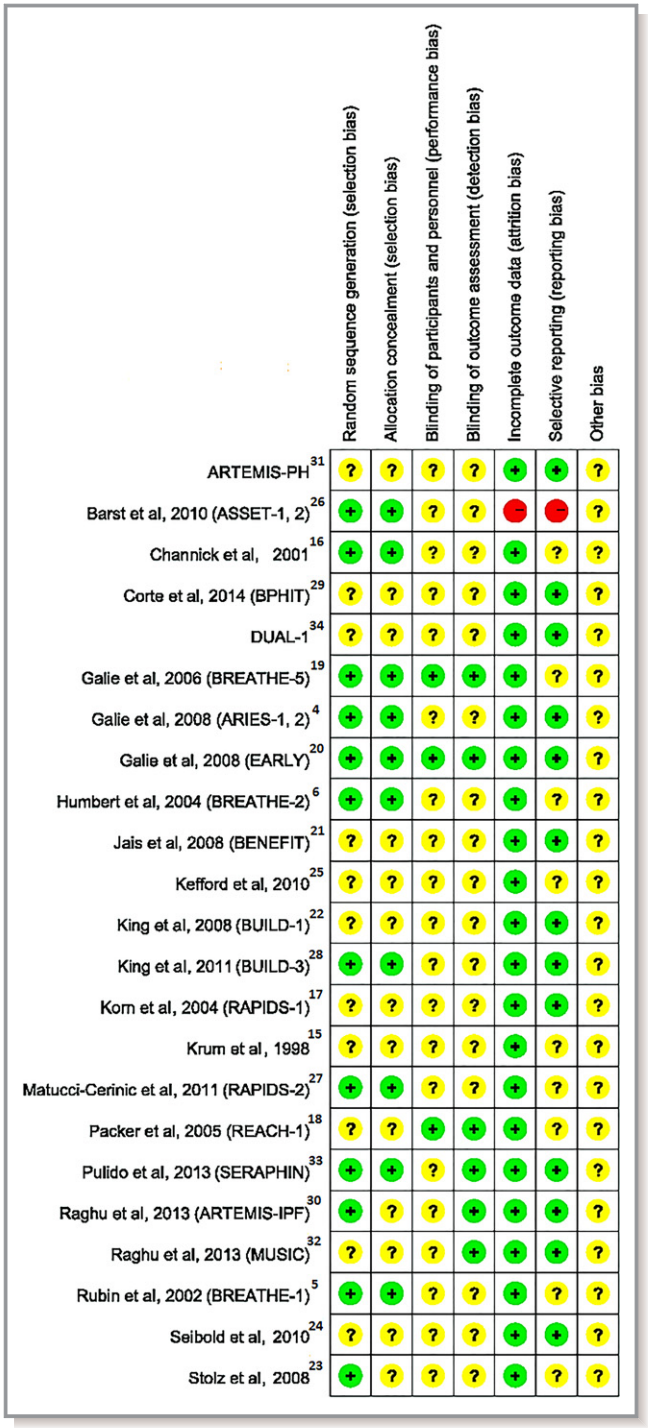

Figure 2. Risk of bias summary: review of authors' judgments about each risk of bias item for each included study. + indicates low risk; −, high risk; ?, unclear risk.

The data did not show a significantly higher risk of dyspnea with ERAs compared with placebo (11.66% versus 10.35%; RR 1.17, 95% CI 0.94–1.46, *P*=0.15) (Figure S2); however, further analyses comparing the 3 ERAs with placebo found that ambrisentan (12.36% versus 7.10%; RR 1.77, 95% CI 1.13–2.76, *P*=0.01) showed significantly higher risk compared with placebo. An increased risk of dyspnea was not observed for other ERA treatment.

As shown in Table 2, no statistical difference was found in the incidence of other known adverse events (ie, thrombocytopenia, cardiac failure, hypotension, palpitation, abdominal pain, gastroesophageal reflux disease, diarrhea, constipation, vomiting, nausea, chest pain, fatigue, flushing, sinusitis, nasopharyngitis, respiratory tract infection, infected skin ulcer, pneumonia, bronchitis, pain in extremity, back pain, leg pain, myalgia, arthralgia, headache, dizziness, syncope, hypoxemia and respiratory failure) between ERA and placebo groups.

Subgroup and Sensitivity Analyses

A sensitivity analysis was performed to assess the weight of each study in each meta-analysis. Sequentially dropping individual trials and then evaluating the overall outcomes failed to identify any individual trials as having influenced the results of the present meta-analysis to a significant extent (Tables 3–5). The results of sensitivity analyses were consistent with and suggested the same global results as each meta-analysis performed.

A subanalysis of drug dosage versus placebo was performed, and the results are shown in Table 6. Considering the risk of abnormal liver function, 3 subanalyses were carried out in the bosentan group (ie, for doses 125, 250, and 500 mg twice daily). All doses showed a significantly higher risk of abnormal liver function compared with placebo: The RRs were 4.71 (95% CI 3.04–7.32, *P*<0.00001) for 125 mg twice daily, 4.93 (95% CI 1.12–21.68, *P*=0.03) for 250 mg twice daily, and 3.76 (95% CI 1.64–8.12, *P*=0.002) for 500 mg twice daily. Interestingly, at dosages of 2.5 and 5.0 mg once daily, the ambrisentan group did not show a significant increase in risk of abnormal liver function compared with placebo. Nevertheless, the ambrisentan group at 10 mg once daily showed a significant decrease in the risk of abnormal liver function (RR 0.11, 95% CI 0.01–0.87, *P*=0.04). Neither dosage of macitentan significantly increased the risk of abnormal liver function compared with placebo. Regarding peripheral edema, a significantly increased risk was found in the bosentan group (RR 1.46, 95% CI 1.05–2.04, *P*=0.03) at the dosage of 125 mg twice daily. The subanalysis of the bosentan group receiving 500 mg twice daily showed considerable heterogeneity (there was only 1 study), even when the random-effects model was used (RR 1.67, 95% CI 0.43–6.49, *P*=0.46). The ambrisentan group at 10 mg once daily showed a significantly higher risk of peripheral edema than placebo (RR 2.40, 95% CI 1.64–3.52, *P*<0.00001). The same risk was not found for ambrisentan at dosages of 2.5 and 5.0 mg once daily, with RRs of 0.29 (95% CI 0.07–1.26, *P*=0.10) and 1.74 (95% CI 0.94–3.21, *P*=0.08),

Table 2. Relative Risk of Known Adverse Events Reported for ERAs in Comparison With Placebo

ADR Outcomes	Studies	Participants	RR (95% CI)	Incidence Rate (%)
Blood and lymphatic system disorder				
Thrombocytopenia	3	995	1.89 (0.74–4.83)	1.85
Anemia	11	2859	2.69 (1.78–4.07)	6.23
Cardiovascular disorders				
Cardiac failure	4	991	0.65 (0.48–0.88)	12.36
Hypotension	6	2684	0.97 (0.69–1.38)	4.44
Palpitation	8	1999	1.28 (0.77–2.14)	3.38
Gastrointestinal disorders				
Abdominal pain	7	1796	1.17 (0.55–2.52)	1.35
Gastroesophageal reflux disease	4	1080	0.55 (0.26–1.20)	1.81
Diarrhea	11	2711	0.90 (0.68–1.20)	6.94
Constipation	7	1301	1.36 (0.88–2.11)	6.82
Vomiting	6	1772	0.74 (0.48–1.13)	3.28
Nausea	11	3204	0.81 (0.64–1.03)	6.57
General disorders				
Peripheral edema	16	3853	1.44 (1.20–1.74)	14.36
Chest pain	8	2909	0.96 (0.71–1.31)	5.69
Fatigue	7	2476	0.98 (0.71–1.35)	6.22
Cough	10	2916	0.73 (0.61–0.88)	11.67
Flushing	8	1586	1.64 (0.97–2.79)	5.03
Hepatobiliary disorders				
Abnormal liver function	23	4854	2.38 (1.36–4.18)	7.91
Infections				
Sinusitis	8	2754	1.17 (0.78–1.75)	3.95
Nasopharyngitis	8	2560	1.15 (0.89–1.48)	10.01
Respiratory tract infection	11	3125	1.0 (0.85–1.19)	15.81
Infected skin ulcer	2	1029	0.82 (0.51–1.32)	5.27
Pneumonia	6	2354	0.94 (0.60–1.48)	3.20
Bronchitis	6	2354	0.98 (0.76–1.28)	9.35
Musculoskeletal and connective tissue disorders				
Pain in extremity	7	2001	0.77 (0.50–1.20)	3.10
Back pain	6	2354	0.71 (0.52–0.98)	5.38
Leg pain	2	155	0.87 (0.34–2.25)	9.90
Myalgia	2	525	1.16 (0.18–7.47)	0.85
Arthralgia	6	2130	0.99 (0.71–1.39)	6.36
Nervous system disorders				
Headache	17	4382	1.09 (0.93–1.29)	13.35
Dizziness	11	3312	1.03 (0.82–1.30)	9.20
Syncope	6	2155	0.80 (0.52–1.23)	3.49
Respiratory disorders				
Dyspnea	12	3061	1.17 (0.94–1.46)	11.66
Hypoxemia	5	2066	1.01 (0.37–2.77)	0.66
Respiratory failure	6	1667	1.84 (0.78–4.34)	1.99

ADR indicates adverse drug reaction; ERA, endothelin receptor antagonists; RR, risk ratio.

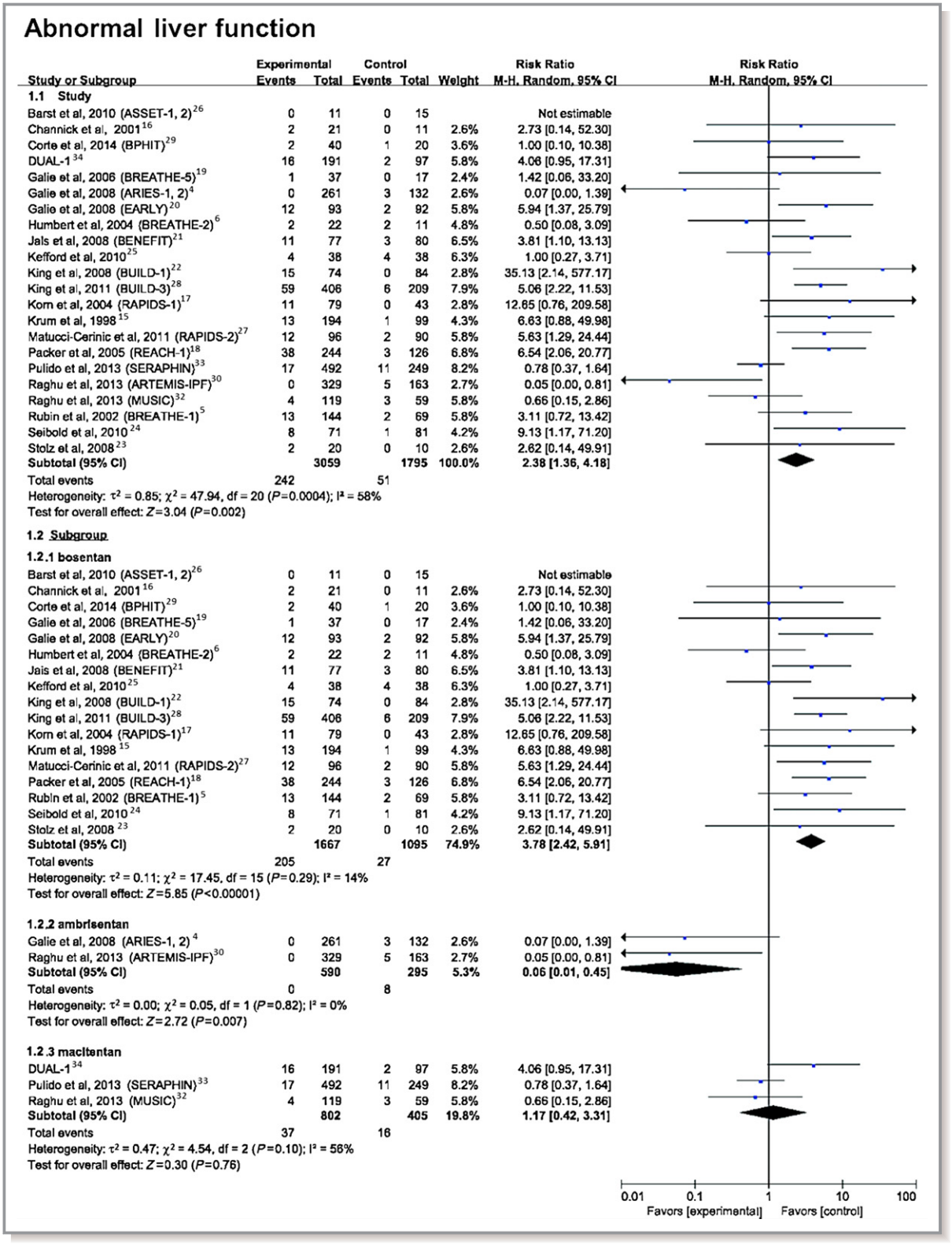

Figure 3. Forest plot with meta-analysis of the risk of abnormal liver function. Risk ratios and 95% CIs for the risk of abnormal liver function with endothelin receptor antagonist treatment. The size of data markers indicates the weight of each trial.

respectively. No difference was found in the macitentan group with dosages of 3 and 10 mg once daily. A significantly increased risk of anemia was found in bosentan group at 500 mg twice daily (RR 6.57, 95% CI 2.11–20.43, *P*=0.001) but not at 125 mg twice daily (RR 0.99, 95% CI 0.38–2.63, *P*=0.99). Because of considerable heterogeneity, the random-

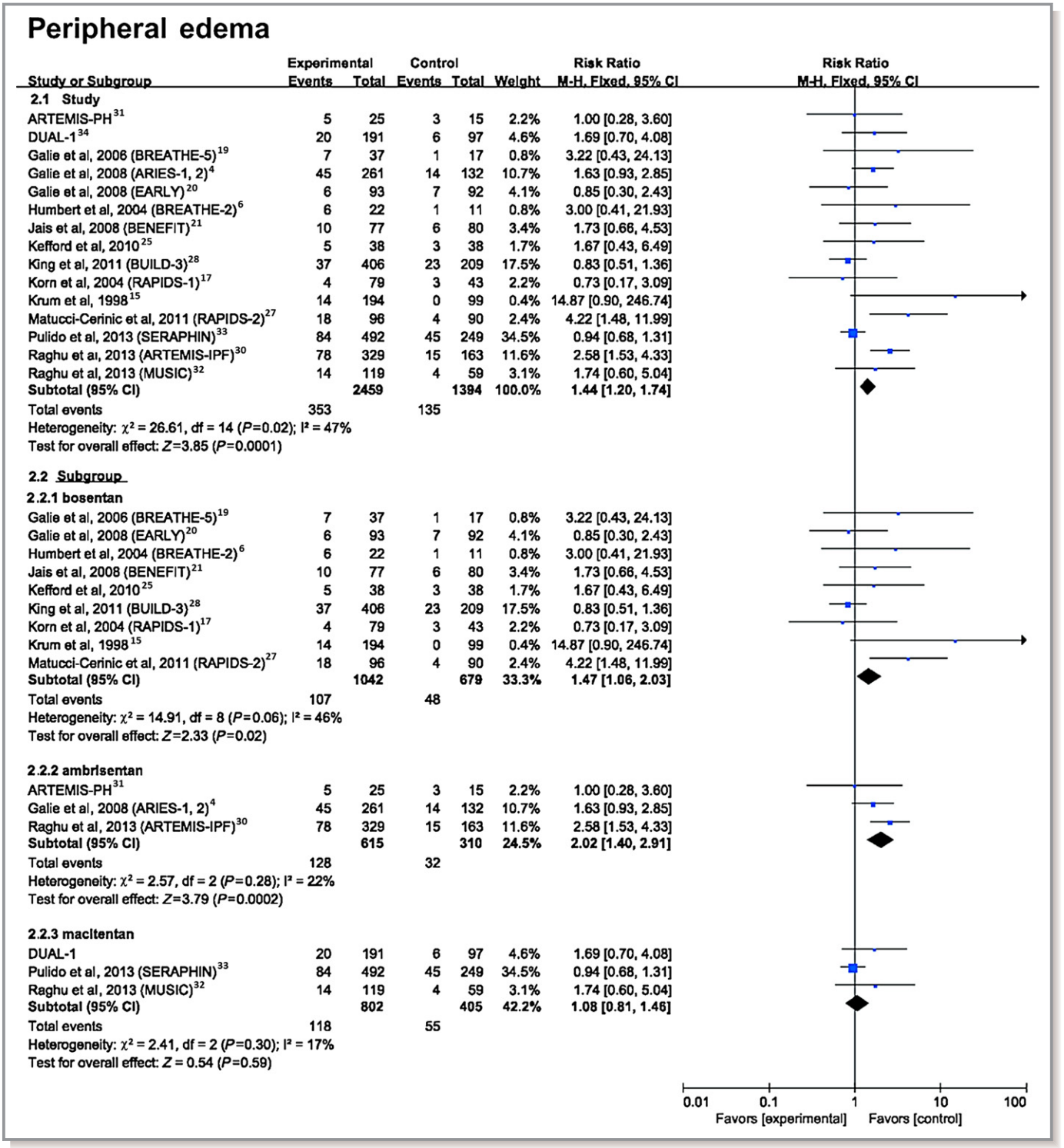

Figure 4. Forest plot with meta-analysis of the risk of peripheral edema. Risk ratios and 95% CIs for the risk of peripheral edema with endothelin receptor antagonist treatment. The size of data markers indicates the weight of each trial.

effects model was used to evaluate the different doses of macitentan, with RRs of 1.51 (95% CI 0.42–5.44, *P*=0.53) for the group treated with 3 mg once daily and 2.87 (95% CI 0.88–9.32, *P*=0.08) for the group treated with 10 mg once daily.

A subanalysis of ERAs versus placebo according to disease type was also performed, and the results are shown in Table 7. Considering the common usage of ERAs, 2 subanalyses including PAH and other diseases were carried out in 3 ERA groups. Regardless of disease type, bosentan

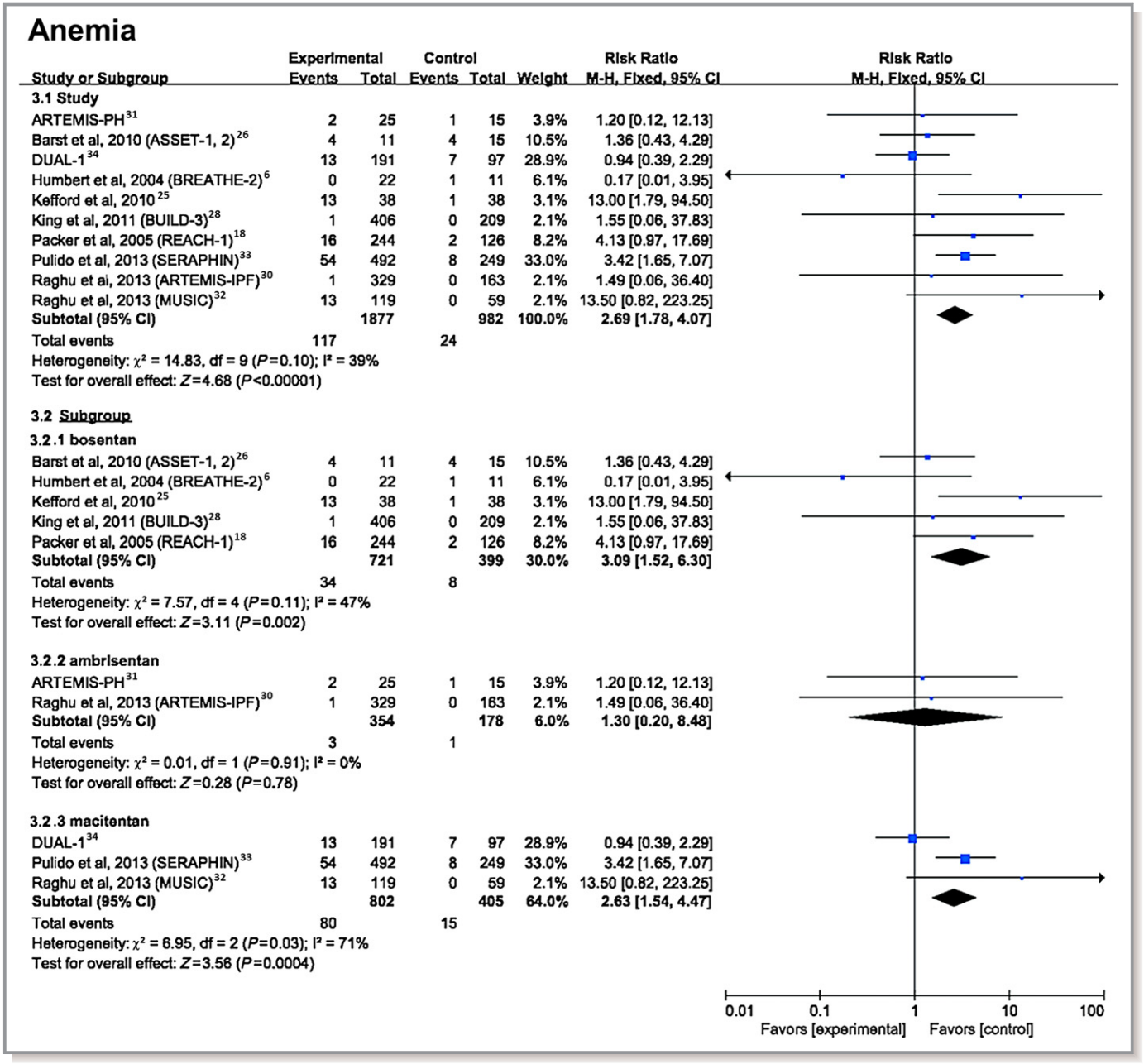

Figure 5. Forest plot with meta-analysis for the risk of anemia. Risk ratios and 95% CIs for the risk of anemia with endothelin receptor antagonist treatment. The size of data markers indicates the weight of each trial.

showed a significantly higher risk of abnormal liver function compared with placebo: The RRs were 2.85 (95% CI 1.52–5.33, P=0.001) in PAH and 5.70 (95% CI 3.54–9.18, P<0.00001) in other diseases. Ambrisentan did not significantly alter the risk of abnormal liver function in PAH (RR 0.07, 95% CI 0.00–1.39, P=0.08) but significantly decreased the risk of abnormal liver function in other diseases (RR 0.05, 95% CI 0.00–0.81, P=0.04). Macitentan did not alter the risk of abnormal liver function in either PAH (RR 0.78, 95% CI 0.37–1.64, P=0.52) or other diseases (RR 1.64, 95% CI 0.27–10.16, P=0.59).

Publication Bias

Visual inspection of funnel plots for the analyses showed moderate symmetry, providing little evidence of publication bias (Figure 6).

Discussion

To the best of our knowledge, this systematic review is the first to pool current evidence for evaluation of all known adverse events of ERAs. Because sitaxsentan was withdrawn

Table 3. Sensitivity Analysis With Meta-Analysis of the Risk of Abnormal Liver Function

Study Omitted	RR	95% CI
Barst et al, 2010 (ASSET-1, 2)[26]	2.38	1.36–4.17
Channick et al, 2001[16]	2.37	1.33–4.22
Corte et al, 2014 (BPHIT)[29]	2.46	1.38–4.38
Galie et al, 2006 (BREATHE-5)[19]	2.41	1.35–4.28
Galie et al, 2008 (EARLY)[20]	2.25	1.25–4.03
Humbert et al, 2004 (BREATHE-2)[6]	2.58	1.46–4.55
Jaïs et al, 2008 (BENEFIT)[21]	2.30	1.26–4.17
Kefford et al, 2010[25]	2.52	1.40–4.53
King et al, 2008 (BUILD-1)[22]	2.21	1.27–3.84
King et al, 2011 (BUILD-3)[28]	2.23	1.23–4.04
Korn et al, 2004 (RAPIDS-1)[17]	2.27	1.28–4.00
Krum et al, 1998[15]	2.27	1.27–4.05
Matucci-Cerinic et al, 2011 (RAPIDS-2)[27]	2.26	1.25–4.05
Packer et al, 2005 (REACH-1)[18]	2.21	1.23–3.96
Rubin et al, 2002 (BREATHE-1)[5]	2.34	1.29–4.23
Seibold et al, 2010[24]	2.24	1.26–3.98
Stolz et al, 2008[23]	2.37	1.33–4.22
Galie et al, 2008 (ARIES-1, 2)[4]	2.61	1.51–4.51
Raghu et al, 2013 (ARTEMIS-IPF)[30]	2.65	1.55–4.54
DUAL-1[34]	2.30	1.27–4.15
Pulido et al, 2013 (SERAPHIN)[33]	2.67	1.54–4.62
Raghu et al, 2013 (MUSIC)[32]	2.58	1.45–4.57

RR indicates risk ratio.

from global markets, bosentan, macitentan, and ambrisentan were included in our analysis, and their adverse event data were extracted from randomized controlled trials. Compared with placebo, the incidence of abnormal liver function, peripheral edema, and anemia were significantly higher in the ERA group. The incidence of cough was significantly lower compared with placebo (Figure S1). Although the incidence of some adverse events described in the package inserts of ERAs were high in the ERA group (ie, dyspnea, nasopharyngitis, respiratory tract infection and headache) (Table 2, Figures S2–S5), no difference was observed in the incidence of these adverse events between ERA and placebo groups.

Abnormal Liver Function

An important finding of the present meta-analysis was that participants receiving ERAs had a higher adverse event rate of abnormal liver function than those given placebo. Further subanalyses of different ERAs found that bosentan significantly increased the risk of elevated liver transaminases,

Table 4. Sensitivity Analysis With Meta-Analysis of the Risk of Peripheral Edema

Study Omitted	RR	95% CI
Galie et al, 2006 (BREATHE-5)[19]	1.42	1.18–1.72
Galie et al, 2008 (EARLY)[20]	1.46	1.21–1.77
Humbert et al, 2004 (BREATHE-2)[6]	1.42	1.18–1.72
Jaïs et al, 2008 (BENEFIT)[21]	1.43	1.18–1.73
Kefford et al, 2010[25]	1.43	1.19–1.73
King et al, 2011 (BUILD-3)[28]	1.57	1.28–1.92
Korn et al, 2004 (RAPIDS-1)[17]	1.45	1.20–1.75
Krum et al, 1998[15]	1.39	1.15–1.67
Matucci-Cerinic et al, 2011 (RAPIDS-2)[27]	1.37	1.13–1.66
ARTEMIS-PH[31]	1.45	1.20–1.75
Galie et al, 2008 (ARIES-1, 2)[4]	1.41	1.16–1.72
Raghu et al, 2013 (ARTEMIS-IPF)[30]	1.29	1.05–1.58
DUAL-1[34]	1.42	1.18–1.72
Pulido et al, 2013 (SERAPHIN)[33]	1.70	1.35–2.13
Raghu et al, 2013 (MUSIC)[32]	1.43	1.18–1.73

RR indicates risk ratio.

whereas ambrisentan significantly decreased the risk of abnormal liver function. No significant difference was noted in comparisons of macitentan and placebo.

The exact mechanism of ERA-induced hepatotoxicity is not fully understood. Previous studies showed that it was likely to involve modulation of various hepatobiliary transporters, affinity for the ETB receptor, or specific hepatic metabolic and clearance pathways.[36] In in vitro studies using sandwich-cultured hepatocytes, bosentan has been shown to inhibit both basolateral sodium-taurocholate cotransporting

Table 5. Sensitivity Analysis With Meta-Analysis of the Risk of Anemia

Study Omitted	RR	95% CI
Barst et al, 2010 (ASSET-1, 2)[26]	2.84	1.83–4.41
Humbert et al, 2004 (BREATHE-2)[6]	2.85	1.86–4.36
Kefford et al, 2010[25]	2.35	1.53–3.63
King et al, 2011 (BUILD-3)[28]	2.71	1.78–4.12
Packer et al, 2005 (REACH-1)[18]	2.55	1.66–3.94
ARTEMIS-PH[31]	2.74	1.80–4.19
Raghu et al, 2013 (ARTEMIS-IPF)[30]	2.71	1.78–4.12
DUAL-1[34]	3.39	2.09–5.50
Pulido et al, 2013 (SERAPHIN)[33]	2.32	1.40–3.85
Raghu et al, 2013 (MUSIC)[32]	2.45	1.61–3.74

RR indicates risk ratio.

Table 6. Subgroup Analysis of ERAs Versus Placebo by Dosage

Subgroups (Doses)	Studies	Participants	RR (95% CI)	*P* Value
Abnormal liver function				
Bosentan (total)	17	2762	3.78 (2.42–5.91)	<0.00001
Bosentan (125 mg BID)	14	1953	4.71 (3.04–7.32)	<0.00001
Bosentan (250 mg BID)	1	139	4.93 (1.12–21.68)	0.03
Bosentan (500 mg BID)	2	446	3.76 (1.64–8.62)	0.002
Ambrisentan (total)	3	885	0.06 (0.01–0.45)	0.007
Ambrisentan (2.5 mg QD)	1	196	0.29 (0.02–5.58)	0.41
Ambrisentan (5.0 mg QD)	1	262	0.15 (0.01–2.78)	0.20
Ambrisentan (10.0 mg QD)	2	691	0.11 (0.01–0.87)	0.04
Macitentan (total)	3	1207	1.17 (0.42–3.31)	0.76
Macitentan (3.0 mg QD)	2	690	1.08 (0.52–2.27)	0.83
Macitentan (10.0 mg QD)	3	863	1.29 (0.69–2.40)	0.42
Peripheral edema				
Bosentan (total)	9	1721	1.47 (1.06–2.03)	0.02
Bosentan (125 mg BID)	8	1645	1.46 (1.05–2.04)	0.03
Bosentan (500 mg BID)	1	76	1.67 (0.43–6.49)	0.46
Ambrisentan (total)	4	925	2.02 (1.40–2.91)	0.0002
Ambrisentan (2.5 mg QD)	1	196	0.29 (0.07–1.26)	0.10
Ambrisentan (5.0 mg QD)	1	262	1.74 (0.94–3.21)	0.08
Ambrisentan (10.0 mg QD)	3	731	2.40 (1.64–3.52)	<0.00001
Macitentan (total)	3	1207	1.08 (0.81–1.46)	0.59
Macitentan (3.0 mg QD)	2	690	0.92 (0.64–1.33)	0.66
Macitentan (10.0 mg QD)	3	863	1.20 (0.86–1.67)	0.27
Anemia				
Bosentan (total)	5	1120	3.09 (1.52–6.30)	0.002
Bosentan (125 mg BID)	3	674	0.99 (0.38–2.63)	0.99
Bosentan (500 mg BID)	2	446	6.57 (2.11–20.43)	0.001
Macitentan (total)	3	1207	2.63 (1.54–4.47)	0.0004
Macitentan (3.0 mg QD)	2	690	1.51 (0.42–5.44)	0.53
Macitentan (10.0 mg QD)	3	863	2.87 (0.88–9.32)	0.08

ERA indicates endothelin receptor antagonist; RR, risk ratio.

polypeptide and organic anion transporting polypeptides as well as the bile salt export pump and the multidrug resistance–associated protein 2, the net effect of which can lead to accumulation of cytotoxic bile acids.[37–39] Furthermore, bosentan, as a dual ERA that competitively binds the ETA receptor with 20 times more affinity than the ETB receptor, is metabolized by cytochrome P450 isoenzymes CYP2C9 and CYP3A4 in the liver and is excreted almost entirely into the bile.[40] The postmarketing surveillance database of 4623 patients receiving bosentan (TRAX-PMS) showed that 7.6% of patients experienced elevated aminotransferases, which was concordant with the present meta-analysis. The severity of liver enzyme elevation was most commonly between 3 and 5 times the upper limit of normal, and there were no cases of fatal liver injury related to bosentan use in TRAX-PMS.[41]

In contrast, ambrisentan had weak inhibition of the bile salt export pump, which may partially explain the relatively low risk of hepatotoxicity.[39] Ambrisentan, as a selective ERA that competitively binds the ETA receptor with 260 times more affinity than the ETB receptor, is metabolized by glucuronidation via the uridine 5′-diphosphate glucuronosyltransferases and, to a lesser extent, by oxidation via CYP3A and CYP2C19 before excretion almost entirely into the bile.[42] Our meta-

Table 7. Subgroup Analysis of ERA Versus Placebo by Diagnosis

Subgroups (Diagnosis)	Studies	Participants	RR (95% CI)	*P* Value
Abnormal liver function				
Bosentan (total)	17	2762	3.78 (2.42–5.91)	<0.00001
Bosentan (PAH)	8	760	2.85 (1.52–5.33)	0.001
Bosentan (others)	9	2002	5.70 (3.54–9.18)	<0.00001
Ambrisentan (total)	3	885	0.06 (0.01–0.45)	0.007
Ambrisentan (PAH)	2	393	0.07 (0.00–1.39)	0.08
Ambrisentan (others)	1	492	0.05 (0.00–0.81)	0.04
Macitentan (total)	3	1207	1.17 (0.42–3.31)	0.76
Macitentan (PAH)	1	741	0.78 (0.37–1.64)	0.52
Macitentan (others)	2	466	1.64 (0.27–10.16)	0.59
Peripheral edema				
Bosentan (total)	9	1721	1.47 (1.06–2.03)	0.02
Bosentan (PAH)	4	429	1.57 (0.85–2.92)	0.15
Bosentan (others)	5	1292	1.43 (0.98–2.09)	0.06
Ambrisentan (total)	4	925	2.02 (1.40–2.91)	0.0002
Ambrisentan (PAH)	3	433	1.52 (0.91–2.54)	0.11
Ambrisentan (others)	1	492	2.58 (1.53–4.33)	0.0004
Macitentan (total)	3	1207	1.08 (0.81–1.46)	0.59
Macitentan (PAH)	1	741	0.94 (0.68–1.31)	0.73
Macitentan (others)	2	466	1.71 (0.87–3.37)	0.12
Anemia				
Bosentan (total)	5	1120	3.09 (1.52–6.30)	0.002
Bosentan (PAH)	2	59	0.93 (0.34–2.54)	0.88
Bosentan (others)	3	1061	5.80 (2.02–16.63)	0.001
Ambrisentan (total)	2	532	1.30 (0.20–8.48)	0.78
Ambrisentan (PAH)	1	40	1.20 (0.12–12.13)	0.88
Ambrisentan (others)	1	492	1.49 (0.06–36.40)	0.81
Macitentan (total)	3	1207	2.63 (1.54–4.47)	0.0004
Macitentan (PAH)	1	741	3.42 (1.65–7.07)	0.0009
Macitentan (others)	2	466	2.72 (0.15–48.16)	0.50

Others include the diagnosis of chronic obstructive pulmonary disease, chronic heart failure, idiopathic pulmonary fibrosis, systemic sclerosis, or HFpEF. ERA indicates endothelin receptor antagonists; HFpEF, heart failure with preserved ejection fraction; PAH, pulmonary arterial hypertension; RR, risk ratio.

analysis showed that the incidence of abnormal liver function in patients receiving ambrisentan was lower than that for placebo. No abnormal liver function occurred in patients treated with ambrisentan in all inclusive study (ARIES-1, ARIES-2, and ARTEMIS-IPF). Subanalyses of different dosages found that ambrisentan at the regular therapeutic dosage (10 mg once daily) had a lower risk of abnormal liver function than placebo. In ARIES-1 and ARIES-2, the incidence of abnormal liver function was 0% in the ambrisentan 10 mg group and 2.3% in the placebo group. In ARTEMIS-IPF, the incidence of abnormal liver function was 0% in the ambrisentan 10 mg group and 3.1% in the placebo group. Interestingly, in an open-label, phase II study of ambrisentan, 36 patients with PAH who had discontinued either bosentan or sitaxsentan due to liver transaminitis were given ambrisentan (Initial: 2.5 mg or 5 mg once daily; at 4-week intervals, as tolerated and necessary, may increase the dose to 10 mg once daily), and no cases of elevated aminotransferase levels were ultimately reported at 12 weeks of follow-up.[43] Moreover, the results of post-marketing surveillance report from Letairis Education and Access Program showed that only 0.72% of patients receiving ambrisentan developed a

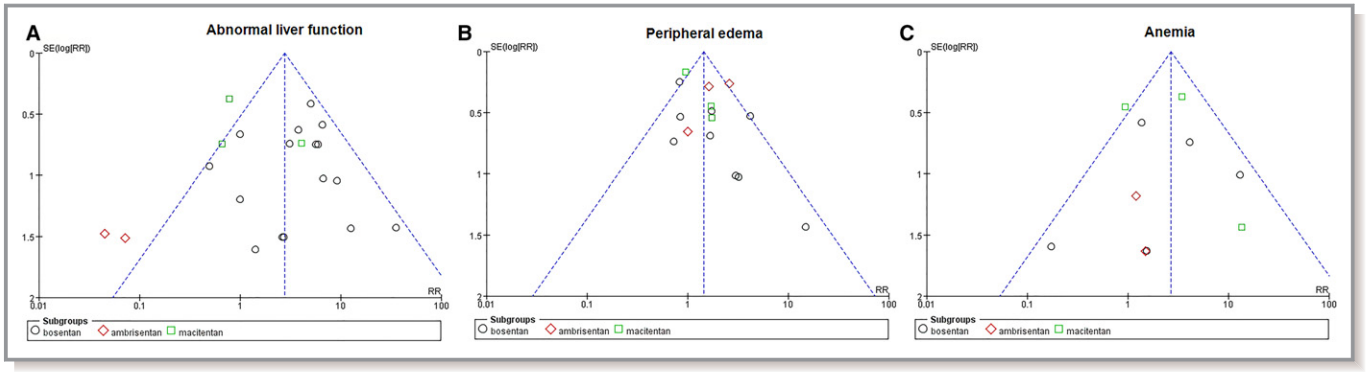

Figure 6. Funnel plot to assess publication bias. Funnel plot of studies included in the meta-analysis of the risk of (A) abnormal liver function, (B) peripheral edema, and (C) anemia. RR indicates risk ratio.

significant hepatic event.[44] Based on data from the literature and findings from our meta-analysis, we thought that ambrisentan had little hepatotoxicity and even showed a protective effect on liver function at the regular therapeutic dosage of 10 mg. Note that the US Food and Drug Administration removed the liver warning from ambrisentan in 2011, which is consistent with our finding.[45]

Interestingly, our data showed that despite their similar chemical structures and affinity for the ETB receptor,[46] macitentan did not appear to have the same hepatotoxicity as bosentan. In vitro, macitentan is a more potent inhibitor of sodium-taurocholate cotransporting polypeptide, organic anion transporting polypeptides, and the bile salt export pump than bosentan,[39] thus further effort is necessary to explore the exact mechanism of ERA-induced hepatotoxicity.

In summary, the current evidence demonstrated that macitentan and ambrisentan conferred a relatively low risk of hepatotoxicity compared with bosentan. Patients on bosentan should undergo more hepatic monitoring in the clinical setting.

Peripheral Edema

Peripheral edema, an important indicator of fluid retention in patients, is a known side effect of ERAs and a clinical consequence of PAH and its worsening.[47] In the present study, there was a significantly higher risk of peripheral edema in the ERA group compared with the placebo group.

Further comparison of the 3 ERAs with placebo showed that bosentan and ambrisentan had significantly higher incidence of peripheral edema, but no significant difference was found in the macitentan group. Peripheral edema was a reported adverse effect of bosentan in 9 RCTs.[6,15,17,19–21,25,27,28] In our further analysis, however, bosentan-mediated peripheral edema did not appear to be a dose-related effect. In the 3 trials conducted on ambrisentan, the incidence of peripheral edema was significantly higher in the treatment groups than in the placebo groups and was usually mild to moderate in severity. Further analysis showed that patients receiving ambrisentan at 10 mg once daily had a significantly higher risk of peripheral edema compared with those receiving placebo. The postmarketing reports in PAH patients showed that peripheral edema commonly occurred within weeks after starting ambrisentan. In addition, a previous study indicated that ambrisentan-induced peripheral edema occurred with greater frequency and severity in elderly patients; 29% of patients aged >65 years developed peripheral edema in the treatment group compared with 4% in the placebo group.[48] Consequently, as the most frequently reported adverse effect of ambrisentan, peripheral edema warrants attention at the clinic. Macitentan, unlike ambrisentan, showed a relatively low risk of peripheral edema.[32–34] The SERAPHIN trial reported that the incidence of peripheral edema was 16% in the macitentan 3 mg group, 18.2% in the macitentan 10 mg group, and 18.1% in the placebo group.[33]

A previous study demonstrated that ERAs caused fluid retention by blocking natriuresis and diuresis mediated by the ETB receptors[49] and possibly by the ETA receptors in the renal collecting ducts.[50] Additional mechanisms, including unopposed precapillary arteriolar vasodilation and changes in capillary permeability, might account for the fluid retention induced by ERAs.[48] In a recent post hoc subgroup analysis, a reduction of brain natriuretic peptide ($P<0.001$) occurred in patients on ambrisentan and with edema compared with the placebo group.[48] This finding suggests that in the ambrisentan population, the mechanism for the presence of peripheral edema is unlikely to be cardiac dysfunction.

Anemia and Other Adverse Events

With respect to anemia, the present meta-analysis showed a significant increase in the bosentan and macitentan groups, but the difference was not statistically significant between the ambrisentan and placebo groups. Although bosentan-

associated anemia was reported in 5 RCTs,[6,18,25,26,28] it was generally mild, remained stable throughout treatment, and did not warrant treatment discontinuation. The ASSET-1 trial reported that the decrease in hemoglobin was greater with bosentan than placebo.[26] A >15% reduction in hemoglobin to an absolute value of <110 g/L occurred in 67% of treated patients but never necessitated discontinuation of bosentan.[26] Consequently, it is currently recommended that hemoglobin levels be monitored every 3 months for the duration of bosentan therapy.[51] Similarly, the data on macitentan derived from 3 trials showing higher incidence of anemia in the treatment group than the placebo group. In the SERAPHIN trial, the incidence of anemia in the 3 mg macitentan once daily, 10 mg macitentan once daily, and placebo groups was 8.8%, 13.2%, and 3.2%, respectively, which reflects a dose-dependent effect of macitentan treatment.[33] Interestingly, our study showed that ambrisentan was not associated with a relatively higher risk of reduction in hemoglobin concentration compared with placebo. Although in the ARIES-1 and ARIES-2 trials, hemoglobin concentrations decreased from baseline to week 12 by a mean of 0.84 g/dL (±1.2 g/dL) in patients treated with ambrisentan, the change in hemoglobin concentration was fairly stable during treatment.[1] The mechanism by which anemia develops during ERAs therapy is unclear; however, it is thought to be partly secondary to increased fluid retention.[52]

Cough is a known adverse event described in the package insert of ERAs. Interestingly, although the reported incidence of cough was >10% in patients receiving bosentan (12.61%), macitentan (10.31%), and ambrisentan (11.58%), the overall pooled results showed a significantly lower risk of cough in ERAs compared with placebo. In addition, both bosentan and macitentan had a significantly lower risk of cough compared with placebo.

There were no significant differences between ERA and placebo groups for other known adverse events reported for ERAs.

Limitations

Several important limitations of our study should be taken into account to place its findings in the proper context. First, the observation time of the clinical trials included in our meta-analysis was inconsistent, from 4 to 96 weeks, which might influence our results. Second, the evaluation criteria of different research centers for adverse events was variable. Third, publication and reporting biases may affect the results; therefore, further design of randomized controlled trials on evaluation of ERA safety and a long-term observation study based on real-world experience are necessary.

In conclusion, our meta-analysis showed that hepatic transaminitis, peripheral edema, and anemia are the main adverse effects among those reported for ERAs. Ambrisentan was associated with higher risk of peripheral edema; macitentan conferred a higher risk of anemia; and bosentan increased a patient's risk of liver transaminitis, peripheral edema, and anemia. The latter results indicate that different monitoring parameters should be considered for different ERAs.

Author Contributions

Pu is the guarantor of the entire manuscript. Pu contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. Wei contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. Gu contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. Li contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. Liu contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. Wu contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. Han contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published.

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Disclosures

None.

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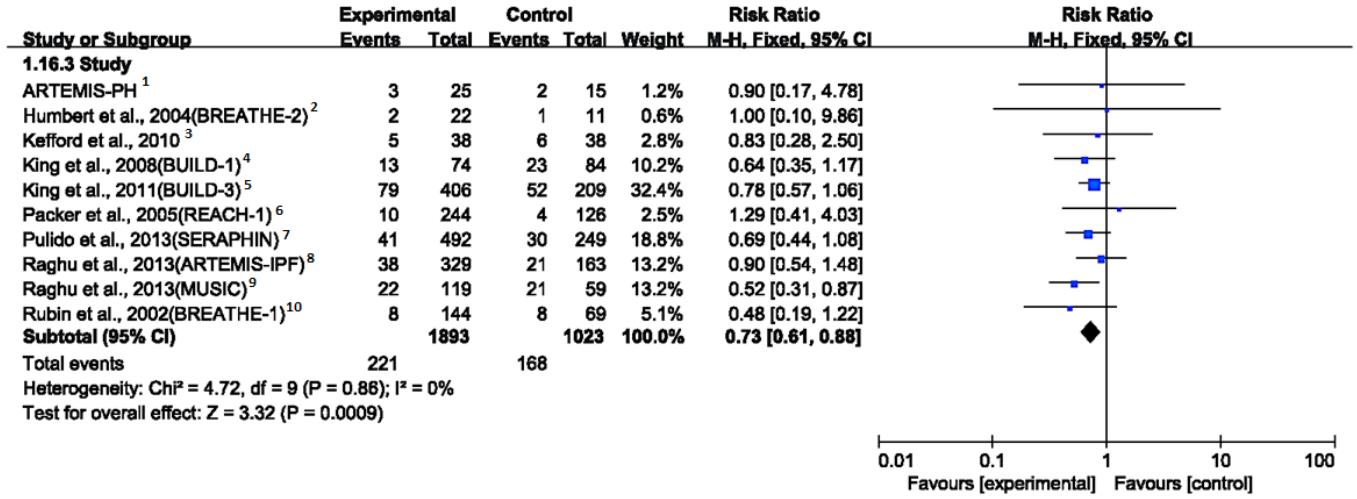
SUPPLEMENTAL MATERIAL

Figure S1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Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.16.3 Study
ARTEMIS-PH [1] 3 25 2 15 1.2% 0.90 [0.17, 4.78]
Humbert et al., 2004(BREATHE-2) [2] 2 22 1 11 0.6% 1.00 [0.10, 9.86]
Kefford et al., 2010 [3] 5 38 6 38 2.8% 0.83 [0.28, 2.50]
King et al., 2008(BUILD-1) [4] 13 74 23 84 10.2% 0.64 [0.35, 1.17]
King et al., 2011(BUILD-3) [5] 79 406 52 209 32.4% 0.78 [0.57, 1.06]
Packer et al., 2005(REACH-1) [6] 10 244 4 126 2.5% 1.29 [0.41, 4.03]
Pulido et al., 2013(SERAPHIN) [7] 41 492 30 249 18.8% 0.69 [0.44, 1.08]
Raghu et al., 2013(ARTEMIS-IPF) [8] 38 329 21 163 13.2% 0.90 [0.54, 1.48]
Raghu et al., 2013(MUSIC) [9] 22 119 21 59 13.2% 0.52 [0.31, 0.87]
Rubin et al., 2002(BREATHE-1) [10] 8 144 8 69 5.1% 0.48 [0.19, 1.22]
Subtotal (95% CI) 1893 1023 100.0% 0.73 [0.61, 0.88]
Total events 221 168
Heterogeneity: Chi² = 4.72, df = 9 (P = 0.86); I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

Figure S2

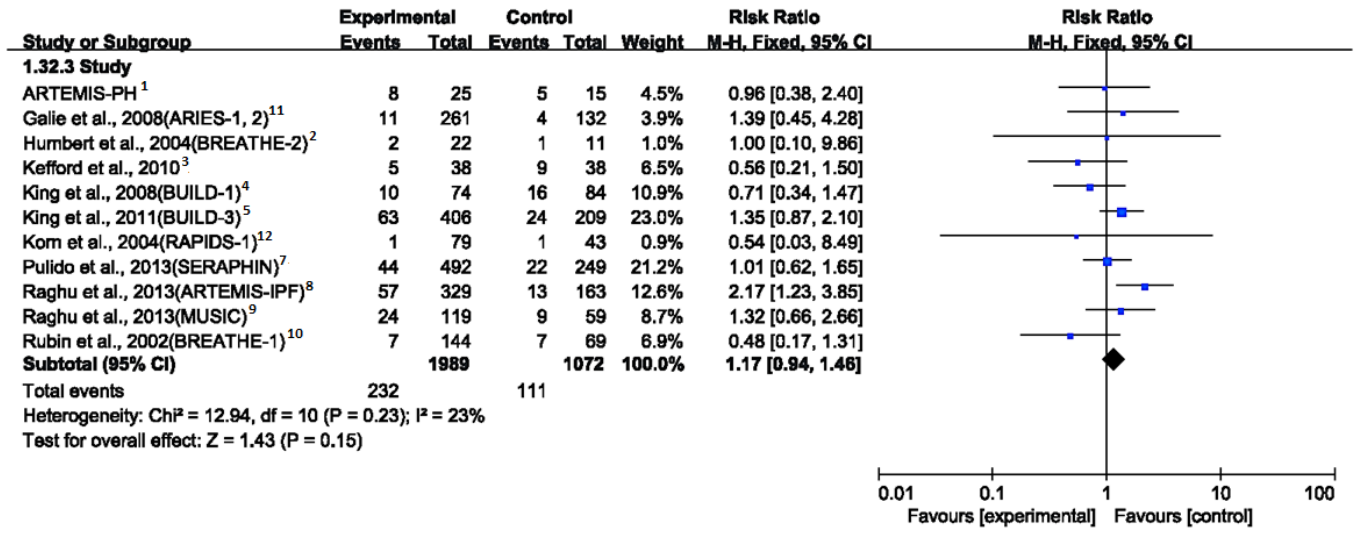
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.32.3 Study
ARTEMIS-PH [1] 8 25 5 15 4.5% 0.96 [0.38, 2.40]
Galie et al., 2008(ARIES-1, 2)[11] 11 261 4 132 3.9% 1.39 [0.45, 4.28]
Humbert et al., 2004(BREATHE-2)[2] 2 22 1 11 1.0% 1.00 [0.10, 9.86]
Kefford et al., 2010[3] 5 38 9 38 6.5% 0.56 [0.21, 1.50]
King et al., 2008(BUILD-1)[4] 10 74 16 84 10.9% 0.71 [0.34, 1.47]
King et al., 2011(BUILD-3)[5] 63 406 24 209 23.0% 1.35 [0.87, 2.10]
Korn et al., 2004(RAPIDS-1)[12] 1 79 1 43 0.9% 0.54 [0.03, 8.49]
Pulido et al., 2013(SERAPHIN)[7] 44 492 22 249 21.2% 1.01 [0.62, 1.65]
Raghu et al., 2013(ARTEMIS-IPF)[8] 57 329 13 163 12.6% 2.17 [1.23, 3.85]
Raghu et al., 2013(MUSIC)[9] 24 119 9 59 8.7% 1.32 [0.66, 2.66]
Rubin et al., 2002(BREATHE-1)[10] 7 144 7 69 6.9% 0.48 [0.17, 1.31]
Subtotal (95% CI) 1989 1072 100.0% 1.17 [0.94, 1.46]
Total events 232 111
Heterogeneity: Chi² = 12.94, df = 10 (P = 0.23); I² = 23%
Test for overall effect: Z = 1.43 (P = 0.15)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

Figure S3

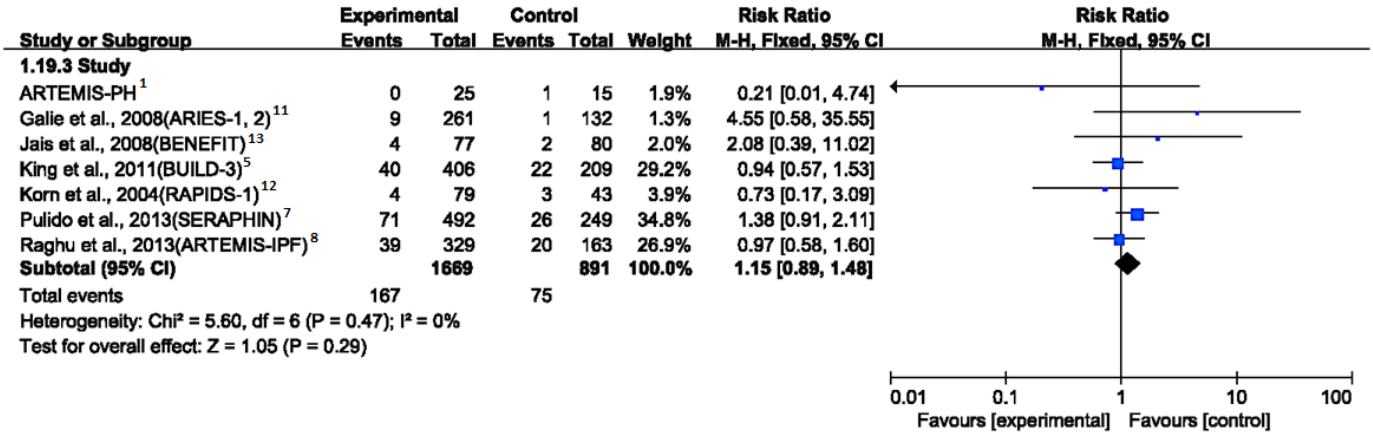
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.19.3 Study
ARTEMIS-PH[1] 0 25 1 15 1.9% 0.21 [0.01, 4.74]
Galie et al., 2008(ARIES-1, 2)[11] 9 261 1 132 1.3% 4.55 [0.58, 35.55]
Jais et al., 2008(BENEFIT)[13] 4 77 2 80 2.0% 2.08 [0.39, 11.02]
King et al., 2011(BUILD-3)[5] 40 406 22 209 29.2% 0.94 [0.57, 1.53]
Korn et al., 2004(RAPIDS-1)[12] 4 79 3 43 3.9% 0.73 [0.17, 3.09]
Pulido et al., 2013(SERAPHIN)[7] 71 492 26 249 34.8% 1.38 [0.91, 2.11]
Raghu et al., 2013(ARTEMIS-IPF)[8] 39 329 20 163 26.9% 0.97 [0.58, 1.60]
Subtotal (95% CI) 1669 891 100.0% 1.15 [0.89, 1.48]
Total events 167 75
Heterogeneity: Chi² = 5.60, df = 6 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

Figure S4

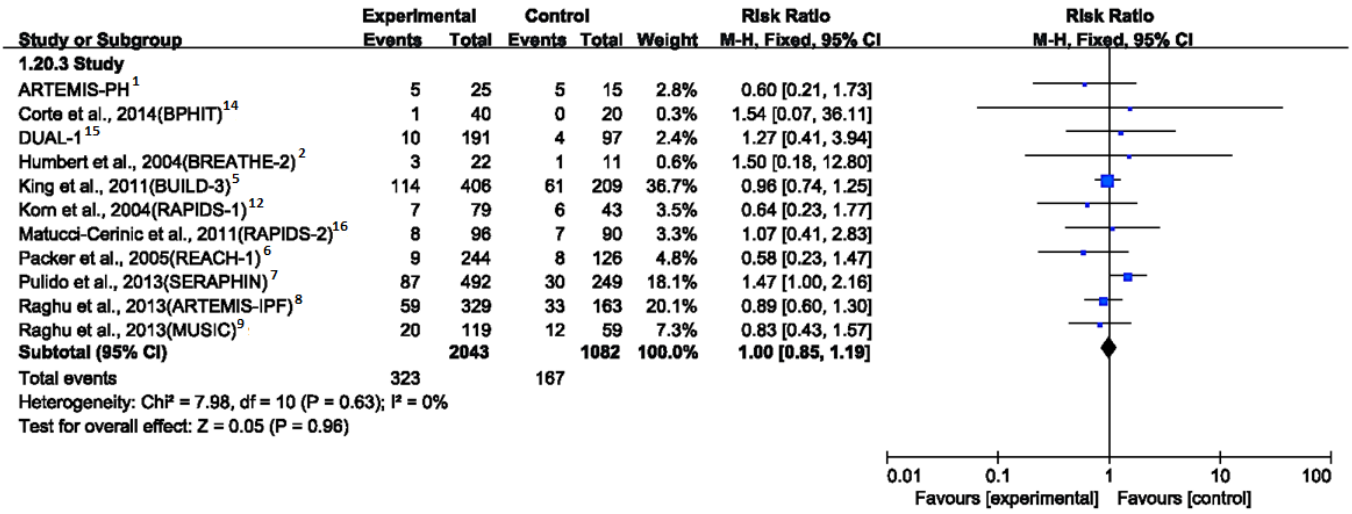
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.20.3 Study
ARTEMIS-PH [1] 5 25 5 15 2.8% 0.60 [0.21, 1.73]
Corte et al., 2014(BPHIT) [14] 1 40 0 20 0.3% 1.54 [0.07, 36.11]
DUAL-1 [15] 10 191 4 97 2.4% 1.27 [0.41, 3.94]
Humbert et al., 2004(BREATHE-2) [2] 3 22 1 11 0.6% 1.50 [0.18, 12.80]
King et al., 2011(BUILD-3) [5] 114 406 61 209 36.7% 0.96 [0.74, 1.25]
Korn et al., 2004(RAPIDS-1) [12] 7 79 6 43 3.5% 0.64 [0.23, 1.77]
Matucci-Cerinic et al., 2011(RAPIDS-2) [16] 8 96 7 90 3.3% 1.07 [0.41, 2.83]
Packer et al., 2005(REACH-1) [6] 9 244 8 126 4.8% 0.58 [0.23, 1.47]
Pulido et al., 2013(SERAPHIN) [7] 87 492 30 249 18.1% 1.47 [1.00, 2.16]
Raghu et al., 2013(ARTEMIS-IPF) [8] 59 329 33 163 20.1% 0.89 [0.60, 1.30]
Raghu et al., 2013(MUSIC) [9] 20 119 12 59 7.3% 0.83 [0.43, 1.57]
Subtotal (95% CI) 2043 1082 100.0% 1.00 [0.85, 1.19]
Total events 323 167
Heterogeneity: Chi² = 7.98, df = 10 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

Figure S5

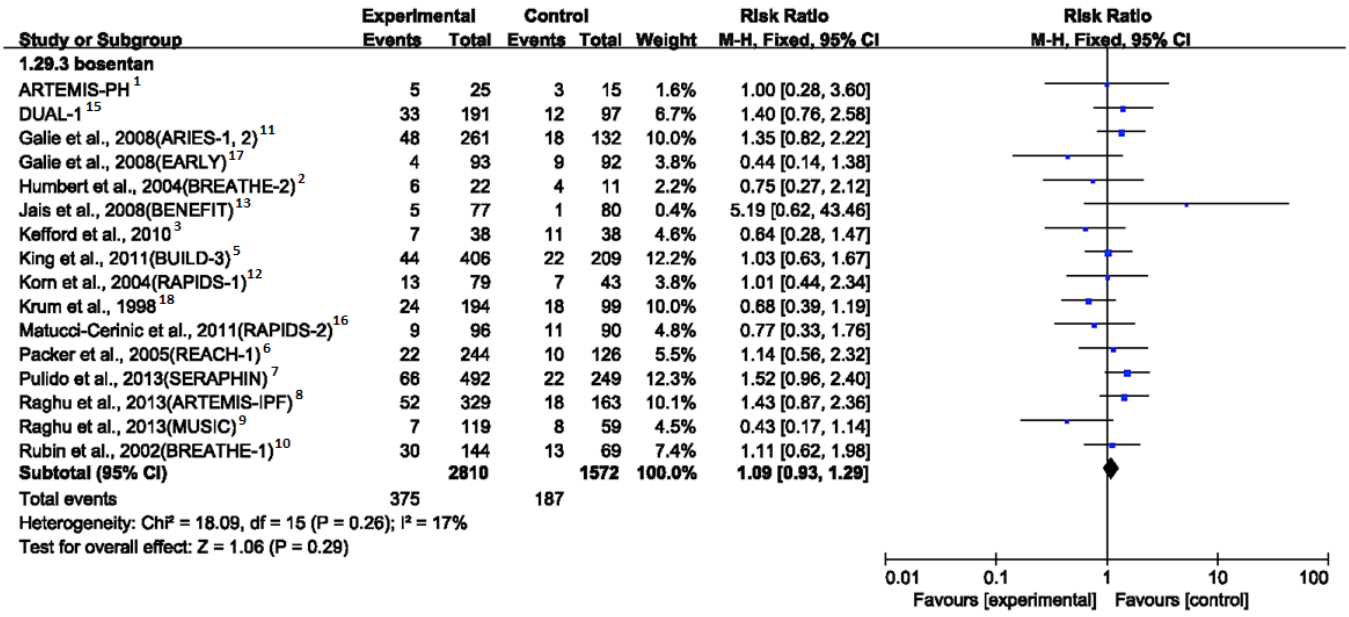
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.29.3 bosentan
ARTEMIS-PH [1] 5 25 3 15 1.6% 1.00 [0.28, 3.60]
DUAL-1 [15] 33 191 12 97 6.7% 1.40 [0.76, 2.58]
Galie et al., 2008(ARIES-1, 2) [11] 48 261 18 132 10.0% 1.35 [0.82, 2.22]
Galie et al., 2008(EARLY) [17] 4 93 9 92 3.8% 0.44 [0.14, 1.38]
Humbert et al., 2004(BREATHE-2) [2] 6 22 4 11 2.2% 0.75 [0.27, 2.12]
Jais et al., 2008(BENEFIT) [13] 5 77 1 80 0.4% 5.19 [0.62, 43.46]
Kefford et al., 2010 [3] 7 38 11 38 4.6% 0.64 [0.28, 1.47]
King et al., 2011(BUILD-3) [5] 44 406 22 209 12.2% 1.03 [0.63, 1.67]
Korn et al., 2004(RAPIDS-1) [12] 13 79 7 43 3.8% 1.01 [0.44, 2.34]
Krum et al., 1998 [18] 24 194 18 99 10.0% 0.68 [0.39, 1.19]
Matucci-Cerinic et al., 2011(RAPIDS-2) [16] 9 96 11 90 4.8% 0.77 [0.33, 1.76]
Packer et al., 2005(REACH-1) [6] 22 244 10 126 5.5% 1.14 [0.56, 2.32]
Pulido et al., 2013(SERAPHIN) [7] 66 492 22 249 12.3% 1.52 [0.96, 2.40]
Raghu et al., 2013(ARTEMIS-IPF) [8] 52 329 18 163 10.1% 1.43 [0.87, 2.36]
Raghu et al., 2013(MUSIC) [9] 7 119 8 59 4.5% 0.43 [0.17, 1.14]
Rubin et al., 2002(BREATHE-1) [10] 30 144 13 69 7.4% 1.11 [0.62, 1.98]
Subtotal (95% CI) 2810 1572 100.0% 1.09 [0.93, 1.29]
Total events 375 187
Heterogeneity: Chi² = 18.09, df = 15 (P = 0.26); I² = 17%
Test for overall effect: Z = 1.06 (P = 0.29)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

Figure Legends

Figure S1: Forrest plot with meta-analysis for the risk of cough.

Figure S2: Forrest plot with meta-analysis for the risk of dyspnea.

Figure S3: Forrest plot with meta-analysis for the risk of nasopharyngitis.

Figure S4. Forrest plot with meta-analysis for the risk of respiratory tract infection.

Figure S5: Forrest plot with meta-analysis for the risk of headache.

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15. Macitentan for the Treatment of Digital Ulcers in Systemic Sclerosis Patients. https://www.clinicaltrials.gov/ct2/show/results/NCT01474109.
16. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, Wigley FM, Black CM, Fessler BJ, Merkel PA, Pope JE, Sweiss NJ, Doyle MK, Hellmich B, Medsger TA Jr, Morganti A, Kramer F, Korn JH, Seibold. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis.* 2011;70:32-38.
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18. Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan Hypertension Investigators. *New Engl J Med.* 1998;338:784-790.