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Original Article

Endothelin-A receptor antagonists in prostate cancer treatment-a meta-analysis

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Abstract: Prostate cancer remains the second leading cause of cancer death in men due to inefficiency of androgen deprivation therapy or androgen blockade. Endothelins (ETs) and the two endothelin receptor family members A and B (ET_A and ET_B) are known to play important roles in the progression of many malignancies, including prostate cancer. However, phase III clinical studies did not reach a unanimous conclusion regarding ET_A receptor antagonists in prostate cancer treatment. Here, we provide a meta-analysis of clinical studies using ET_A receptor antagonists to treat prostate cancer, especially the hormone refractory prostate cancer (HRPC). Data were extracted from nine studies that used Zibotentan or Atrasentan, two selective ET_A receptor antagonists, to treat prostate cancer and meet the selection criteria. The results indicated that the overall survival (OS) and the progression-free survival (PFS) of patients treated with Zibotentan did not show significant difference with the patients treated with placebo (pooled hazard ratio (HR) for OS, 0.86, 95% CI 0.70-1.06; pooled HR for PFS, 0.98, 95% CI 0.91-1.06). No statistically significant difference was detected either as to the OS and PFS of patients between the Atrasentan treated group and the group treated with placebo (pooled HR for OS, 0.99, 95% CI 0.90-1.08; pooled HR for PFS, 0.94, 95% CI 0.86-1.02). Notably, the level of prostate-specific antigen (PSA) and the incidence of bone pain were significantly lower in the Atrasentan treated patients compared to the controls (pooled HR for time of PSA progression, 0.87, 95% CI 0.78-0.97; and pooled relative risk (RR) for bone pain, 0.68, 95% CI 0.48-0.97). In addition, increasing of PSA and bone alkaline phosphatase (BALP) were significantly delayed with Atrasentan treatment ($P<0.05$). Together, these data suggest that Atrasentan has an effect on cancer-related bone pain and skeletal-events in patients with prostate cancer.

Keywords: ET_A receptor antagonist, Atrasentan, Zibotentan, prostate cancer, meta-analysis

Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer and is also one of the leading causes of cancer death in men in the United States (second to lung cancer). The standard treatment for advanced prostate cancer includes androgen-deprivation combined with androgen blockade. However, due to unresponsiveness to androgen blockade, the prognosis of hormone refractory prostate cancer (HRPC) remains poor. Advanced HRPC is characterized by development of painful bone metastasis. The docetaxel-based chemotherapy was reportedly to be able to improve its survival, but affects only half of the patients with metastatic HRPC [1-3]. New therapies are needed to improve survival as well as to maintain or improve the quality of life for patients diagnosed with HRPC [4].

Endothelins (ETs) are short peptides that are known to be involved in the pathogenesis of multiple diseases, including cancer (majorly prostate cancer) and cancer metastasis [5]. There are two endothelin receptor family members A and B (ET_A and ET_B) that belong to the G protein-coupled receptor (GPCR) superfamily [6, 7]. ET_A interacts with a pertussis-insensitive G protein and activates multiple signaling pathways, including PKC and MAPK etc [8]. These pathways work synergistically to promote cell proliferation, which are mediated primarily by endothelin-1 (ET-1) through the endothelin-A

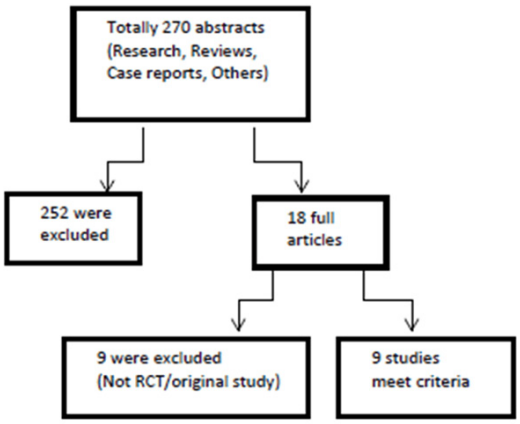

Figure 1. Flowchart showing the literature searching and selection.

(ET_A) receptor [9, 10]. As a weak mitogen for prostate cancer cell lines, ET-1 strongly inhibits chemotherapy-induced apoptosis both in vitro and in vivo [3]. ET-1 has also been implicated multiple functions during angiogenesis, cell invasion, tumor cell proliferation, and apoptosis that affect tumor progression [11-22]. Inhibition of ET_A receptor in prostate cancer may restore its sensitivity to docetaxel-based chemotherapy. To evaluate the clinical effectiveness and to guide clinical practice, we performed a meta-analysis to determine the efficacy of ET_A receptor antagonists, herein Atrasentan or Zibotentan, in treatment of HRPC.

Methods

Search strategy

The MEDLINE bibliographical database was searched for eligible articles up to the end of 2014. Following keywords were used for the searching: "endothelin", "Atrasentan", "ZD4054", "Aibotentan" and "prostate cancer". Google academic searching was also performed to obtain additional information that may be missed by above searching methods.

Inclusion criteria

Randomized clinical trials that evaluated the therapeutic efficacy of the endothelin-A receptor antagonist Atrasentan and Zibotentan with placebo control for treatment of prostate cancer were included for analysis. Conference abstracts providing sufficient data to assess the quality of the studies or the results were described in detail were also included. No pharmacokinetic studies, animal studies, laboratory studies, and non-randomized trials were included for this study. All the studies provided approval from institutional review board with appropriate consent [22].

Data extraction

Data were collected by two reviewers who independently examined the titles and abstracts of the studies using above searching criteria. Obviously ineligible studies were excluded by initial screening of the abstracts. Full texts of all relevant studies were reviewed and disagreement was determined by a third reviewer [22, 23]. The following information was extracted from each paper which includes: the trial's name, first author, year of publication, journal, number of patients in both groups, age, hazard ratios (HR) for OS, PFS and time to first 50% increase in PSA and their 95 % confidence intervals (CI), and the incidence of bone pain.

Quality assessment

Assessment of the trials was conducted using the methods as previously described [24]. Briefly, following aspects were considered for quality assessment: 1) Randomization (the trial was described as randomized); 2) Generation of random numbers using random number table, computer, tossed coins or shuffled cards etc.; 3) Double-blind study-design; 4) Using a proper allocation concealment; and, 5) Clearly reporting the number and reasons for dropouts. The assessment were recorded and scored ranging from 0 to 5 with 5 as the highest quality [25].

Statistical analysis

Hazard ratios (HR) for OS, PFS and time to first 50% increase in PSA, relative risk (RR) for incidence of bone pain were calculated and compared between the two groups: endothelin-A receptor antagonist treated patients or placebo controls. A statistical test with a P value <0.05 was considered to be significant. The values of HR and RR>1 reflect more progression or deaths and more toxicities in endothelin-A receptor antagonist treated patients. We estimated the degree of heterogeneity among the trials using the χ^2 statistics (with a P-value <0.10 considered significant) and the I^2 test

Table 1. Nine randomized controlled trials included in the meta-analysis

Trial	Study design	Number	HR for OS	HR for PFS	HR for PSA	Jadad Score
Joel 2012	zibotentan	299	0.87	1.01	N	5
phase III	placebo	295				
Karim 2013	Docetaxel+zibotentan	524	1.00	1.00	N	5
phase III	Docetaxel+placebo	528				
Miller 2013	zibotentan	703	1.13	0.89	N	3
phase III	placebo	712				
Nicholas 2010	zibotentan	107	0.83	1.06	N	3
phase II	placebo	107				
Nicholas 2008	zibotentan	107	0.55	0.88	N	3
phase II	placebo	107				
Michael 2007	atrasentan	408	0.97	0.89	0.86	4
phase III	placebo	401				
David 2013	Docetaxel+atrasentan	498	1.04	1.02	N	4
phase III	Docetaxel+placebo	496				
Joel 2008	atrasentan	467	0.92	0.92	0.92	4
phase III	placebo	474				
Michael 2003	atrasentan	89	N	0.80	0.75	4
phase II	placebo	104				

(25%, 50%, and 75% represent low, moderate and high heterogeneity respectively). When significant heterogeneity ($P<0.1$ or $I^2>50\%$) was achieved, we used the random effect model to combine the effect sizes of the included studies. If no significant heterogeneity was found, we selected a fixed effect to pool the data [26]. All CI had two-sided probability coverage of 95%. Potential publication bias was estimated using the Begg's test. We used a forest plot to analyze and to display the results. All calculations were accomplished using the STATA (version 11.0).

Results

Selection of the nine clinical trial studies

We retrieved 270 articles from MEDLINE bibliographical database. 252 papers that were neither RCTs, nor original studies were excluded from this study. Studies that did not involve either of the target drug Atrasentan or Zibotentan were also excluded. After reviewing of the remaining 18 articles, only 9 studies met our inclusion criteria and are outlined in **Figure 1**. Among these 9 articles, 5 studies evaluated Zibotentan treated patients [4, 27-30]. Three of them described the results of phase III trials, while the other 2 studies described the results of phase II trials. All these studies were conducted on patients with hormone-refractory prostate cancer. The rest (four) of the studies evaluated Atrasentan treated patients [3, 31-33], including 3 phase III trials and one phase II trials. Detailed information about these studies is provided in **Table 1**. The Jaded scoring system was used to assess the quality of the methods in these studies.

Effect of Zibotentan on hormone-refractory prostate cancer

To determine the effect of Zibotentan on hormone-refractory prostate cancer, we pooled the overall survival (OS) and progression-free survival (PFS) and compared to the controls treated with placebo. The results showed that Zibotentan did not significantly improve the OS (pooled HR for OS, 0.86, 95% CI 0.70-1.06, **Figure 2A**) and PFS (pooled HR for PFS, 0.98, 95% CI 0.91-1.06, **Figure 2B**) of the patients. Heterogeneity was found across the five studies for OS ($I^2=76.5\%$, $P=0.002$), we then used a random model for meta-analysis to calculate the overall survival. No heterogeneity was shown for PFS ($I^2=0.0\%$, $P=0.627$) and a fixed model was applied for analysis of the progression-free survival. The fun- nel plots were symmetrical and the results of Begg's test in our meta-analyses of OS were shown ($Pr>|z|=0.462$, $P>0.05$) and PFS ($Pr>|z|=0.806$, $P>0.05$, **Figure 5**).

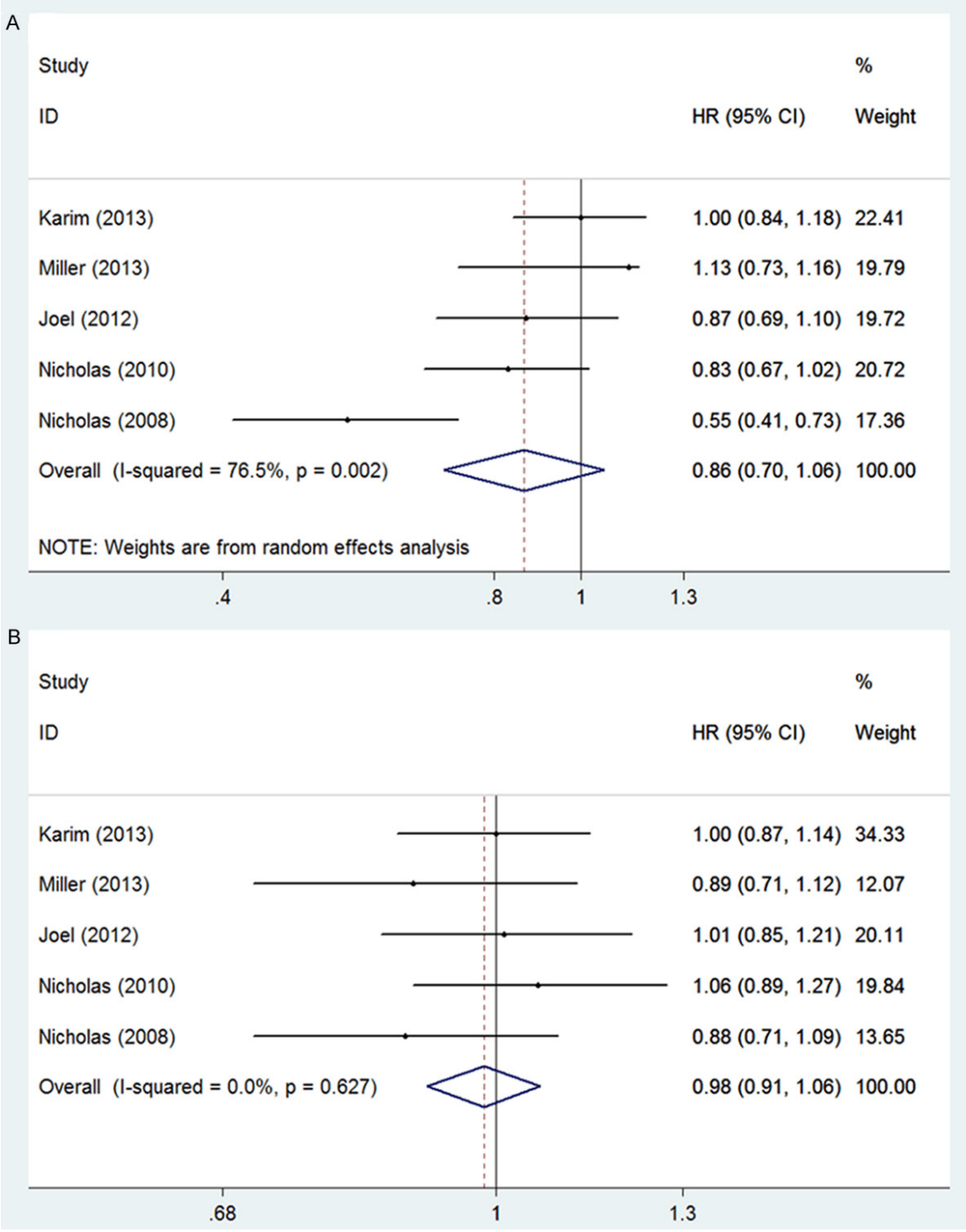

Figure 2. Meta-analysis of effects of Zibotentan on hormone-refractory prostate cancer A: OS (pooled HR for OS, 0.86, 95% CI 0.70-1.06); B: PFS (pooled HR for PFS, 0.98, 95% CI 0.91-1.06).

The efficacy of Atrasentan

No statistically significant difference was detected in overall survival (pooled HR for OS, 0.99, 95% CI 0.90-1.08, **Figure 3A**) and progression-free survival (pooled HR for PFS, 0.94, 95% CI 0.86-1.02, **Figure 3B**) between the Atrasentan treated group and the placebo-treated group.

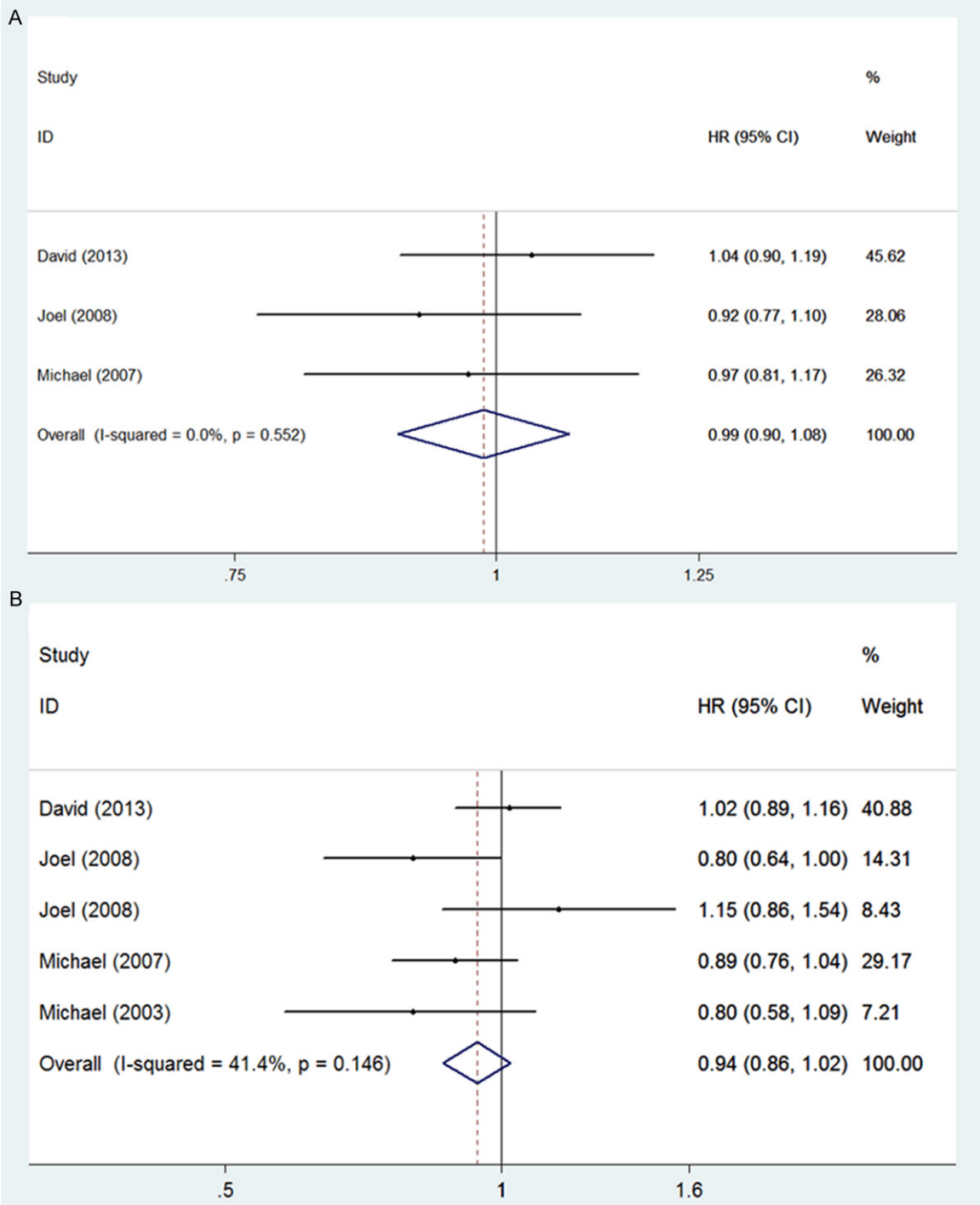

Figure 3. Meta-analysis of effects of Atrasentan on hormone-refractory prostate cancer A: OS (pooled HR for OS, 0.99, 95% CI 0.90-1.08); B: PFS (pooled HR for PFS, 0.94, 95 % CI 0.86-1.02).

As to the time to first 50% increase in PSA, Atrasentan significantly extended the time of PSA progression (HR, 0.87; 95% CI, 0.78-0.97, **Figure 4A**), while the bone pain relative risk (RR =0.68, 95% CI, 0.48-0.97, **Figure 4B**) significantly decreased in Atrasentan-treated group compared to the control group. No heterogeneity was shown for overall survival, progression-free survival, Time to first 50% increase in PSA and bone pain relative risk and a fixed model was applied for analysis of these parameters. A Begg's funnel plot and a Begg's test were used

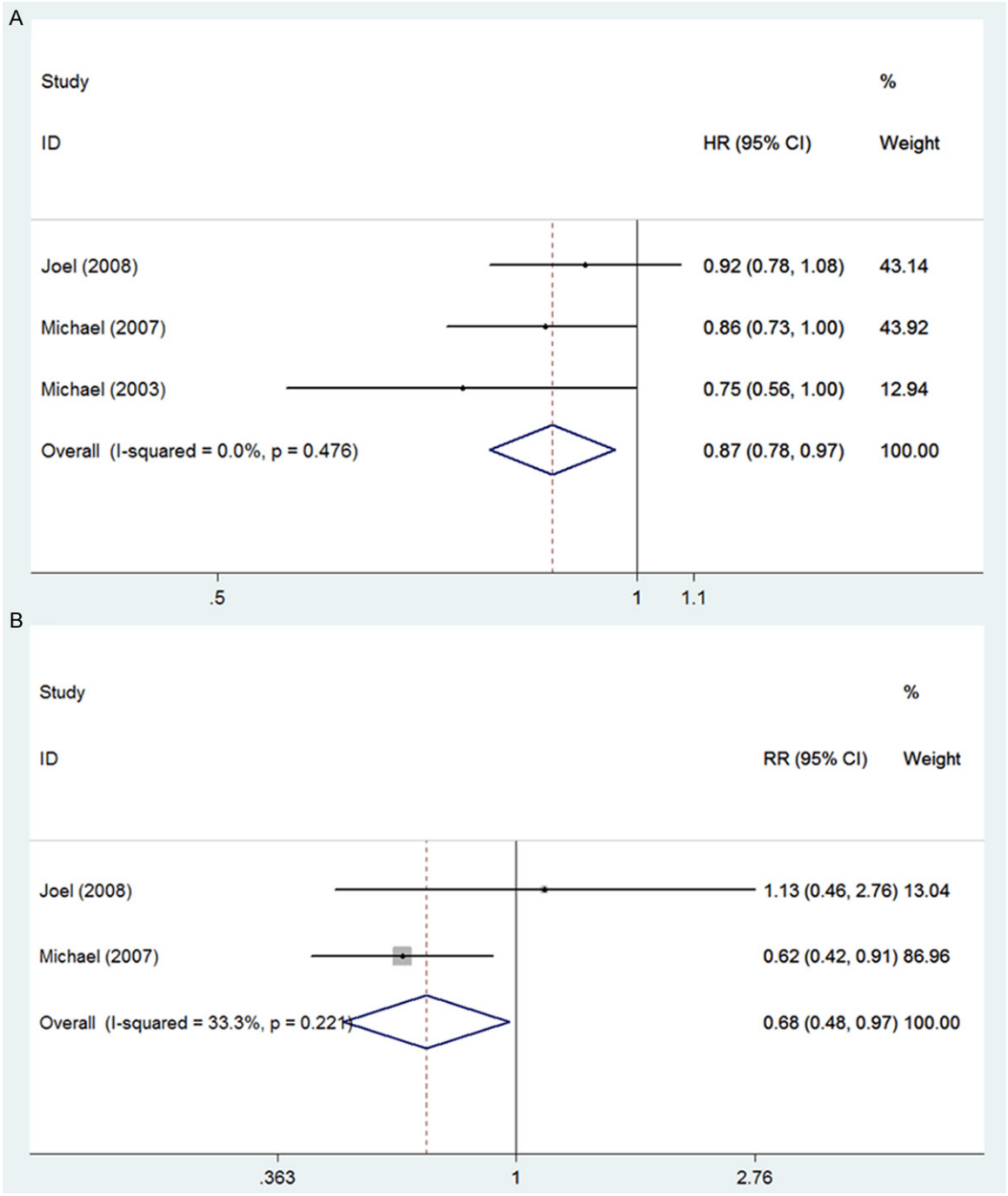

Figure 4. Meta-analysis of effects of Atrasentan on hormone-refractory prostate cancer A: TTPSA (pooled HR for TTPSA, 0.87, 95% CI 0.78-0.97); B: Bone pain relative risk (pooled RR for bone pain, 0.68, 95% CI 0.48-0.97).

to assess for publication bias for these studies. The result showed no obvious asymmetry, indicating no publication bias.

Discussion

The endothelins (ET) are a group of proteins that act through G-protein coupled receptors. Recently, the ET axis, i.e. the ET-1 acting through the endothelin A receptor (ET_A) pathway, has been implicated an essential role in the pathogenesis of many cancers, especially prostate cancer. ET-1 may work through activation of multiple pathways that involve angiogenesis, osteogenesis, cell proliferation, migration, invasion, and epithelial-mesenchy-

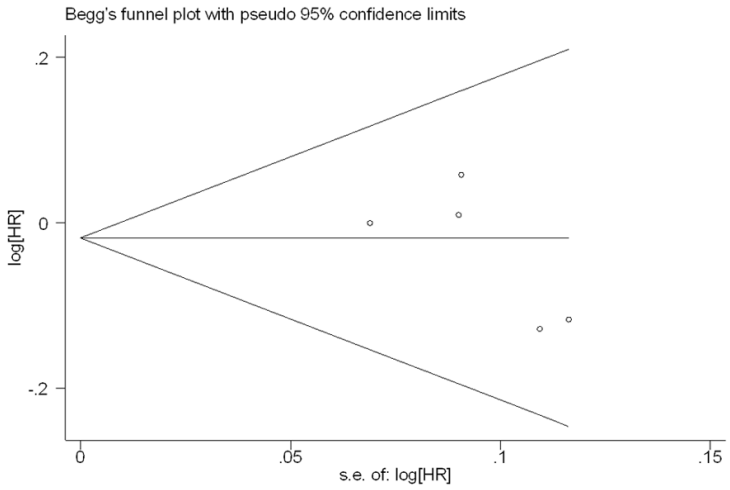

Figure 5. Funnel plot analysis of potential publication bias.

mal transition [34]. In recent years, multiple phase III clinical trials using ET_A receptor antagonists have been conducted in prostate cancer patients, but, the results were very inconsistent. Joel and his colleagues have shown that treatment with Atrasentan resulted in a significantly slower rate of PSA increase and a significant attenuation of BALP activity. The time to initial presentation with skeletal metastases showed a tendency to delay, but no significant improvement in survival or time to cancer progression was detected [32]. However, a recent study of a phase II clinical trial indicated that ZD4054, another ET_A receptor antagonist called Zibotentan, offers a promising result of improving the overall survival in patients with HRPC and bone metastases [4]. These results demonstrated the inconsistency of these clinical trials using ET_A receptor antagonists as therapeutics for HRPC.

According to this meta-analysis, neither Zibotentan nor Atrasentan showed statistically significant improvement of OS and PFS in treated patients compared to the ones with placebo therapy. Treatment with Atrasentan resulted in a significantly slower rate of PSA increase, a decrease of bone pain relative risk, and a delay in the time to initial presentation with skeletal metastases. The discrepancy between phase II clinical trial and phase III is partially due to median drug exposure in the phase II study was shorter. Data about subsequent systemic anticancer therapy usage was also lower than in phase III study. Although Asian populations with prostate cancer have better OS rates than Caucasian patients, indicating a possible genetic influence, contribution of geographical basis for these differences may not be excluded, as discontinuations because of adverse events were more frequent at US sites than other regions [30, 32, 35, 36].

In summary, there are many ET_A receptor antagonists that have been reported, but the number of available randomized studies that examined their role in HRPC treatment are still lacking and may not reach the needed statistics power [37]. Notably, these studies were randomized controlled trials with significant homogeneity and should give rise to convincing data. Based on current meta-analysis, endothelin inhibitors do not have an established role in advanced prostate cancer. However, the slow increase of PSA level and decrease of the bone-related BALP activity in Atrasentan treated patients worth further investigation regarding its efficacy in controlling bone pain and skeletal complications in patients with HRPC.

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Disclosure of conflict of interest

None.

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