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Adverse events risk associated with angiogenesis inhibitors addition to therapy in ovarian cancer: a meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: Inhibition of angiogenesis has been regarded as an attractive treatment strategy for advanced or recurrent ovarian cancer. We conduct this meta-analysis to investigate the risk of adverse events of special interest related to angiogenesis inhibitors (AIs) in ovarian cancer.

PATIENTS AND METHODS: Databases from PubMed, Web of Science and Cochrane library up to December 2015 were searched to identify relevant studies. Eligible studies included prospective randomized controlled phase II/III clinical trials evaluating therapy with or without AIs for ovarian cancer. Summary relative risk (RR) and 95% confidence intervals (CIs) were calculated using random-effects or fixed-effects according to the heterogeneity among included trials.

RESULTS: A total of 7,761 patients from ten clinical trials were included in the meta-analysis. Pooled RR showed that the use of AIs was associated with a statistically increased risk in four of the adverse outcomes studied: arterial thromboembolic events (RR = 2.0), gastrointestinal (GI) perforation (RR = 3.86), proteinuria (RR = 2.44), and hypertension (RR = 5.39). No statistically significant differences were found for hemorrhagic events (p = 0.07), venous thromboembolic events (p = 0.13), or fatal adverse events (p = 0.26).

CONCLUSIONS: The addition of AIs to therapy in ovarian cancer did significantly increase the risk of arterial thromboembolic events, GI perforation, proteinuria and hypertension, but not for venous thromboembolic events, hemorrhagic events, or fatal adverse events.

Key Words:
Adverse events, Angiogenesis inhibitors, Ovarian cancer, Meta-analysis, Safety.

Introduction

Ovarian cancer is the fourth most common cause of cancer-related deaths in women, with an estimated 200,000 cases and 125,000 deaths occurring annually worldwide[1]. Most patients have advanced disease at the time of diagnosis, and are therefore incurable with surgery alone. The prognosis for advanced ovarian cancer is dismal. For the past decade, platinum/paclitaxel combination therapy is the standard treatment for advanced ovarian cancer[2,3]. Although most ovarian cancer patients initially have good responses to platinum/paclitaxel combinations, almost all patients have disease recurrence or progression. Obviously, it is necessary to develop novel agents and combination regimens to achieve greater survival benefits for ovarian cancer.

In the past decades, a better understanding of the molecular events involved in the tumor angiogenesis of ovarian cancers has led to development of novel targeted agents for the management of advanced and recurrent disease. Currently, bevacizumab, an antibody targeting VEGF, has been approved for use in advanced ovarian cancer due to its potential survival benefits[4,5]. Other novel angiogenesis inhibitors (AIs), such as nintedanib, sorafenib, pazopanib and cediranib, are currently being under investigation[6-9]. Thus, the use of AIs in ovarian cancer is expected to increase in the near future, and it would be useful for clinicians to clearly know the severe adverse events (AEs) related to AIs in the treatment of advanced ovarian cancer. Although AIs are generally regarded as well-tolerated, angiogenesis inhibition related toxicity profile has been reported with the most common AEs being hypertension[10-18], proteinuria[19,20], and hemorrhagic events[21-24]. However, to our best knowledge, there is no specific systematic review and meta-analysis focusing on the adverse events (AEs) associated with AIs in ovarian cancer. We, therefore, conduct this comprehensive meta-analysis of randomized controlled trials to

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assess the overall risk of severe AEs related to AIs in the treatment of advanced and recurrent ovarian cancer.

Patients and Methods

Data Sources

Selection of Studies

The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (up to December 2015), and Web of Science (up to December 2015) databases were searched for articles using "bevacizumab", "avastin", "angiogenesis inhibitors", "sorafenib", "sunitinib", "vandetanib", "pazopanib", "cediranib", "axitinib", "nintedanib", "aflibercept", "ovarian cancer", "prospective", "randomized controlled trial" and "humans". We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences that took place between Jan 2004 and Jan 2015. Each publication was reviewed and in cases of duplicate publication only the most complete, recent, and updated report of the clinical trial was included in the meta-analysis.

To assess the relationship between the use of AIs and clinically significant adverse events, we studied AEs classified as grade ≥3 by the NCI-CTC. To be included in the meta-analysis, a study had to satisfy the following requirements: (1) prospective randomized controlled trial of patients with advanced or recurrent ovarian cancer; (2) participants assigned to treatment with or without AIs; (3) available data regarding adverse outcomes of interest (grade ≥ 3 AEs of ATEs, VTEs, proteinuria, hypertension, GI perforation, hemorrhagic events and fatal adverse events) and sample size.

Data extraction and clinical end points

Data extraction and analysis were conducted independently by two independent investigators and any discrepancy between the reviewers was resolved by consensus according to the Quality of Reporting of Meta-Analyses (QUOROM) guidelines[25].

For each study, the following information was extracted: first author, year of publication, trial phase, treatment arms, number of patients in treatment and controlled groups, median age, median progression-free survival, adverse outcomes of interest (grade ≥ 3 AEs of ATEs, VTEs, proteinuria, hypertension, GI perforation, hemorrhagic events and fatal adverse events), and dosage of angiogenesis inhibitors.

Statistical Analysis

To calculate relative risk (RR), patients assigned to AIs were compared only with those assigned to control treatment in the same trial. For each meta-analysis, the Cochran Q statistic and I^2 score were first calculated to determine heterogeneity among the proportions of the included trials[26,27]. For $p < 0.10$ values of the Cochran Q statistic, the assumption of homogeneity was deemed invalid and a random-effects model was reported[28]. Otherwise, results from the fixed-effects model were reported. Finally, potential publication biases were evaluated for severe AEs using Begg's and Egger's tests[29]. A two-tailed p-value of < 0.05 without adjustment for multiplicity was considered statistically significant. The results of the meta-analysis were reported as classic forest plots. The Jadad scale was used to assess the quality of included trials based on the reporting of the studies' methods and results. All statistical analyses were performed by using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ, USA).

Results

Search Results

A total of 113 studies were identified from the database search, of which 15 reports were retrieved for full-text evaluation. Ten trials met the inclusion criteria and were included in this systematic review[4,5,30-37] (Figure 1). Table I showed the baseline characteristics of the included studies. Overall, a total of 7761 patients from ten trials were included. Seven trials were double-blinded, randomized, placebo-controlled trials, thus had a Jadad score of 5. The other three trials had a Jadad score of 3. Table II described the distribution of the number of patients and associated reported AEs in each of the treatment arms for each of the included studies.

Heterogeneity

No observed heterogeneity for VTEs, ATEs, GI perforation, proteinuria, hemorrhagic events or fatal adverse events was found excepting for hypertension (I^2 = 68.0%, p = 0.002, Table II). We thus used random-effect model to pool the risk of hypertension related to AIs.

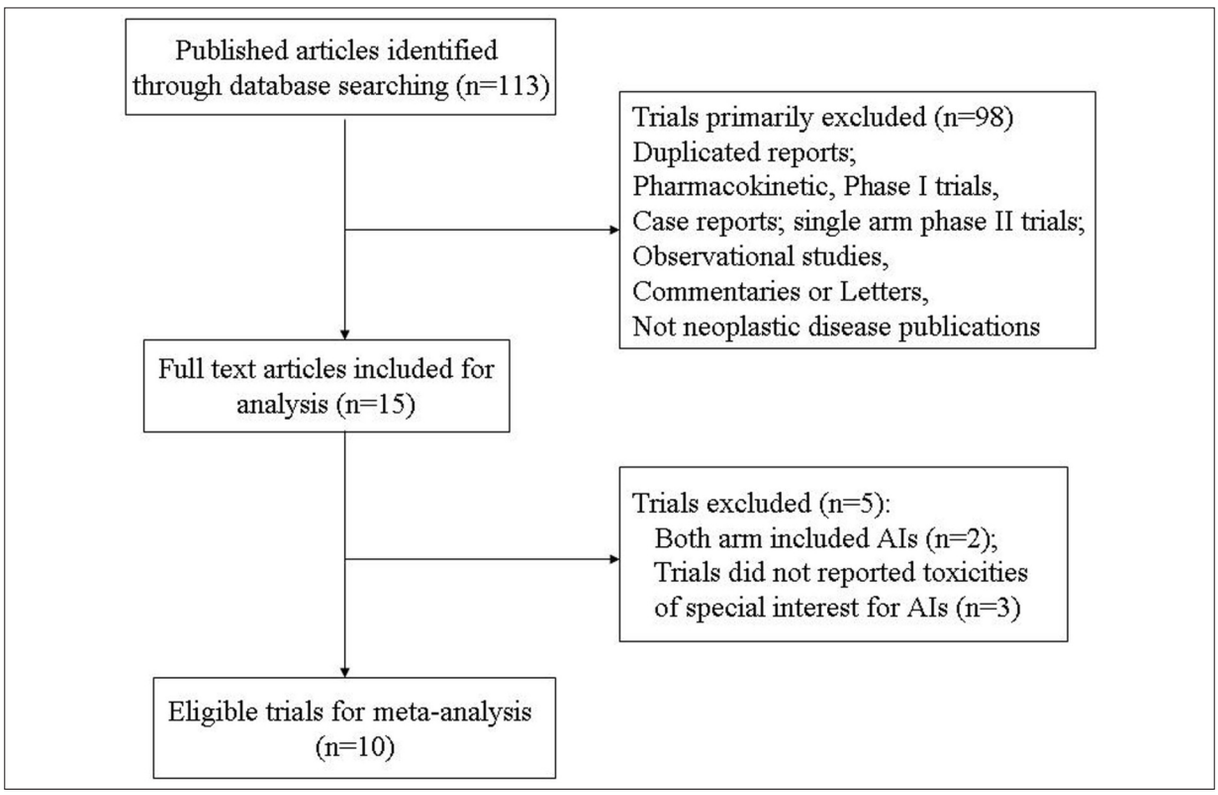

Figure 1. Studies eligible for inclusion in the meta-analysis.

Table I. Baseline characteristic of included 10 trials for analysis.

Author/year	Phase	Line of treatment	No. of patients	Treatment regimens	Median age, y	Median PFS, m	Median OS, m
Burger RA et al/2011	III	First-line	1873	Bevacizumab-initiation +PTX+CBP	60	11.2	39.3
				Bevacizumab-throughout +PTX+CBP	60	10.3	38.7
				Placebo +PTX+CBP	60	14.1	39.7
Perren TJ et al/2011	III	First-line	1528	Bevacizumab 2.5 mg/kg/wk+PTX+CBP	57	19	NR
				PTX+CBP	57	17.3	NR
Karlan BY et al/2012	II	Second-line	161	AMG 386 10 mg/kg+PTX	59	7.2	NR
				AMG386 3 mg/kg+PTX	60	5.7	NR
				Placebo +PTX	62	4.6	NR
Gotlieb WH et al/2012	II	Second-line	55	Aflibercept 4 mg/kg	60	1.4	3
				Placebo	53.5	0.6	3.7
Aghajanian C et al/2014	III	Second-line	484	Bevacizumab 5 mg/kg/wk+chemotherapy	61	12.4	35.2
				Placebo +chemotherapy	60	8.4	33.3
du Bois A et al/2014	III	Maintenance	940	Pazopanib 800 mg qd po	56	17.9	NR
				Placebo	57	12.3	NR
Monk BJ et al/2014	III	Second-line	919	Trebananib 15 mg/kg+PTX	60	7.2	19
				Placebo +PTX	59	5.4	17.3
Pujade-Lauraine E et al/2014	III	Second-line	361	Bevacizumab 5 mg/kg/wk+chemotherapy	62	6.7	16.6
				Chemotherapy	61	3.4	13.3
Pignata S et al/2015	II	Second-line	74	Pazopanib 800 mg qd po +PTX	58	6.35	19.1
				PTX	56	3.49	13.7
du Bois A et al/2015	III	First-line	1366	Nintedanib 200 mg bid po+ PTX+CBP	58	17.2	NR
				Placebo +PTX+CBP	58	16.6	NR

Abbreviations: NR, not reported; PFS, progression free survival; PTX, paclitaxel; CBP, carboplatin.

Table II. Relative risk of adverse outcomes for clinical trials included in the meta-analysis.

Adverse outcome (grade ≥ 3)	Trials (n)	No. of patients (n)		Incidence, % (95%)				
		AIs, Events/total	Controls, events/total	AIs	Controls	I^2	Relative risk (95%)	*p*
ATEs	8	52/4331	21/3186	1.3 (0.7-2.2)	0.9 (0.6-1.3)	0%	2.0 (1.21-3.31)	0.007
VETs	10	178/3921	101/2786	4.4 (3.3-5.8)	3.8 (2.7-5.3)	0%	1.20 (0.95-1.52)	0.26
GI perforation	8	41/2706	8/2185	1.9 (1.1-3.0)	0.6 (0.3-1.2)	0%	3.86 (1.83-8.17)	< 0.001
Hypertension	9	347/3183	59/2646	9.3 (4.8-17.5)	1.8 (0.9-3.8)	68%	5.39 (2.80-10.35)	< 0.001
Proteinuria	7	63/3429	22/2736	1.8 (0.8-4.0)	1.0 (0.5-2.2)	37%	2.44 (1.51-3.94)	< 0.001
Hemorrhagic events	4	20/1782	6/1283	1.2 (0.8-1.9)	0.7 (0.3-1.4)	0%	2.24 (0.93-5.40)	0.072
FAEs	10	52/4398	29/3247	1.3 (0.7-2.3)	1.1 (0.8-1.6)	0%	1.31 (0.82-2.07)	0.26

$I^2 \geq 50\%$ suggests high heterogeneity across studies. *Abbreviation:* AIs, angiogenesis inhibitors; ATEs, arterial thromboembolic events; VETs, venous thromboembolic events; GI perforation, gastrointestinal perforation; FAEs, fatal adverse events;

AEs Reported in Trials and Pooled Effects

Venous and Arterial Thromboembolic Events

A total of nine trials reported VTEs data. The pooled incidence of VTEs was 178 (4.4%) in AIs arms and 101 (3.8%) in control arms. The pooled RR showed that the use of AIs did not increase the risk of VTEs when compared to controls (RR = 1.20; 95% CI 0.95-1.52; p = 0.26; Figure 2A).

A total of 73 patients with ATEs was reported, 52 (1.3%) in AIs arms and 21 (0.9%) in control arms. The RR among the included studies ranged from 0.791 to 9.10. And the pooled results found a significantly increased risk of ATEs associated with AIs using a fixed effect model [RR=2.00; 95% confidence interval (CI) 1.21–3.31; p = 0.007, Figure 2B].

GI Perforation

Eight of ten trials reported GI perforation data with 41 (1.9%) patients in AIs arms, and 8 (0.6%) in control arms. We also observed an increased risk of GI perforation with AIs-containing regimens using a fixed effect model (RR = 3.86; 95% CI: 1.83-8.17, $p < 0.001$, Figure 2C).

Proteinuria

Seven trials reported severe proteinuria with 63 (1.8%) patients in the AIs arms, while 22 (1.0%) were observed in the control arm. The pooled RR showed that the use of AIs significantly increased the risk of proteinuria when compared to controls with RR = 2.44, (95%CI: 1.51-3.94, $p < 0.001$) (Figure 2D).

Hypertension

Nine trials reported hypertension data with a total of 406 patients experiencing grade ≥3 hypertension. The pooled prevalence of severe hypertension was more frequently (9.3%) in AIs group than those in the control group (1.8%). The pooled RR was 5.39 (95% CI 2.80-10.35; $p < 0.001$) using a fixed-effect model (Figure 2E).

Hemorrhagic Events

A total of 26 severe hemorrhagic events were reported in four included trials; 20 (1.2%) in AIs arms and 6 (0.7%) in control arms. This conferred an overall RR of developing hemorrhagic events of 2.24 (95% CI: 0.93-5.40, p = 0.072) (Figure 2F).

Grade 5 Toxicities

There was no fatal adverse event reported in the trial conducted by Pignata S. et al[30]. A total of 81 patients with FAEs was reported in other nine trials, 52 (1.3%) in AIs arms and 29 (0.8%) in control arms. This conferred a pooled RR of developing grade 5 events of 1.31 (95% CI 0.82-2.07; p = 0.26) (Figure 3).

Publication Bias

No publication bias was detected for the AEs studied excepting for hypertension by either the Begg or Egger tests (Begg's test, p = 0.044; Egger's test, p = 0.07, Table III).

Discussion

Tumor angiogenesis is a fundamental process for the tumor growth as it ensures oxygen and

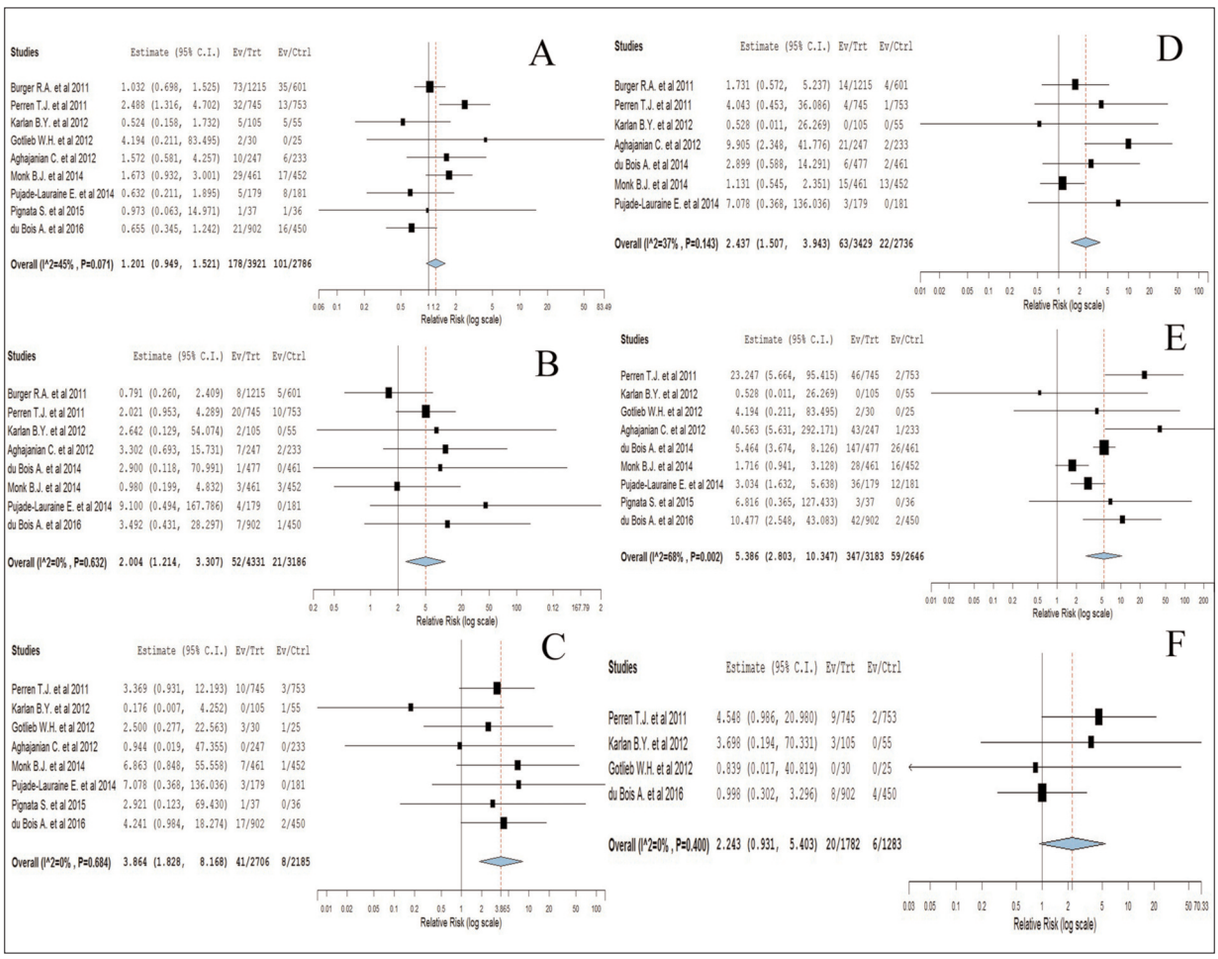

Figure 2. Risk of severe adverse outcomes associated with AIs treatment compared with control treatment [All graphs show risk ratio (RR) for each study and summary RR obtained for ***(A)*** venous thromboembolic events (VTEs), ***(B)*** arterial thromboembolic events (ATEs), ***(C)*** GI perforation, ***(D)*** proteinuria, ***(E)*** hypertension, ***(F)*** hemorrhagic events]. The size of squares corresponds to the weight of the study in the meta-analysis. The diamond plot represents the overall results of the included trials.

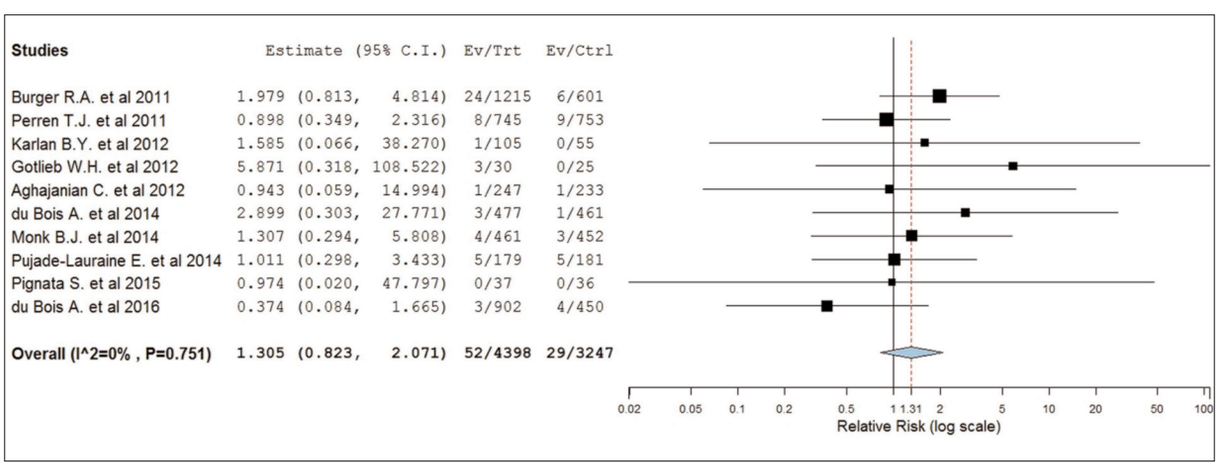

Figure 3. Risk of fatal adverse events associated with AIs treatment compared with control treatment.

Table III. Publication bias Begg and Egger test (*p*-value).

	Begg	Egger
ATEs	0.46	0.59
VETs	0.80	0.98
GI perforation	0.19	0.53
Hypertension	0.88	0.45
Proteinuria	0.044	0.07
Hemorrhagic event	0.60	0.84
Fatal adverse event	0.38	0.43

nutrients supply to proliferating cells through the development of new blood vessels, which might cause tumor progression and metastasis. As a result, angiogenesis is a valid target in the treatment of solid tumors including ovarian cancer. Although AIs are generally well tolerated, these drugs have been reported with a higher risk of severe AEs. However, it has been difficult to assess these toxicities in individual randomized clinical trials due to the limited sample size for analysis. We thus carry out this meta-analysis of ten randomized clinical trials with a total of 7761 patients to investigate the relationship between those AEs and AIs use. The pooled results show that the addition of AIs to therapy in ovarian cancer is associated with a significantly increased risk of developing grade ≥ 3 ATEs, GI perforation, proteinuria, and hypertension in comparison with controls, while no significant relationship is found between AIs use and risk of fatal adverse events, hemorrhagic events, or VTEs.

The study of hypertension shows the highest RR with 7.55, and this event is clinically significant for ovarian cancer. As we know, severe hypertension including hypertensive crisis may cause significant cardiovascular damage with a possible life-threatening consequence, and limit the use of AIs. Therefore, it is particularly important for all clinicians to monitor and treat hypertension in a timely manner and appropriately to prevent long-term complications from toxicities. We also find that the use of AIs significantly increases the risk of severe proteinuria, which is consistent with previously published meta-analyses[19,20,38]. The clinical significance of severe proteinuria is evident, because severe proteinuria may cause significant morbidity with a possible consequence of renal failure and fatality. Additionally, severe proteinuria may also limit the use of AIs, thereby compromising its efficacy. Thus, clinicians should recognize the risk of proteinuria with appropriate vigilance and management. GI perforation is a rare but serious adverse events associated with AIs. In present study, we find the use of AIs significantly increases the risk of GI perforation in ovarian cancer patients. Based on our findings, it is recommended to consider the number of prior chemotherapy regimens and abdominal surgeries in ovarian cancer patients and to exclude tumor involvement of the bowel by physical examination and CT-scan upon start of treatment with angiogenesis inhibitors[39]. Endoscopic evaluation is advised in patients with symptoms possibly related to GI ulcer during treatment[40]. Interestingly, although previous meta-analyses have shown a higher risk of hemorrhagic events with AIs, our study does not find a significantly increased risk of hemorrhagic events associated with AIs in ovarian cancer. One possible explanation for this is that there is lack of included trials reporting severe hemorrhagic events with a total of four trials including for analysis.

Several previous meta-analyses[41-47] have shown an increased risk of vascular events (ATEs and VTEs) associated with AIs. However, all of these studies include all tumor types to describe the risk of these AEs, and it is unclear whether the use of AIs would increase the risk of vascular events in ovarian cancer patients. In our study focusing on ovarian, no significant association is found between AIs usage and risk of venous thromboembolic events, while the use of AIs significantly increase the risk of severe arterial thromboembolic events. *Additionally, grade 5 fatal adverse outcomes* are rare and more frequent in the AIs arm than in the control arm (1.3% *vs.* 1.1%, respectively). However, the use of AIs does not significantly increase the risk of FAEs in ovarian cancer, thus the use of AIs remains justified in these patients.

Our study has several limitations needed to be considered. First, our study is a study-level meta-analysis, and individual patient information is not available. Thus, confounding variables at the patient level, such as co-morbidities, concomitant medications, specific age and previous therapies could not be incorporated into the analysis. Second, we include patients treated with different AIs. While each of these drugs targeting angiogenesis pathway, these drugs have different potencies, which might increase the heterogeneity among studies. Third, toxicity data in RCTs have been reported to be suboptimal and variable as toxicity is usually not the primary outcome measure. Furthermore, there is some degree of sub-

jectivity in the process by which investigators in trials adjudicate whether a patient's death was the result of an adverse event, cancer progression or other unrelated causes. Finally, as in all meta-analyses, our results may be biased as a result of potential publication bias. However, a funnel plot evaluation for the severe AEs does not indicate publication bias excepting for proteinuria.

Conclusions

The addition of bevacizumab to therapy in advanced or recurrent ovarian cancer is associated with a statistically increased risk of arterial thromboembolic events, GI perforation, proteinuria and hypertension. However, no significantly increased risk of venous thromboembolic events, hemorrhagic events, or fatal adverse events is observed in ovarian cancer receiving AIs-containing regimens. These observations may aid medical oncologists in weighing up the risks and benefits associated with AIs in treating patients with advanced or recurrent ovarian cancer.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
2) Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, Mannel RS, DeGeest K, Hartenbach EM, Baergen R; Gynecology Oncology Group: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003; 21: 3194-3200.
3) du Bois A, Lück HJ, Meier W, Adams HP, Möbus V, Costa S, Bauknecht T, Richter B, Warm M, Schröder W, Olbricht S, Nitz U, Jackisch C, Emons G, Wagner U, Kuhn W, Pfisterer J; Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003; 95: 1320-1329.
4) Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Kurzeder C, du Bois A, Sehouli J, Kimmig R, Stähle A, Collinson F, Essapen S, Gourley C, Lortholary A, Selle F, Mirza MR, Leminen A, Plante M, Stark D, Qian W, Parmar MK, Oza AM; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011; 365: 2484-2496.
5) Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente M, Birrer MJ, Liang SX; Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011; 365: 2473-2483.
6) Hainsworth JD, Thompson DS, Bismayer JA, Gian VG, Merritt WM, Whorf RC, Finney LH, Dudley BS. Paclitaxel/carboplatin with or without sorafenib in the first-line treatment of patients with stage III/IV epithelial ovarian cancer: a randomized phase II study of the Sarah Cannon Research Institute. Cancer Med 2015; 4: 673-681.
7) Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, Rimel B, Buss MK, Nattam S, Hurteau J, Luo W, Quy P, Whalen C, Obermayer L, Lee H, Winer EP, Kohn EC, Ivy SP, Matulonis UA. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 2014; 15: 1207-1214.
8) Coleman RL, Moon J, Sood AK, Hu W, Delmore JE, Bonebrake AJ, Anderson GL, Chambers SK, Markman M. Randomised phase II study of docetaxel plus vandetanib versus docetaxel followed by vandetanib in patients with persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma: SWOG S0904. Eur J Cancer 2014; 50: 1638-1648.
9) Harter P, Sehouli J, Kimmig R, Rau J, Hilpert F, Kurzeder C, Elser G, du Bois A. Addition of vandetanib to pegylated liposomal doxorubicin (PLD) in patients with recurrent ovarian cancer. A randomized phase I/II study of the AGO Study Group (AGO-OVAR 2.13). Invest New Drugs 2013; 31: 1499-1504.
10) Qi WX, He AN, Shen Z, Yao Y. Incidence and risk of hypertension with a novel multi-targeted kinase inhibitor axitinib in cancer patients: a systematic review and meta-analysis. Br J Clin Pharmacol 2013; 76: 348-357.
11) Qi WX, Lin F, Sun YJ, Tang LN, He AN, Yao Y, Shen Z. Incidence and risk of hypertension with pazopanib in patients with cancer: a meta-analysis. Cancer Chemother Pharmacol 2013; 71: 431-439.
12) Qi WX, Shen Z, Lin F, Sun YJ, Min DL, Tang LN, He AN, Yao Y. Incidence and risk of hypertension with vandetanib in cancer patients: a systematic review and meta-analysis of clinical trials. Br J Clin Pharmacol 2013; 75: 919-930.
13) Qi WX, Shen Z, Tang LN, Yao Y. Risk of hypertension in cancer patients treated with aflibercept: a systematic review and meta-analysis. Clin Drug Investig 2014; 34: 231-240.
14) Wu S, Chen JJ, Kudelka A, Lu J, Zhu X. Incidence and risk of hypertension with sorafenib in patients

with cancer: a systematic review and meta-analysis. Lancet Oncol 2008; 9: 117-123.

15) Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. Acta Oncol 2009; 48: 9-17.

16) Ranpura V, Pulipati B, Chu D, Zhu X, Wu S. Increased risk of high-grade hypertension with bevacizumab in cancer patients: a meta-analysis. Am J Hypertens 2010; 23: 460-468.

17) Funakoshi T, Latif A, Galsky MD. Risk of hypertension in cancer patients treated with sorafenib: an updated systematic review and meta-analysis. J Hum Hypertens 2013; 27: 601-611.

18) Kim SH, Lee GW, Go SI, Cho SH, Kim HJ, Kim HG, Kang JH. A phase II study of irinotecan, continuous 5-fluorouracil, and leucovorin (FOLFIRI) combination chemotherapy for patients with recurrent or metastatic gastric cancer previously treated with a fluoropyrimidine-based regimen. Am J Clin Oncol 2010; 33: 572-576.

19) Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. Am J Kidney Dis 2007; 49: 186-193.

20) Zhang ZF, Wang T, Liu LH, Guo HQ. Risks of proteinuria associated with vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: a systematic review and meta-analysis. PLoS One 2014; 9:e90135.

21) Qi WX, Tang LN, Sun YJ, He AN, Lin F, Shen Z, Yao Y. Incidence and risk of hemorrhagic events with vascular endothelial growth factor receptor tyrosine-kinase inhibitors: an up-to-date meta-analysis of 27 randomized controlled trials. Ann Oncol 2013; 24: 2943-2952.

22) Je Y, Schutz FA, Choueiri TK. Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. Lancet Oncol 2009; 10: 967-974.

23) Hapani S, Sher A, Chu D, Wu S. Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology 2010; 79: 27-38.

24) Duffy A, Wilkerson J, Greten TF. Hemorrhagic events in hepatocellular carcinoma patients treated with antiangiogenic therapies. Hepatology 2013; 57: 1068-1077.

25) Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354: 1896-1900.

26) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

27) Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005; 28: 123-137.

28) DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015; 45: 139-145.

29) Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997; 315: 629-634.

30) Pignata S, Lorusso D, Scambia G, Sambataro D, Tamberi S, Cinieri S, Mosconi AM, Orditura M, Brandes AA, Arcangeli V, Panici PB, Pisano C, Cecere SC, Di Napoli M, Raspagliesi F, Maltese G, Salutari V, Ricci C, Daniele G, Piccirillo MC, Di Maio M, Gallo C, Perrone F; MITO 11 investigators. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. Lancet Oncol 2015; 16: 561-568.

31) du Bois A, Kristensen G, Ray-Coquard I, Reuss A, Pignata S, Colombo N, Denison U, Vergote I, Del Campo JM, Ottevanger P, Heubner M, Minarik T, Sevin E, de Gregorio N, Bidzi ski M, Pfisterer J, Malander S, Hilpert F, Mirza MR, Scambia G, Meier W, Nicoletto MO, Bjørge L, Lortholary A, Sailer MO, Merger M, Harter P; AGO Study Group led Gynecologic Cancer Intergroup (GCIG)/European Network of Gynaecologic Oncology Trials Groups (ENGOT) Intergroup Consortium. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2016; 17: 78-89.

32) Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D, Ray-Coquard I. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014; 32: 1302-1308.

33) Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, Oaknin A, Ray-Coquard I, Provencher DM, Karlan BY, Lhommé C, Richardson G, Rincón DG, Coleman RL, Herzog TJ, Marth C, Brize A, Fabbro M, Redondo A, Bamias A, Tassoudji M, Navale L, Warner DJ, Oza AM. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014; 15: 799-808.

34) du Bois A, Floquet A, Kim JW, Rau J, del Campo JM, Friedlander M, Pignata S, Fujiwara K, Vergote I, Colombo N, Mirza MR, Monk BJ, Kimmig R, Ray-Coquard I, Zang R, Diaz-Padilla I, Baumann KH, Mouret-Reynier MA, Kim JH, Kurzeder C, Lesoin A, Vasey P, Marth C, Canzler U, Scambia G, Shimada M, Calvert P, Pujade-Lauraine E, Kim BG, Herzog TJ, Mitrica I, Schade-Brittinger C, Wang Q, Crescenzo R, Harter P. Incorporation of pazopanib in maintenance therapy of ovarian cancer. J Clin Oncol 2014; 32: 3374-3382.

35) Karlan BY, Oza AM, Richardson GE, Provencher DM, Hansen VL, Buck M, Chambers SK, Ghatage

P, Pippitt CH Jr, Brown JV 3rd, Covens A, Nagarkar RV, Davy M, Leath CA 3rd, Nguyen H, Stepan DE, Weinreich DM, Tassoudji M, Sun YN, Vergote IB. Randomized, double-blind, placebo-controlled phase II study of AMG 386 combined with weekly paclitaxel in patients with recurrent ovarian cancer. J Clin Oncol 2012; 30: 362-371.

36) Gotlieb WH, Amant F, Advani S, Goswami C, Hirte H, Provencher D, Somani N, Yamada SD, Tamby JF, Vergote I. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Oncol 2012; 13: 154-162.

37) Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012; 30: 2039-2045.

38) Wu S, Kim C, Baer L, Zhu X. Bevacizumab increases risk for severe proteinuria in cancer patients. J Am Soc Nephrol 2010; 21: 1381-1389.

39) Walraven M, Witteveen PO, Lolkema MP, van Hillegersberg R, Voest EE, Verheul HM. Antiangiogenic tyrosine kinase inhibition related gastrointestinal perforations: a case report and literature review. Angiogenesis 2011; 14: 135-141.

40) Tol J, Cats A, Mol L, Koopman M, Bos MM, van der Hoeven JJ, Antonini NF, van Krieken JH, Punt CJ. Gastrointestinal ulceration as a possible side effect of bevacizumab which may herald perforation. Invest New Drugs 2008; 26: 393-397.

41) Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, Bergsland E, Ngai J, Holmgren E, Wang J. Hurwit H. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007; 99: 1232-1239.

42) Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA 2008; 300: 2277-2285.

43) Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. J Clin Oncol 2010; 28: 2280-2285.

44) Schutz FA, Je Y, Azzi GR, Nguyen PL, Choueiri TK. Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes. Ann Oncol 2011; 22: 1404-1412.

45) Chen XL, Lei YH, Liu CF, Yang QF, Zuo PY, Liu CY, Chen CZ, Liu YW. Angiogenesis inhibitor bevacizumab increases the risk of ischemic heart disease associated with chemotherapy: a meta-analysis. PLoS One 2013; 8:e66721.

46) Qi WX, Min DL, Shen Z, Sun YJ, Lin F, Tang LN, He AN, Yao Y. Risk of venous thromboembolic events associated with VEGFR-TKIs: a systematic review and meta-analysis. Int J Cancer 2013; 132: 2967-2974.

47) Sonpavde G, Je Y, Schutz F, Galsky MD, Paluri R, Rosenberg JE, Bellmunt J, Choueiri TK. Venous thromboembolic events with vascular endothelial growth factor receptor tyrosine kinase inhibitors: a systematic review and meta-analysis of randomized clinical trials. Crit Rev Oncol Hematol 2013; 87: 80-89.