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Risk of Arterial and Venous Thromboembolic Events with Bevacizumab, An Antibody Against Vascular Endothelial Growth Factor a (VEGF-A): A Meta-Analysis

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Abstract

Abstract- Introduction: Bevacizumab, a humanized antibody against VEGF, is effective within the treatment of patients with several cancers. However, like several therapeutic agents, important side effects such as arterial thromboembolism, venous thromboembolism, hypertension, neutropenia, proteinuria, and hemorrhage are related to bevacizumab. Thromboembolism is one of the leading causes of morbidity and mortality in patients with cancer. Considerations have arisen relating to the chance of venous and arterial thromboembolism with the novel antiangiogenic agent bevacizumab: a recombinant humanized monoclonal antibody to a vascular endothelial growth factor which is wide employed in cancer treatment. Methodology: We performed a meta-analysis of published clinical trials of bevacizumab to quantify the risk of Thromboembolic events. Fourteen studies following PRISMA guidelines and matching inclusion and exclusion criteria were collected in which a group of patients was either treated with Bevacizumab and concurrent chemotherapy and another group treated with Placebo and the same chemotherapy. We calculated the Relative risk (RR). P<0.05 was considered statistically significant. We used R version 3.3.1 (The R Foundation for Statistical Computing) for the analysis. Results: Total 12,280 patients were included. Bevacizumab was associated with an increased risk of Arterial Thromboembolic Events at a high dose (R.R=1.6002; 95

Index terms— bevacizumab, avastin, cancer, side effects, arterial thromboembolism, venous thromboembolism.

1 Introduction

ngiogenesis is a process that results in the proliferation of new blood vessels and plays an important role in growth, progression, and metastasis of the tumor. The vascular endothelial growth factor (VEGF) promotes the development of angiogenesis and over expression of the VEGF that is related to poor prognosis in numerous malignancies (1,2). This process mainly occurs by vascular endothelial growth factor signaling pathway that includes two main target components that are VEGF ligands and VEGF receptors (VEGFRs). Bevacizumab, a humanized monoclonal antibody against VEGF, has shown benefit in the treatment of patients with various malignancies such as metastatic colorectal cancer, non-small-cell lung carcinoma, by many phase III studies. There is much favorable evidence of the benefits of phase II clinical trials in patients with pancreatic cancer, renal cell cancer, and prostatic adenocarcinoma. Though bevacizumab is usually well-tolerated, it may be related to symptomatic side effects like delayed wound healing, hemorrhage, leukoencephalopathy, neutropenia, proteinuria, and nephrotic syndrome, gastrointestinal perforation and congestive heart failure.(3) Bevacizumab conjointly contributes to the event of arterial and venous thromboembolism, a typical complication resulting in morbidity and mortality in patients with malignancy. (4) We hypothesized that sample sizes in randomized

control trials were not powered and large to reveal significantly increased risk. Hence we performed a Meta-analysis of published phase 2 and 3 randomized clinical trials of bevacizumab to determine the risk of arterial and venous thromboembolic events.

2 II.

3 Methodology a) Data Source

We carried out a systematic search of existing databases and after careful scrutiny by two independent researchers; Fourteen studies were selected for inclusion in the analysis. The search was done based on the preferred reporting system for meta-analysis (PRISMA) guidelines. 5 An independent review of citations from scientific databases like clinical trials.gov, Pub med central, NCBI, NIH, Cochrane Library, and Google scholar from January 2004 to January 2015 was conducted. Keywords, bevacizumab, Avastin, cancer, human studies, and clinical trial, Arterial Thromboembolic Events (ATE), Venous Thromboembolic Events (VTE) were included in the search. The search was limited only to the articles published in the English language.

4 b) Data extraction and clinical end points

All study-related Randomized controlled trials (RCTs) using either: A proper method of allocation concealment (e.g., sealed opaque envelopes), Studies that were double-blind, single-blind, studies that were in Phase 2 or Phase 3 trial were only included. Direct comparison of trials with patients treated by Bevacizumab with concurrent chemotherapy and placebo with concurrent chemotherapy in the clinical trials (phase 2 or 3) of cancer were included. The inclusion criteria of the study included the participants greater than or equal to 18 years of age, the studies which included bevacizumab plus a concurrent therapy and placebo with a concurrent therapy, the dose of Bevacizumab should be 2.5mg/kg/week for low dose regimen or greater than or equal to 5mg/kg/week for high dose regimen. The Exclusion criteria of the study included trials including patients treated previously with Bevacizumab or another similar or other malignancies within five years (unless low risk of recurrence), Also the studies with history of abdominal fistula, Gastrointestinal Perforation, intra-abdominal abscess, clinical signs or symptoms of gastrointestinal obstruction, and requirement of parenteral nutrition, non-healing wound, ulcer. Bone fracture, bleeding diathesis, coagulopathy, known CNS disease (except for treated brain metastasis), clinically significant cardiovascular disease, a major surgical procedure within 28 days of enrollment, or anticipated to occur while participating in the study were excluded from the analysis, unpublished research work or trials were excluded. The outcomes were measured for Thromboembolic events, according to National Cancer Institute Common Terminology Criteria Version 3.The outcome was measured after six cycles for six studies and till overall survival in eight studies. Data were extracted from studies meeting the above criteria. Those studies in which data was unclear asked from respective authors. In some studies, data could not obtain by the inquiry were excluded. Authors assured that the study included was only those in which allocation of both the groups were adequately randomized, and there was not any conflict of interest as well as match to inclusion and exclusion criteria. Also, the concurrent treatment was the same for the group with Bevacizumab therapy and Placebo therapy.

5 c) Statistical analysis

The outcome of the occurrence of Arterial Thromboembolic Event (ATE) and Venous Thromboembolic Event(VTE) was recorded from both the groups (Bevacizumab and Placebo), and Relative Risk (RR) was calculated with 95% Confidence Interval and funnel as well as forest plot was obtained. R version 3.3.1 (The R Foundation for Statistical Computing) was used for analysis. A P-value less than 0.05 were considered significant. The presence of small-study effects or publication bias was assessed by funnel plot and eggers value was also calculated. P-value of eggers test, >0.05 is considered to have less publication bias.

6 III.

7 Results

Total

8 a) Relative Risk of Arterial Thromboembolic Events (ATE) with Bevacizumab at a low dose (2.5mg/kg/cycle) versus Placebo

There are seven clinical trials for determining the Risk of Arterial Thromboembolic Events (ATE), including 3691 patients (1866 in the Bevacizumab group and 1825 in the placebo group). The Relative Risk of Arterial Thromboembolic Events (ATE) with patients treated with Bevacizumab and concurrent therapy was 1.0974 times more than placebo and concurrent therapy with 0.856 to 1.4062 C.I and p-value is 0.4625 which is statistically insignificant. P-value of Egger's test is 0.5725.

9 b) Relative Risk of Arterial Thromboembolic Events (ATE) with Bevacizumab at a high (5mg/kg/cycle) versus Placebo

There are seven clinical trials for determining the Risk of Arterial Thromboembolic Events (ATE), including 8457 patients (4575 in the Bevacizumab group and 3882 in the placebo group). The Relative Risk of Arterial Thromboembolic Events (ATE) with patients treated with Bevacizumab and concurrent therapy were 1.6002 times more than placebo and concurrent therapy with 1.1604 to 2.2066 C.I and p-value is 0.0041which is statistically significant. P-value of Egger's test is 0.67535.

10 c) Relative Risk of Venous Thromboembolic Events (VTE) with Bevacizumab at a low dose (2.5mg/kg/cycle) versus Placebo

There are seven clinical trials for determining the Risk of Venous Thromboembolic Events (VTE), including 3691patients (1866 in the Bevacizumab group and 1825 in the placebo group). The Relative Risk of Venous Thromboembolic Events (VTE) with patients treated with Bevacizumab and concurrent therapy was 0.9143 times more than placebo and concurrent therapy with 0.7617 to 1.0975 C.I and p-value is 0.3361 which is statistically insignificant. P-value of Egger's test is 0.457.

11 d) Relative Risk of Venous Thromboembolic Events (VTE) with Bevacizumab at a high dose (5mg/kg/cycle and above) versus Placebo

There are ten clinical trials for determining the Risk of Venous Thromboembolic Events (VTE), including 9379patients (5045 in the Bevacizumab group and 4334 in the placebo group). The Relative Risk of Venous Thromboembolic Events (VTE) with patients treated with Bevacizumab and concurrent therapy was 1.2243 times more than placebo and concurrent therapy with 1.0375 to 1.4448 C.I and p-value is 0.0166 which is statistically significant. P-value of Egger's test is 0.5878.

12 Assessment of Publication Bias

As indicated by the p-value of Egger's Test and funnel plots, no publication bias was reported in the selection of studies (Supplementary File).

IV.

13 Discussion

Thromboembolic events are one of the major causes of death in patients with cancer. This paper has tried to show the thromboembolic events associated with bevacizumab-: Anti VEGF at both high and low doses. The safety of this drug is still not clear due to lack of powered clinical trials. So to overcome this we have performed meta-analysis, which includes 14 randomized clinical trials including, 12,280 patients. However, many previous systematic reviews and metaanalysis showed the adverse effect of bevacizumab but not as per the dosage. In this paper, we attempted to associate thromboembolic events with bevacizumab, at different doses by using meta-analysis.

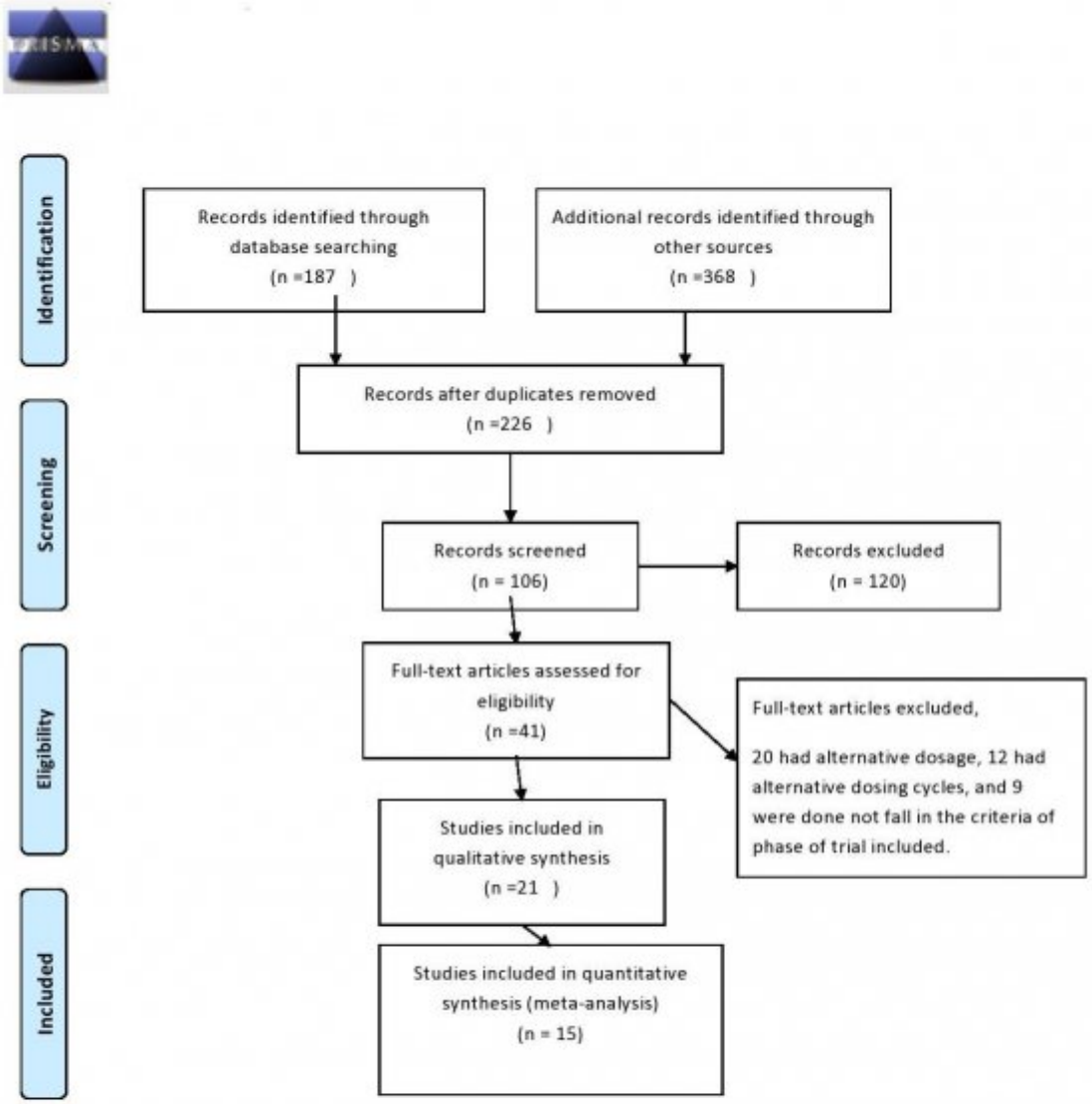
Due to the anti-VEGF effect of bevacizumab it may result in the development of venous thromboembolism.

Bevacizumab may expose subendothelial procoagulant phospholipids resulting in thrombosis by inhibiting VEGF induced endothelial regeneration and may reduce the production of nitric oxide and prostacyclin and also causes inhibition of VEGF that causes overproduction of erythropoietin that leads to increased hematocrit and blood viscosity . (21)(22)(23) Also bevacizumab could increase the discharge of procoagulant from the neoplasm into the blood due to its cytotoxic effect and also increase the expression of pro-inflammatory cytokines leading to damage and in situ thrombus formation. (24) The hallmark behind any arterial thromboembolism is that the instability of atherosclerotic plaque, activation of platelets, and decreased anti-inflammatory effect of VEGF exposure leading to plaque instability and ruptures, which leads to thromboembolism. (24,25) Our meta-analysis shows that high dose bevacizumab is related to a significant increased risk of arterial occlusion in patients who received treatment for metastatic cancers of lung, ovarian, colorectal, and pancreatic and kidney that was similar to the study of Scappaticci, Frank A., Jamey R. Skillings, Scott N. Holden, Hans-Peter Gerber, Kathy Miller, Fairooz Kabbinavar, Emily Bergsland. Our metaanalysis additionally shows the increased risk of venous occlusion with a high dose of bevacizumab that was similar to the study of Shobha rani Nalluri, David Chu, Roger Keresztes, Xiaolei Zhu, Shenhong Wu. Due to the increasing use of angiogenesis inhibitors in patients with many metastatic cancers owing to the associated survival benefit, it's important that oncologists monitor and manage these side effects befittingly to confirm that patients receive maximum benefit from bevacizumab therapy.

V.

14 Conclusion

The association of Thromboembolic events with new agents presents a challenge for recognition as a result of several RCTs might not be powered to reveal a significant relationship. Our meta-analysis has overcome B this limitation of individual trials and incontestable that bevacizumab is also related to a considerably increased risk of arterial and venous Thromboembolic events at the high dose. This finding can facilitate physicians and patients to acknowledge the danger of venous thromboembolism with the administration of bevacizumab at high doses, and so thromboembolic events ought to be monitored. [1] [2]



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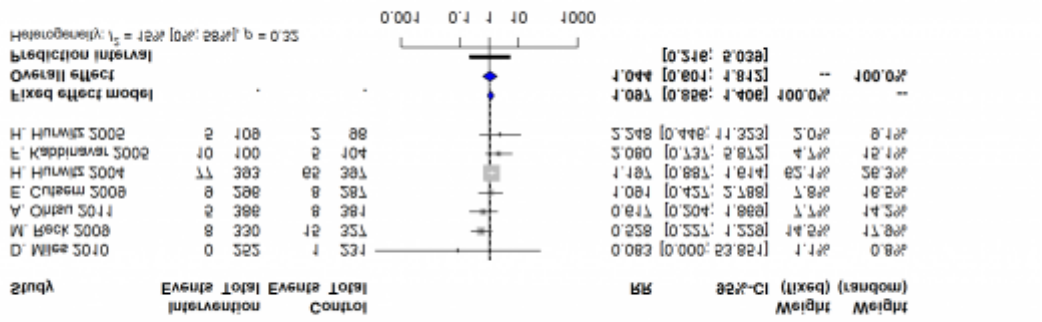

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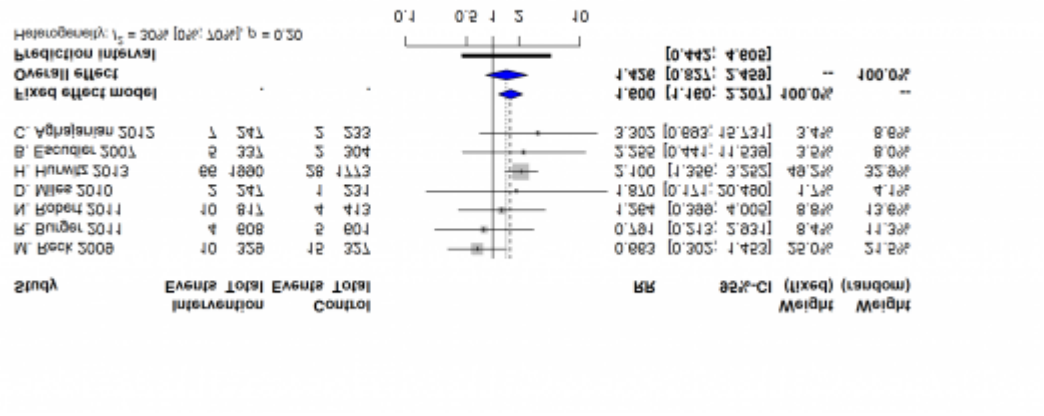

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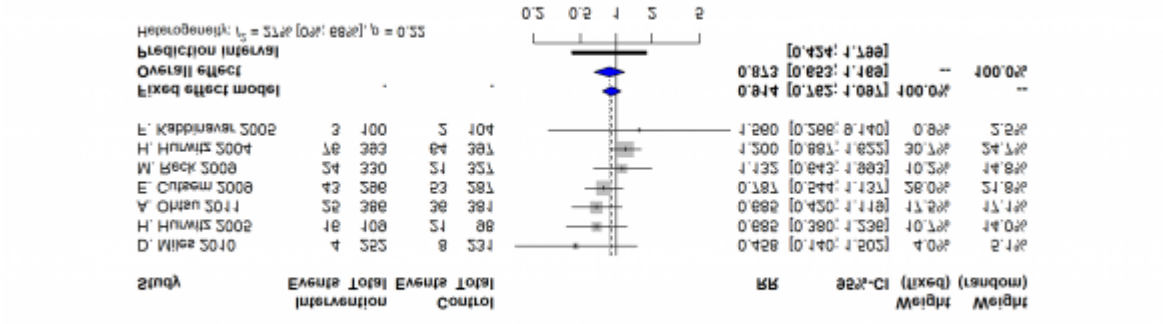
Figure 3: Figure 3 :Figure 4 :Figure 5 :



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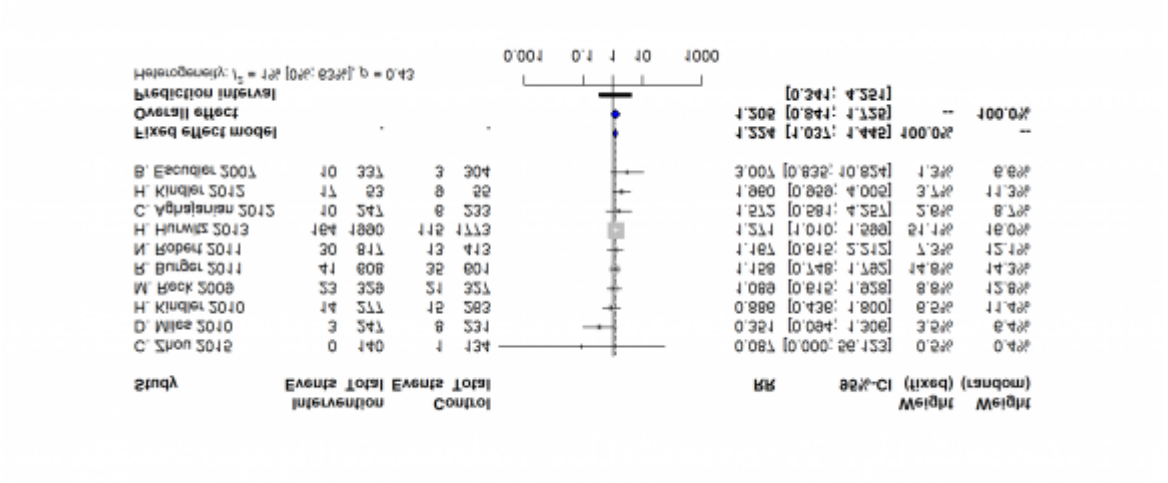

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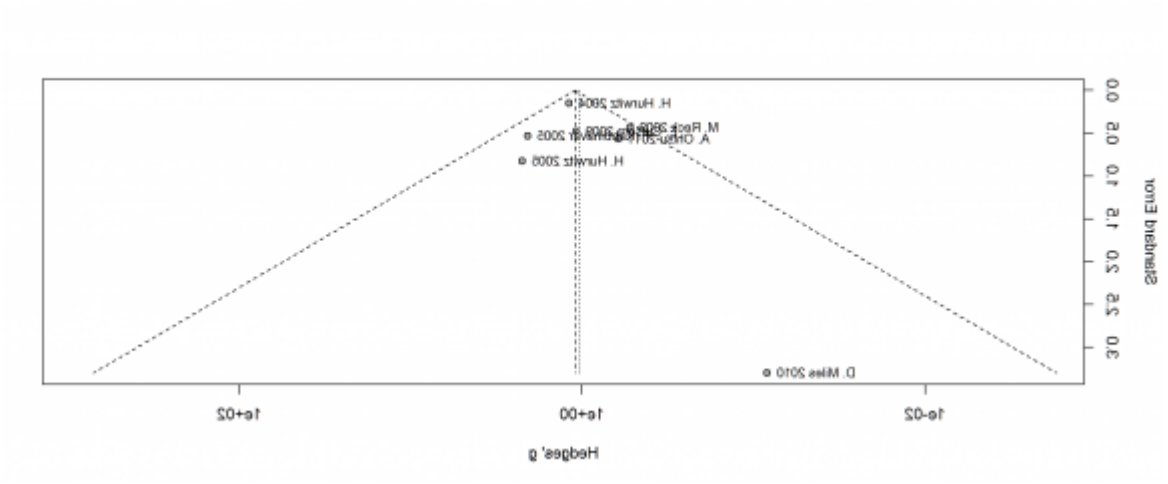

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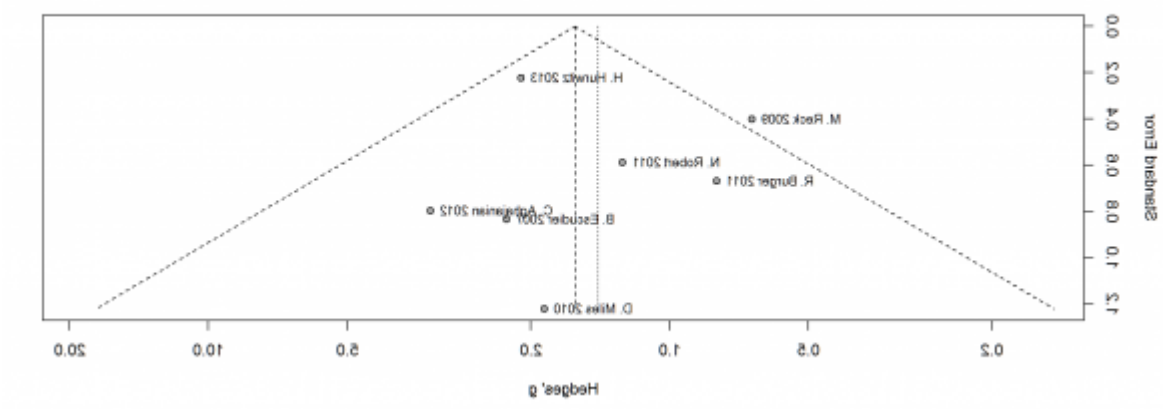

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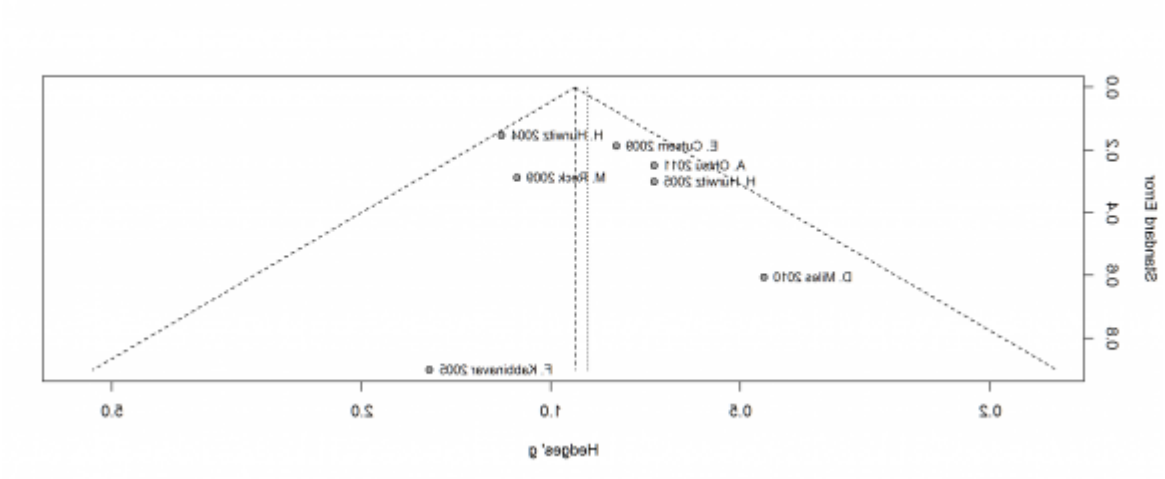

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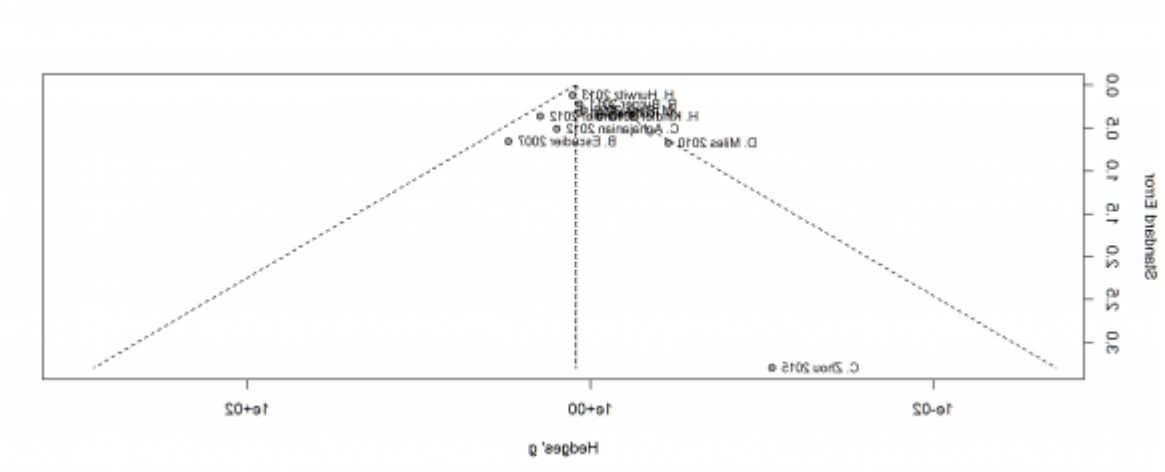

Figure 9:

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Figure 10: Table 1 :

2

Study Name	Trial Phase	Underlying Malignancy	Bevacizumab Dose	Concurrent Treatment
A .Ohtsu 2011 et al 6	3	Advanced gastric cancer	2.5mg/kg/every week	Fluropyrimidine-Cisplatib
B .Escudier 2007 et al 7	3	metastatic renal cell carcinoma	5mg/kg/week	interferon Alfa
C .Aghajanian 2012 et al 8	3	Peritoneal, or Fallopian Tube cancer. Recurrent Epithelial Ovarian, Primary	week 5mg/kg every	gemcitabine plus carboplatin;
C .Zhou 2015 et al 18	3	Recurrent Non squamous non small cell lung cancer	5mg/kg every week	Pacitaxel or carboplatin
D .Miles 2010 et al 9	3	HER 2-metastatic Breast cancer	2.5mg/kg/week	Docetaxel
D .Miles 2010 et al 9	3	HER 2-metastatic Breast cancer	5mg/kg/week	Docetaxel
E .Cutsem 2009 et al 10	3	Metastatic Pancreatic Cancer	2.5mg/kg/week	Gemcitabine and erlotinib
F .Kabbinavar et al 2005	11 2	Metastatic Colon Cancer	2.5mg/kg every week	Bolus fluorouracil and leucovorin
H. Hurwitz 2004 et al 12	2	Metastatic Colon Cancer	2.5mg/kg/week	Irinotecan, bolus fluorouracil and leucovorin
H .Hurwitz 2005 et al 13	3	Metastatic Colorectal Cancer	2.5mg/kg/week	irinotecan/fluorouracil/leucov
H .Hurwitz 2013 et al 14	3	Metastatic Colorectal Cancer	5mg/kg/week	Chemotherapy
H .Kindler 2010 et al 19	3	advanced pancreatic cancer	5 mg/kg/week	Gemcitabine
H .Kindler 2012 et al 20	2	Malignant Mesothelioma	5mg/kg every week	gemcitabine cisplatin
M .Reck 2009 et al 15	3	Nonsquamous Non-Small-Cell Lung Cancer	2.5mg/kg every week	Cisplatin and gemcitabine
M .Reck 2009 et al 15	3	Nonsquamous Non-Small-Cell Lung Cancer	5mg/kg every week	Cisplatin and gemcitabine
N .Robert 2011 et al 16	3	HER 2-locally recurrent or metastatic Breast cancer	5mg/kg every week	Capecitabine taxane anthracycline
R. Burger 2011 et al 17	3	Ovarian Cancer	5mg/kg every week	Carboplatin Pacitaxel

Figure 11: Table 2 :

[Arteriosclerosis (2002)] , Thrombosis Arteriosclerosis . 2002 Sep 1. 22 p. .

[Kabbinavar et al. (2005)] 'Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial'. F F Kabbinavar , J Schulz , M Mccleod , T Patel , J T Hamm , J R Hecht , R Mass , B Perrou , B Nelson , W F Novotny . *Journal of Clinical Oncology* 2005 Jun 1. 23 (16) p. .

[Kuenen et al.] *Analysis of coagulation cascade and endothelial cell activation during inhibition of vascular endothelial growth factor/vascular endothelial growth factor receptor pathway in cancer patients*, B C Kuenen , M Levi , J C Meijers , A K Kakkar , V W Van Hinsbergh , P J Kostense , H M Pinedo , K Hoekman .

[Ohtsu et al. (2011)] 'Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study'. A Ohtsu , M A Shah , E Van Cutsem , S Y Rha , A Sawaki , S R Park , H Y Lim , Y Yamada , J Wu , B Langer , M Starnawski . *J Clin Oncol* 2011 Oct 20. 29 (30) p. .

[Hurwitz et al. (2005)] 'Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer'. H I Hurwitz , L Fehrenbacher , J D Hainsworth , W Heim , J Berlin , E Holmgren , J Hambleton , W F Novotny , F Kabbinavar . *Journal of Clinical Oncology* 2005 May 20. 23 (15) p. .

[Escudier et al. (2007)] *Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. The Lancet*, B Escudier , A Pluzanska , P Koralewski , A Ravaud , S Bracarda , C Szczylik , C Chevreau , M Filipek , B Melichar , E Bajetta , V Gorbunova . 2007 Dec 22. 370 p. .

[Hurwitz et al. (2004)] 'Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer'. H Hurwitz , L Fehrenbacher , W Novotny , T Cartwright , J Hainsworth , W Heim , J Berlin , A Baron , S Griffing , E Holmgren , N Ferrara . *New England journal of medicine* 2004 Jun 3. 350 (23) p. .

[Kilickap et al. (2003)] 'Bevacizumab, bleeding, thrombosis, and warfarin'. S Kilickap , H Abali , I Celik . *Journal of Clinical Oncology* 2003 Sep 15. 21 (18) p. 3542.

[Zhou et al. (2015)] 'BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer'. C Zhou , Y L Wu , G Chen , X Liu , Y Zhu , S Lu , J Feng , J He , B Han , J Wang , G Jiang . *Journal of Clinical Oncology* 2015 May 26. 33 (19) p. .

[Hesser et al. (2004)] 'Down syndrome critical region protein 1 (DSCR1), a novel VEGF target gene that regulates expression of inflammatory markers on activated endothelial cells'. B A Hesser , X H Liang , G Camenisch , S Yang , D A Lewin , R Scheller , N Ferrara , H P Gerber . *Blood* 2004 Jul 1. 104 (1) p. .

[Hurwitz et al. (2013)] *Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. The oncologist*, H I Hurwitz , N C Tebbutt , F Kabbinavar , B J Giantonio , Z Z Guan , L Mitchell , D Waterkamp , J Tabernero . 2013 Sep 1. 18 p. .

[Kindler et al. (2010)] 'Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303)'. H L Kindler , D Niedzwiecki , D Hollis , S Sutherland , D Schrag , H Hurwitz , F Innocenti , M F Mulcahy , E O'reilly , T F Wozniak , J Picus . *Journal of Clinical Oncology* 2010 Aug 1. 28 (22) p. 3617.

[Burger et al. (2011)] 'Incorporation of bevacizumab in the primary treatment of ovarian cancer'. R A Burger , M F Brady , M A Bookman , G F Fleming , B J Monk , H Huang , R S Mannel , H D Homesley , J Fowler , B E Greer , M Boente . *New England Journal of Medicine* 2011 Dec 29. 365 (26) p. .

[Kindler et al. (2012)] 'Multicenter, doubleblind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma'. H L Kindler , T G Karrison , D R Gandara , C Lu , L M Krug , J P Stevenson , P A Jänne , D I Quinn , M N Koczywas , J R Brahmer , K S Albain . *Journal of Clinical Oncology* 2012 Jul 10. 30 (20) p. 2509.

[Aghajanian et al. (2012)] 'OCEANS: a randomized, double-blind, placebocontrolled phase III trial of chemotherapy with or without bevacizumab in patients with platinumsensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer'. C Aghajanian , S V Blank , B A Goff , P L Judson , M G Teneriello , A Husain , M A Sovak , J Yi , L R Nycum . *Journal of clinical oncology* 2012 Jun 10. 30 (17) p. 2039.

[Miles et al. (2010)] 'Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer'. D W Miles , A Chan , L Y Dirix , J Cortés , X Pivot , P Tomczak , T Delozier , J H Sohn , L Provencher , F Puglisi , N Harbeck . *Journal of Clinical Oncology* 2010 May 24. 28 (20) p. .

[Van Cutsem et al. (2009)] 'Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer'. E Van Cutsem , W L Vervenne , J Bennouna , Y Humblet , S Gill , J L Van Laethem , C Verslype , W Scheithauer , A Shang , J Cosaert , M J Moore . *Journal of clinical oncology* 2009 Mar 23. 27 (13) p. .

[Reck et al. (2009)] 'Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL'. M Reck , J Pawel , P Zatloukal , R Ramlau , V Gorbounova , V Hirsh , N Leighl , J Mezger , V Archer , N Moore , C Manegold . *Journal of Clinical Oncology* 2009 Feb 2. 27 (8) p. .

[Beller et al. ()] 'PRISMA for Abstracts: Reporting Systematic Reviews in Journal and Conference Abstracts'. E M Beller , P P Glasziou , D G Altman . *PLoS Med* 2013. 10 (4) p. e1001419.

[Robert et al. (2011)] 'RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer'. N J Robert , V Diéras , J Glaspy , A M Brufsky , I Bondarenko , O N Lipatov , E A Perez , Yardley Da Chan , S Y Zhou , X Phan , SC . *Journal of clinical oncology* 2011 Mar 7. 29 (10) p. .

[Tebbutt et al. (2011)] 'Risk of arterial thromboembolic events in patients with advanced colorectal cancer receiving bevacizumab'. N C Tebbutt , F Murphy , D Zannino , K Wilson , M M Cummins , E Abdi , A H Strickland , R M Lowenthal , G Marx , C Karapetis , J Shannon . *Annals of oncology* 2011 Jan 27. 22 (8) p. .

[Nalluri et al. (2008)] 'Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a metaanalysis'. S R Nalluri , D Chu , R Keresztes , X Zhu , S Wu . *Jama* 2008 Nov 19. 300 (19) p. .

[ZacharyI (2001)] 'Signaling mechanisms mediating vascular protective actions of vascular endothelial growth factor'. ZacharyI . *American Journal of Physiology-Cell Physiology* 2001 Jun 1. 280 (6) p. .

[Ebos et al. (2009)] 'Tumor and hostmediated pathways of resistance and disease progression in response to antiangiogenic therapy'. J M Ebos , C R Lee , R S Kerbel . *Clinical Cancer Research* 2009 Aug 15. 15 (16) p. .

[Ferrara (2004)] *Vascular endothelial growth factor: basic science and clinical progress. Endocrine reviews*, N Ferrara . 2004 Aug 1. 25 p. .

[Tam et al. (2006)] *VEGF modulates erythropoiesis through regulation of adult hepatic erythropoietin synthesis. Nature medicine*, B Y Tam , K Wei , J S Rudge , J Hoffman , J Holash , S K Park , J Yuan , C Hefner , C Chartier , J S Lee , S Jiang . 2006 Jul. 12 p. 793.