REVIEW

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The incidence of macular atrophy in patients with long-term use of anti-vascular endothelial growth factor (VEGF) in age-related macular degeneration (AMD): a systematic review and meta-analysis

Nyoman Yuni Suryani Dharmaputri P.[1], Putu Putri Titamia Saraswati[1], Ni Made Ari Suryathi[2], Ari Andayani[2*]

[1]Medical Doctor, Faculty of Medicine, Universitas Udayana;
[2]Ophthalmology Study Program, Faculty of Medicine, Universitas Udayana.

*Corresponding author:
Ari Andayani;
Ophthalmology Study Program, Faculty of Medicine, Universitas Udayana;
dr.ariandayani@gmail.com

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ABSTRACT

Background: Age-related macular degeneration (AMD) is the chief factor in sightlessness in affluent nations. Visual symptoms at a late stage of AMD are frequently severe and irreversible and might include drastically reduced center vision in both eyes. Patients with nAMD are mostly preserved with anti-vascular endothelial growth factor (VEGF) medications. Chronic anti-VEGF treatment, however, has also been connected to the emergence of macular atrophy (MA). This study aims to determine the prevalence of MA in AMD patients who have been on anti-VEGF medications for a long time.

Methods: The literature research was performed by systematically searching PubMed, Cochrane, ScienceDirect, and Google Scholar using the search terms "macular atrophy", "Anti-VEGF", "age-related macular degeneration", and "trial". The Review Manager v.5.4 and R statistical software v.3.3 are used in this study.

Results: The study includes 2094 individuals from 7 clinical trial trials. Anti-VEGF therapy had an overall proportion of MA episodes in MDA patients of 0.29 (95% CI 0.24 - 0.34). Between the anti-VEGF and control groups, there is no discernible difference in the risk of MA (OR 1.44; 95% CI 0.34 - 6.04; p=0.39). Additionally, there is no discernible difference between the comparison group and anti-VEGF regarding mean MA area scores (MD 0.03; 95% CI -0.28 - 0.34; p=0.85).

Conclusion: The incidence of MA in long-term anti-VEGF use with other comparators in AMD was not significantly different.

Keywords: age-related macular degeneration, anti-VEGF, macular atrophy.
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INTRODUCTION

The macula lutea is most impacted by age-related macular degeneration (AMD), a degenerative condition of the human retina. For people over 55, AMD is the leading cause of blindness in industrialized nations. By 2040, there are projected to be 288 million AMD cases worldwide, up from 196 million in 2020. The most significant number of people with this disease infection is anticipated to be in Asia.[1,2]

Early, moderate, and late phases of AMD are the different categories. The early and intermediate stages are categorized by macular deposits (drusen) and pigmentary abnormalities; visual symptoms are frequently absent or mild. AMD, in its late stages, can be either neovascular or atrophic. Visual symptoms at this stage can include severely diminished central vision in both eyes, typically severe and irreversible. Previously, more than 90% of severe vision loss in AMD was caused by nAMD.[1,3,4]

Patients with nAMD are mostly treated with anti-vascular endothelial growth factor (VEGF) medications. VEGF is essential for eye neovascularization in several disorders. In nAMD, VEGF is assumed to be the primary factor promoting angiogenesis and vascular permeability.[1,5] Macular atrophy (MA) is frequently associated with or follows AMD.[6] Chronic anti-VEGF therapy has also been linked to the progress of MA, but whether this is due to the disease's natural history or as a result of treatment is unclear.[7] This study aims to determine the prevalence of MA in AMD patients who have been on anti-VEGF medications for a long time.

METHOD

Search strategy

The literature research was performed by systematically searching PubMed, Cochrane, ScienceDirect, and Google Scholar using the search terms "macular atrophy", "Anti- VEGF", "age-related macular degeneration", and "trial". All databases were searched up to October 2023.

Selection criteria

All authors screened the candidate study. Studies were considered if they satisfied the following requirements: original research publications that contained MA events in patients who had used anti-VEGF for AMD for a long time, the kind and administration of anti-VEGF medication, and the length of follow-up.

Data extraction and risk of bias assessment

The following data was gathered and presented in the table from the eligible articles, including general information (first author, publication year, study design, country), baseline characteristics (trial name, population of AMD, age, type and administration of anti-VEGF treatment), event of MA, and MA area score. RoB 2 is used to assess the quality and risk of bias, and a revised Cochrane risk-of-bias method for randomized trials was utilized.

Statistical analysis

The main conclusions of this study included proportional differences, such as odds ratio (OR) and mean difference. The Cochran Q-test and I2 test were used to evaluate and determine the studies' heterogeneity. I2 > 50% and p 0.01 were regarded as indicators of considerable heterogeneity. The fixed effects model was employed unless there was sufficient heterogeneity, in which case the random effects model was applied. Additionally, Egger's tests and funnel plots were performed to assess any potential publication bias accurately. P-values less than 0.05 were considered statistically significant for all statistical analyses, which were carried out using Review Manager v.5.4 and R statistical software v.3.3.

RESULTS

PRISMA flowchart

The literature review found 1327 studies to be possibly relevant to this investigation. After reviewing the title and abstract, 1258 research papers were disqualified. Thirty-four papers were evaluated more thoroughly, 13 studies were successfully retrieved, and 7 studies were gathered for additional investigation. Figure 1 shows the PRISMA flow chart for study selection.

Features of the study

The analysis includes 7 trials, each with 2094 participants. The reported investigations were all clinical trials. Most of the studies were conducted in America, and the participants' average age was over 70. All trials included a follow-up period of more than 12 months. Table 1 lists each attribute of the included studies.

Study outcomes

Most studies report the use of Ranibizumab as an anti-VEGF therapy regimen which describe in Table 2. Anti-VEGF administration is carried out either orally or by injection. Overall, anti-VEGF administration was reported to have no significant effect on the incidence of MA in MDA.

Risk of bias analysis

Four research studies raise some doubts based on the risk of bias analysis. In the data reporting and selection domain, three studies showed a substantial risk of bias. On the other hand, the other three studies exhibited a minimal risk of bias. Figure 2 displays the outcomes of the description of the bias risk.

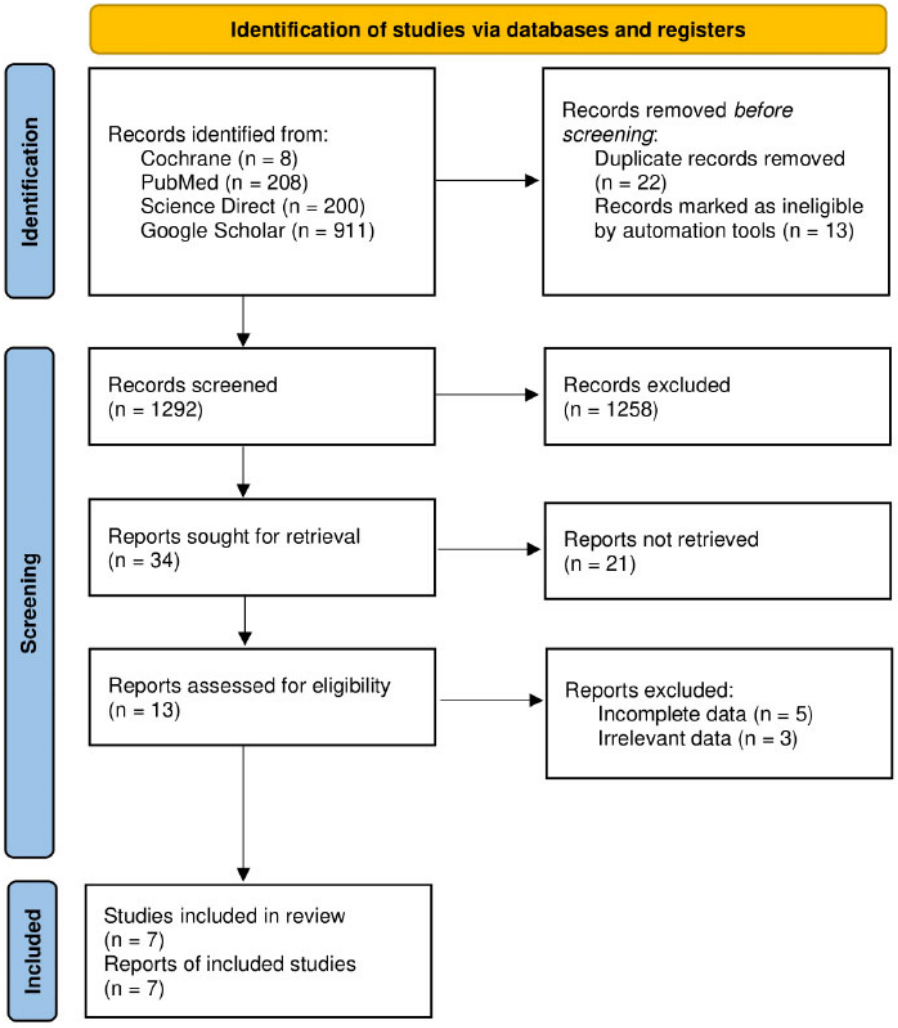

Figure 1. PRISMA flowchart.

Table 1. Study characteristics

Author, year	Study design	Country	Trial name	Population		Mean age ± SD (y)	Follow-up duration (m)
				Event of MA	Total		
Abdelfattah, 2016[8]	Multicenter, randomized, controlled clinical trial	United States	TREX-AMD	8	52	80 ± 8.4	18
Bailey, 2019[9]	Reading center analysis of data from a randomized controlled trial.	Germany	IVAN	64	248	77.5 ± 7.5	24
Blodi, 2023[10]	Phase 3, double-masked, randomized, sham-controlled clinical trial	United States	MARINA	99	318	N.A.	24
Gillies, 2019[11]	Phase 4, randomized, partially masked, multicenter study	Australia	RIVAL	78	225	76.6 ± 8.5	24
Jaffe, 2022[12]	Phase 2, multicenter, randomized, active treatment controlled, dose-ranging study.	United States	LADDER	85	209	73.8 ± 8.4	24
Sadda, 2018[13]	Multicenter, prospective, randomized, double-masked, active treatment controlled clinical trial phase 3.	United States	HARBOR	229	778	78.8 ± 8.4	24
Spooner, 2020[14]	Retrospective, multicenter study	Australia	MANEX	59	264	76.9 ± 8.8	48

Table 2. Study outcomes

Author, year	Anti-VEGF treatment		Main Results
	Type	Administration	
Abdelfattah, 2016[8]	Ranibizumab	Monthly dosing with intravitreal ranibizumab (0.5 mg)	Ranibizumab did not show a statistically significant influence on new MA development in eyes with neovascular AMD, whether dosed monthly or per TREX regimen
Bailey, 2019[9]	Ranibizumab, bevacizumab	Ranibizumab 0.5 mg; bevacizumab 1.25 mg	In eyes taking anti-VEGF medication for more than 2 years, macular atrophy frequently occurs within a nAMD lesion.
Blodi, 2023[10]	Ranibizumab	Ranibizumab 0.3 mg and 0.5 mg	Ranibizumab-treated eyes had new macular atrophy, found more frequently than sham-treated eyes.
Gillies, 2019[11]	Ranibizumab, aflibercept	Ranibizumab 0.5 mg; aflibercept 2.0 mg	In nAMD patients treated with the same T&E regimen, there were no appreciable changes in the rate of development or expansion of MA for 24 months between ranibizumab and aflibercept.
Jaffe, 2022[12]	PDS ranibizumab, monthly intravitreal ranibizumab	PDS ranibizumab (10 mg/ml, 40 mg/ml, 100 mg/ml); monthly intravitreal ranibizumab 0.5 mg	There was no proof that the PDS caused worse MA as compared to monthly intravitreal ranibizumab 0.5-mg injections.
Sadda, 2018[13]	Ranibizumab	Monthly 0.5 mg or 2.0 mg injection	New MA was detected in 29% of study eyes after 24 months of treatment. Thus, the benefits of ranibizumab for neovascular AMD outweighed the risk of MA development over 24 months.
Spooner, 2020[14]	Ranibizumab, aflibercept, bevacizumab	PRN (Three loading doses of anti-VEGF injections), T&E (Three monthly loading doses of anti-VEGF treatment)	There is no association between anti-VEGF T&E and PRN treatment strategies with the risk of developing new macular atrophy during the four years of follow-up or the progression of pre-existing macular atrophy at year 4. Eyes treated with a T&E regimen received more injections and had better visual outcomes than those treated with a PRN approach.

Quantitative analysis

The analysis showed that the overall proportion of MA events in MDA patients who were given anti-VEGF therapy was 0.29 (95% CI 0.24 - 0.34). Furthermore, there was significant heterogeneity among studies ($\chi 2$ <0.001; I2 = 97%). The forest plot is described in Figure 3. Furthermore, the studies' heterogeneity was insignificant ($\chi 2$ = 0.21; I2 = 35%). Figure 4 describes the forest plot.

Publication bias

The likelihood of publication bias was also examined. The Egger test revealed that a quantitative study of the tendency for publication bias was not significant (p>0.05). The Funnel plot is displayed in

Figure 2. Risk of bias among studies.

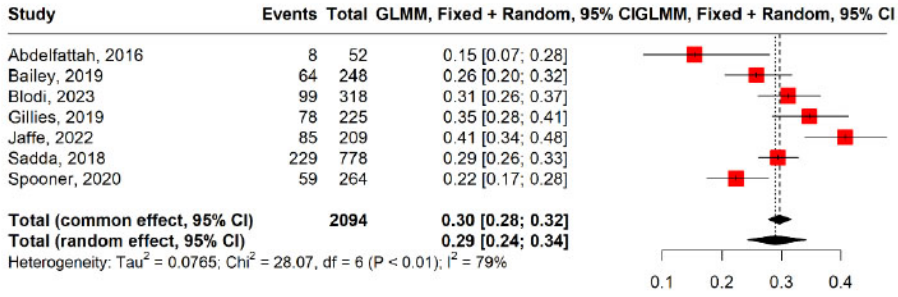

Figure 3. MA incidence across studies Our analysis found no discernible difference between the anti-VEGF and comparator group in terms of the risk of MA (odds ratio [OR] 1.44; 95% CI 0.34 - 6.04; p=0.39). Additionally, there was a large amount of study heterogeneity ($\chi 2$ = 0.03; I2 = 71%). Additionally, according to our research, there was no discernible change in the mean MA area scores between the anti-VEGF and control groups (Mean difference [MD] 0.03; 95% CI -0.28 - 0.34; p=0.85).

Figure 5 and Figure 6A-B as a qualitative analysis. There was symmetry in the funnel plot, which suggests a low probability of publishing bias.

DISCUSSION

This study demonstrates that patients with AMD who utilize anti-VEGF for a prolonged period have a rather significant incidence of MA. Due to the degradation of photoreceptors, pigment epithelium, and choriocapillaries, MA, which is present in neovascular AMD (nAMD), results in a significant loss of central vision. Stylani et al. (2021) showed that 50% of neovascular AMD patients taking anti-VEGF therapy who did not already have MA at the beginning of treatment developed MA over a minimum of 6 years.[15]

The choroid may thin as a result of anti-VEGF treatment for AMD. When compared to unaffected eyes, eyes with MA have thinner choroids. The MA area increases in correlation with a thinner choroid. Anti-VEGF medications might make AMD patients' choroidal thinning worse, raising their chance of MA and degrading their visual outcomes.[16,17] The choroid and choriocapillaris must develop in the presence of VEGF produced by RPE. Since aberrant neovascularization in these patients occurs before the loss of choroidal circulation from atrophy, anti-VEGF drugs may cause the sickness to revert to its earlier atrophic state. To increase the risk of MA in one eye, the MNV subtype, advancing age, and choroidal thickness may interact.[17]

Under the variable dosage regimen, when fewer injections were required, the incidence of MA was greater. If further injections were needed because the illness was acting up, the risk of MA did not increase. The incidence of MA in people with treated nAMD ranges from 18% to 61% in the literature, depending on the imaging techniques and language employed.11 De novo MA formation is prevalent and complicated in nAMD treated with anti-VEGF. There is little to no evidence that the type of treatment or systemic risk factors have any impact, and most risk factors identified so far are ocular.[18,19]

An important hallmark of nAMD eyes with a high propensity for MA development is elevated VEGF levels. It would stop the wounded macula from atrophying and fibrosing. Some potential pathogenic pathways in MA include the ones listed below 1) the natural progression of the underlying dry AMD, 2) the negative consequences of CNV expansion or retraction, and 3) interference with basal VEGF levels. In nAMD eyes being treated with anti-VEGF therapy, aqueous humor cytokine levels can be used to forecast the onset of MA. Significant decrease in IP-10 effects and persistent inflammation have an impact on MA incidence.[20]

Some limitations to this study should be noted when interpreting the findings. First, this study's data sources do not include all worldwide regions, which may restrict the findings' representativeness. Additionally, few studies compare the prevalence of MA among long-term anti-VEGF users with those of other comparators. Thus, the number of included studies described quantitatively is relatively small.

CONCLUSION

Some of the included studies revealed that long-term anti-VEGF treatment for AMD patients significantly increases the risk of MA. The research, however, showed no discernible difference between the incidence of MA in long-term anti-

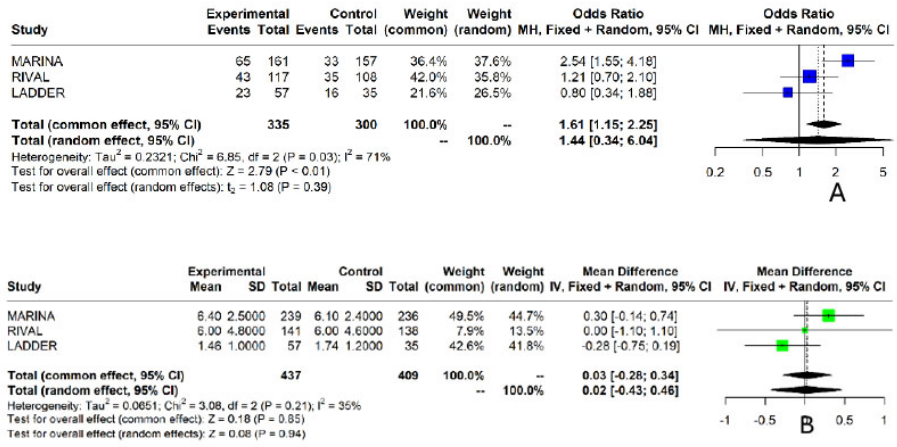

Figure 4. (A) Odd ratio for MA; (B) Mean difference of MA area between patient given anti-VEFG vs comparator.

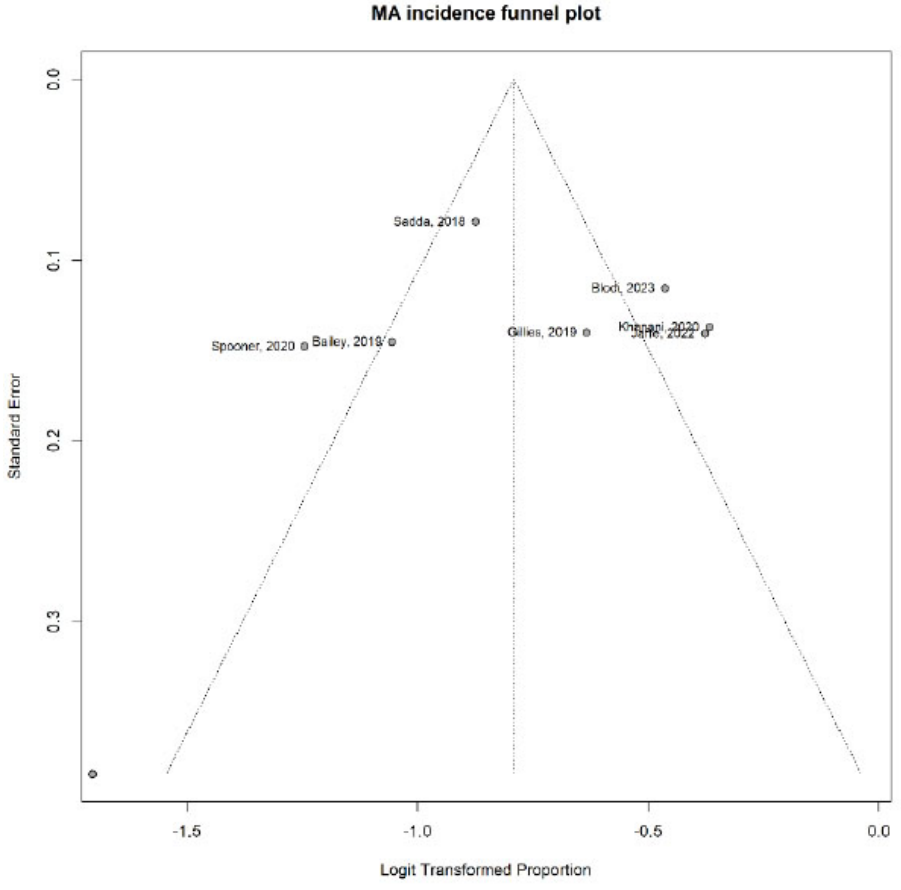

Figure 5. Funnel plot for MA incidence across studies.

VEGF users and other comparators in AMD. MA is a challenge for eye health as a complication or long-term treatment effect of nAMD; therefore, enhancing awareness of the risk factors behind the formation of MA might promote research and development of new medicines to treat this illness.

ETHICAL CLEARANCE

Publication ethics are not necessary for this research as it is a review article.

CONFLICT OF INTEREST

None.

FUNDING

None.

AUTHOR CONTRIBUTION

All authors accepted the final manuscript.

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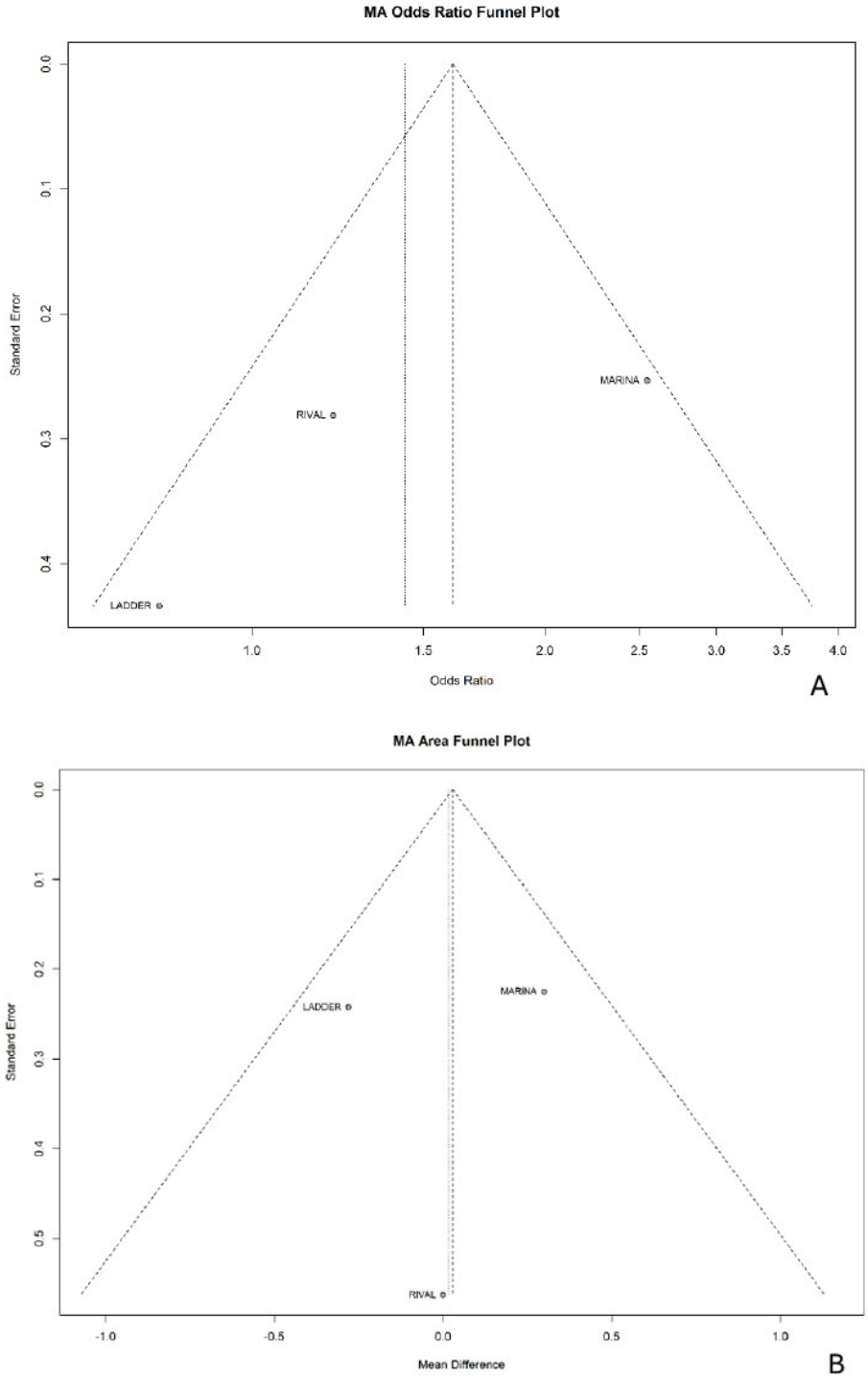

Figure 6. (A) A funnel plot is used for the odd ratio of MA; (B) a funnel plot is used for the mean difference of MA area between patients given anti-VEFG vs comparator.

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