

RESEARCH LETTER

Doxycycline is not Effective in Reducing Abdominal Aortic Aneurysm Growth: A Mini Systematic Review and Meta-Analysis of Randomised Controlled Trials

Despite extensive study, no effective drug treatment has been found for prevention of abdominal aortic aneurysms (AAA).¹ Furthermore, no treatment has been able to reduce or halt the growth of AAAs.¹

One hypothesis is to target metalloproteinases (MMP), activated in the inflammatory response in the aneurysm wall. Doxycycline has been shown to reduce the level of MMPs in both animal models and humans.² Animal models have shown that this effect leads to a significant reduction in aneurysm growth, which has led investigators to perform these studies in humans.²

A systematic review and meta-analysis was performed of randomised controlled trials analysing the effect of doxycycline compared with placebo in the reduction of aneurysm growth (PROSPERO CRD42020201058).

The review followed the PRISMA guidelines. Medline, Embase, and CENTRAL were searched from inception to July 2020 for all studies reporting on the effect of doxycycline vs. placebo on unexposed patients on aneurysm growth prior to repair (search strategy detailed in PROSPERO). Articles were screened and data were appraised and extracted by two authors (RGM and MRR). Data were pooled using a random effects model, and quantitative analysis was performed with Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration, 2020). Statistical heterogeneity was reported through the I^2 measure. The main outcome was the mean difference in aneurysm growth (diameter) during the time of the study. These were computed as mean (standard deviation, SD). When studies reported median (instead of mean), or confidence interval (instead of SD), the values were computed using the methods described by Wan *et al.*³ and using the RevMan calculator, respectively.

The secondary outcome was the risk ratio of aneurysm repair.

The electronic database yielded 695 articles, of which, after title/abstract review, 20 papers were evaluated in full text. Of these, three were included in the qualitative and quantitative synthesis.^{2,4,5}

Of the three studies included, all were randomised placebo controlled clinical trials. All three studies analysed different daily doses of doxycycline and also had different follow up periods. Baxter *et al.*⁴ studied 100 mg twice daily for an intended follow up of two years, Meijer *et al.*² studied 100 mg once daily for an intended follow up of 18 months, and Mosorin *et al.*⁵ studied 150 mg once daily for three months, for an intended follow up of 18 months. Baseline aneurysm diameters also varied. In the Baxter *et al.*⁴ study, patients were included with a diameter

between 3.5 and 5.0 cm for men and 3.5 and 4.5 cm for women. Meijer *et al.*² included patients with AAAs between 3.5 and 5.0 cm, and Mosorin *et al.*⁵ included patients with AAAs between 3.0 and 5.5 cm.

Outcome assessment and definition of aortic diameter varied, leading to a potential measurement bias. In the Baxter *et al.*⁴ study, outcome was assessed by CT and the maximum transverse diameter was measured perpendicular to the centre line. Both Meijer *et al.*² and Mosorin *et al.*⁵ used abdominal ultrasound to assess the outcome. Meijer *et al.*² defined the diameter as the largest inner to inner aortic wall measurement of the anteroposterior distance perpendicular to the blood flow, and Mosorin *et al.*⁵ as the largest abdominal aortic diameter, either anteroposterior or transverse.

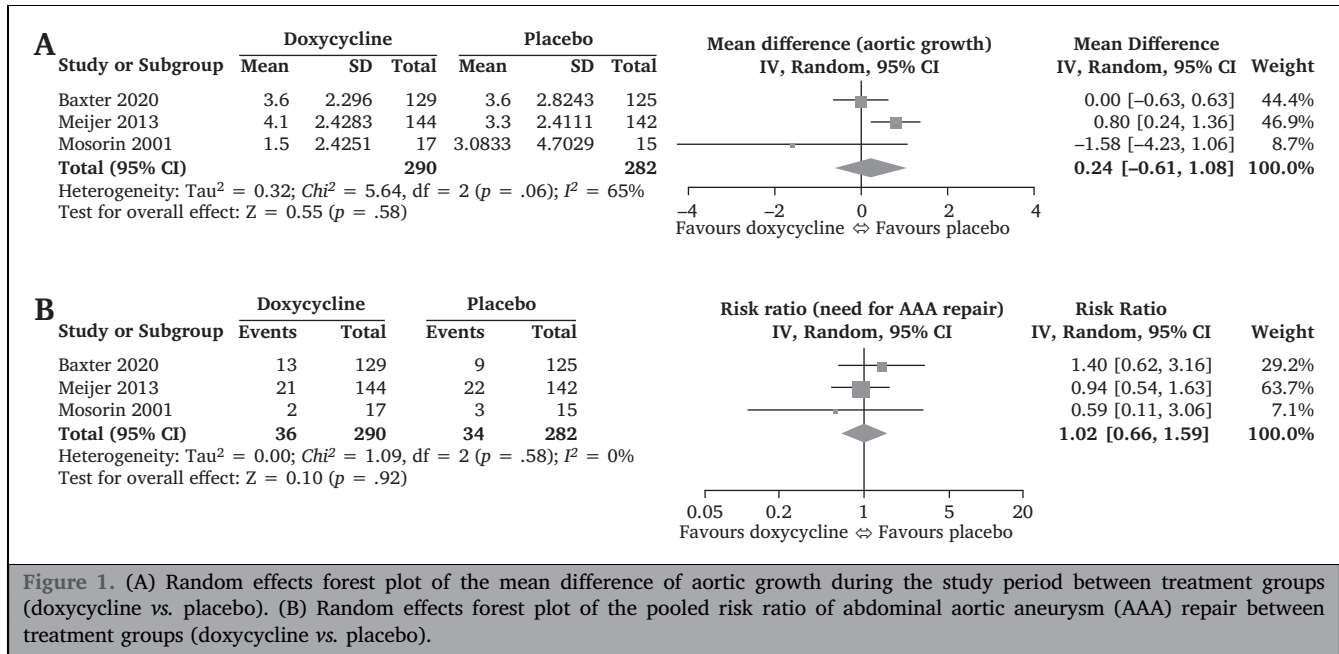
Overall, 572 patients were analysed, 290 patients in the doxycycline arm and 282 in the placebo arm. Complete follow up, regarding aneurysm growth at the end of the study was present in only 432 patients. Baseline aneurysm diameter was similar in both groups except in the Mosorin *et al.*⁵ study, in which there was statistically non-significant higher baseline diameter in the placebo group.

The Mosorin *et al.*⁵ study was considered to have high risk of bias because of unclear risk regarding sequence generation, selective outcome reporting, and resulting from baseline differences. Both the Baxter *et al.* and Meijer *et al.* studies^{2,4} were considered to have low risk of bias.

Overall, doxycycline did not show a reduction in aneurysm growth during the study period, with a pooled mean difference between treatment groups of 0.24 mm (95% CI -0.61 – 1.08; $p = .58$; I^2 65%) (Fig. 1A). Doxycycline also did not reduce the need for aneurysm repair, with a pooled risk ratio of achieving a diameter eligible for repair of 1.02 (95% CI 0.66 – 1.59; $p = .92$; I^2 0%) (Fig. 1B).

These results demonstrate that doxycycline was not effective in preventing either small AAA growth or the need for repair, at therapeutic dosage.

The MMP pathway has been described previously and multiple animal and *ex vivo* models have demonstrated its role in aortic dilation, as well as the inhibitory effect of doxycycline on these molecules, both by inhibition of the inflammatory cascade and probably by direct effect on the production of these proteins (post-translation blockage).^{2,4–6} However, other cellular effects of doxycycline have been described namely, a mitochondrial dysfunction affecting cell function and proliferation which may have a deleterious effect on aneurysm wall and further reduce its regenerative ability.^{6,7} One may argue, in conclusion, that doxycycline, in its multiple cellular effects may not be an adequate strategy to inhibit this pathway, suggesting the need for a more selective intervention in its effect on MMPs or perhaps a need to start challenging previous beliefs regarding this pathophysiological pathway and their translational models.



REFERENCES

- 1 Wanhainen A, Verzini F, van Herzele I, Allaire E, Bown M, Cohnert T, et al. European Society for Vascular Surgery (ESVS) 2019 Clinical practice guidelines on the management of abdominal aorto-iliac aneurysm. *Eur J Vasc Endovasc Surg* 2019;**57**:8–93.
- 2 Meijer CA, Stijnen T, Wasser MN, Hamming JF, van Bockel JH, Lindeman JH. Pharmaceutical Aneurysm Stabilisation Trial Study Group. Doxycycline for stabilization of abdominal aortic aneurysms: a randomized trial. *Ann Intern Med* 2013;**159**:815–23.
- 3 Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;**14**:135.
- 4 Baxter BT, Matsumura J, Curci JA, McBride R, Larson L, Blackwelder W, et al. Effect of doxycycline on aneurysm growth among patients with small infrarenal abdominal aortic aneurysms/ a randomized clinical trial. *JAMA* 2020;**323**:2029–38.
- 5 Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M, et al. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. *J Vasc Surg* 2001;**34**:606–10.
- 6 Waard V, Wanga S, Wust RC, Balm R, Houtkooper RH, Vries CJ, et al. Doxycycline inhibits mitochondrial and cellular function in

aorta smooth muscle cells. *Arterioscler Thromb Vasc Biol* 2019;**39**:A656.

- 7 Wüst RCI, Houtkooper RH, Auwerx J. Confounding factors from inducible systems for spatiotemporal gene expression regulation. *J Cell Biol* 2020;**219**:e202003031.

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