

# Medical Management of abdominal aortic aneurysms (AAA) - Will it work?

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Abdominal aortic aneurysm (AAA) is a potentially lethal disease process which is common (4-9%) but easily and inexpensively detected by ultrasound.<sup>1</sup> The starting point for the medical management of AAA is early detection. **Despite the high frequency of AAA in the elderly, routine screening has not been advocated.** The reasons for this is that most (9/10) AAA detected in screening programs are small. Since less than one percent (1/10 of the 4-9% with AAA) of individuals screened have an aneurysm that will require treatment at the time of detection, screening is not considered cost-effective. In addition, this information may put the patient in a quandary as they are made aware that they have an asymptomatic but life-threatening problem for which no immediate therapy is recommended. If there were a safe medical treatment that could be initiated at the time of detection, this perspective on aneurysm screening would likely change drastically because all small aneurysms would then warrant immediate treatment.

If aneurysm growth were slowed but not arrested, wouldn't that just delay surgery to a future date when the patient might be at higher risk for repair?

The answer to this is "Maybe" and here is the reason that this question must be addressed in carefully controlled studies. If a medical treatment reduced the growth rate by 10-20%, then the delay prior to the time when intervention were required would not be very long. This strategy might put the patients at greater risk. On the other hand, consider the effects of 30-50% inhibition of AAA growth. (Fig 1)

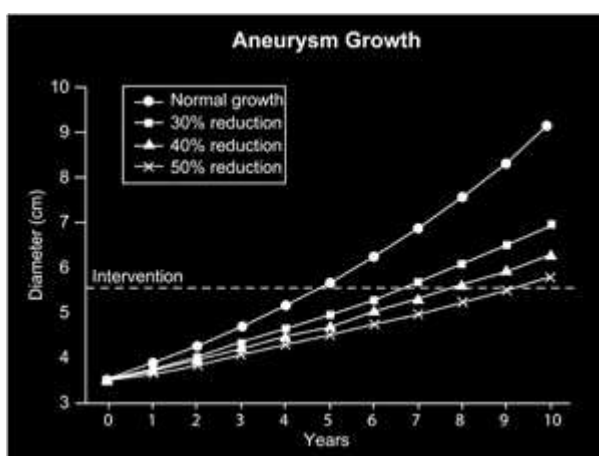


Fig1 - Click image to view larger version

This figure shows the effect of reducing AAA growth rate by 30, 40 and 50%. As a group, AAA patients have a relatively high mortality from all causes (6-7%/year). Thus, a significant decrease in the growth rate means that many patient will die of other causes before

their aneurysm reaches a size requiring intervention (5-5.5 cm). When physicians and surgeons were surveyed and asked what level inhibition of AAA growth they would consider useful, they said it should inhibit growth by at least 30%.<sup>2</sup> This seems a reasonable approach considering the long term effects shown in figure 1.

What about propranolol for inhibiting expansion of infrarenal aortic aneurysms?

There are several reasons to think that propranolol might work including:

- Its ability to reduce blood pressure, heart rate and shear stress
- In experimental studies, it has some favorable biochemical effects
- In retrospective studies it decreases the proportion of AAA which grow rapidly
- It inhibits aneurysm expansion in patients with Marfan Syndrome

Despite all of this suggestive evidence, prospective trials show that it doesn't work.<sup>3</sup> In addition, the drug was very poorly tolerated in many of the patients because of its numerous side-effects.

What is the role of matrix metalloproteinases or MMPs in AAA?

Histologic studies of human aneurysm tissue show that there is destruction of the well-organized lamellar structure of the aorta. The proteins that are damaged include elastin and collagen, both very durable proteins. The MMPs were implicated because of their ability to degrade these proteins. Several members of the MMP family are found in abundance in human AAA tissue. In order to find out if they had a causal role in this process or were simply bystander proteins that accompanied an inflammatory response, MMP inhibitors were evaluated in animal models of AAA. This approach was effective in blocking aneurysm formation. The first study to assess the potential role of MMP inhibitors used doxycycline and the inhibitor.<sup>4</sup>

Experimental studies in the 1980's had shown that doxycycline was a broad spectrum MMP inhibitor. This side effect was independent of its antibiotic activity. Two other important steps were taken on the way toward a trial of doxycycline in AAA patients. When doxycycline was given to patients prior to aortic aneurysm repair, aortic tissue levels of MMPs were decreased.<sup>5</sup> Since the doses of doxycycline used in animal models of AAA were extremely high (50-100 mg/kg) in comparison to the normal human dose (2-3 mg/kg), the circulating levels in animals and AAA patients were compared and found to be comparable. That is, patients taking 200 mg of doxycycline per day achieved circulating doxycycline levels that were seen in the animal models.<sup>6</sup> Taken together, these data suggested that doxycycline should inhibit the rate of AAA expansion in patients.

Are there clinical data to show that doxycycline will work?

The first prospective trial comparing doxycycline to placebo has now been published.<sup>7</sup>

This was a small trial with 32 patients randomized to 3 months of

doxycycline or placebo. They were then followed for 18 months at six-month intervals with ultrasound. When analyzed over the entire 18-month period, there were no differences in the growth rate between the placebo and doxycycline-treated patients. When interval analysis was done at 0-6, 6-12 and 12-18 months, less growth was observed in the doxycycline group compared to the placebo group in both the 6-12 month time period and the 12-18 month time period.

While the experimental data leading up to the first clinical trial are promising, we have to keep in mind that chronic diseases such as atherosclerosis and AAA cannot be precisely mimicked in animal models. We are all aware of studies where exciting experimental findings did not translate into improved outcomes when finally tested in clinical trials. Some of the clinical trials of MMP inhibitors in neoplastic disease have been disappointing despite promising experimental results. The first clinical trial in AAA patients suggests that doxycycline may well work. This trial was small and despite randomization, there were differences between groups in the percent of smokers (more smokers in the placebo group) and the initial aneurysm size (larger aneurysms in the placebo group). However, this study is an important starting point for larger prospective trials, which are currently under development. Hopefully these trials will demonstrate the efficacy of a new and exciting approach to the treatment of aneurysmal disease.

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