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ORIGINAL RESEARCH

Effect of Two Years of Doxycycline Treatment on Infrarenal Aortic Neck Diameter[‡]

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Objective: Endovascular aneurysm repair (EVAR) is a widely used option for patients with suitable vascular anatomy who have a large infrarenal abdominal aortic aneurysm (AAA). Neck diameter is the primary anatomical determinant of EVAR eligibility and device durability. Doxycycline has been proposed to stabilise the proximal neck after EVAR. This study explored doxycycline mediated aortic neck stabilisation in patients with small AAA, monitored by computed tomography over two years.

Methods: This was a multicentre prospective randomised clinical trial. Subjects from the Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^{3}CT, NCT01756833) were included in this secondary *a priori* analysis. Female baseline AAA maximum transverse diameter was between 3.5 and 4.5 cm, and male was between 3.5 and 5.0 cm. Subjects were included if they completed pre-enrolment and two year follow up computed tomography (CT) imaging. Proximal aortic neck diameter was measured at the lowest renal artery, and 5, 10, and 15 mm caudal to this point; mean neck diameter was calculated from these values. Unpaired, two tailed parametric t test analysis with *post hoc* Bonferroni correction was used to detect differences between neck diameters in subjects treated with placebo *vs.* doxycycline at baseline and two years.

Results: One hundred and ninety-seven subjects (171 male, 26 female) were included in the analysis. All patients, regardless of treatment arm, demonstrated larger neck diameter caudally, a slight increase in diameter at all anatomical levels over time, and greater growth caudally. There was no statistically significant difference in infrarenal neck diameter between treatment arms at any anatomical level at any time point, nor mean change in neck diameter over two years.

Conclusion: Doxycycline does not demonstrate infrarenal aortic neck growth stabilisation in small AAA followed for two years by thin cut CT imaging using a standardised acquisition protocol and cannot be recommended for mitigation of growth of the aortic neck in patients with untreated small abdominal aortic aneurysms.

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INTRODUCTION

Abdominal aortic aneurysm (AAA) has been estimated to impact 3–5.4% of the growing elderly population in the United States.[1] Management of AAA involves serial imaging to monitor growth of maximum transverse diameter (MTD) and repair is recommended when this value reaches 5.5 cm in males and 5.0 cm in females, due to elevated risk of rupture.[2] Endovascular aneurysm repair (EVAR) is a minimally invasive approach to treat AAAs and compared with open repair, has been associated with reduced intra-operative mortality,[3,4] peri-operative mortality,[5] and recovery time.[6]

Infrarenal aortic neck size is a key anatomical determinant for EVAR eligibility and patients who have met maximum transverse diameter (MTD) criteria for repair but whose neck size exceeds suitability for currently available

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EVAR devices will be deferred to open AAA repair or complex EVAR. Furthermore, post-EVAR, late aortic neck dilation in the absence of a sutured anastomosis may lead to subsequent loss of seal and fixation with adverse late outcomes including acute endograft migration and development of type Ia endoleak, which may lead to catastrophic AAA rupture.[7] Thus, stabilisation of the aortic neck is a meaningful pharmacological target for patients with AAA both before and after repair.

The association between elevated expression of matrix metalloproteinases (MMPs) and AAA is well established,[8] with a proposed mechanism of MMP mediated degradation of the aortic wall leading to its outward expansion. Preoperative treatment with doxycycline prior to elective AAA repair has previously been associated with reduced MMP-9 expression,[9] and the effect of doxycycline on post-EVAR aortic neck dilation has been explored in a small randomised trial.[10]

In order to assess whether metalloproteinase inhibition via doxycycline stabilises growth of the proximal aortic neck, this study analysed 197 patients with AAAs between 3.5 and 5.0 cm from the Non-invasive Treatment of AAA Clinical Trial (N-TA^{3}CT, NCT01756833) to determine whether the aortic neck is stabilised over two years.

MATERIAL AND METHODS

The data included in this study were collected from N-TA^{3}CT, a multicentre, randomised, double blind, placebo controlled, clinical trial. The primary outcome of N-TA^{3}CT was change in AAA maximum transverse diameter over two years, as measured by multiplanar computed tomography (CT). The study design, including image quality requirements (CT imaging with slice thickness $\leq$2.5 mm, reconstruction overlap minimum 50%, contrast not required), subject selection, details of the randomisation process and power analysis used to determine sample size, and the primary findings of N-TA^{3}CT have been published previously.[11,12] The protocol was approved by the Institutional Review Boards at all clinical sites, core laboratories, and coordinating centres. All randomised patients gave written informed consent. The primary outcomes demonstrated that two years of doxycycline 100 mg orally twice daily did not significantly affect maximum transverse diameter growth, which is the primary indicator for elective AAA repair as described above.[12] Pre-specified (*a priori*) secondary analysis included comparison of neck diameter between the two randomised treatment groups, and is the topic of this report.

Subject selection

Subjects were included in this neck analysis if they had imaging at both pre-enrolment (baseline) and two years post-enrolment, and both imaging timepoints included the proximal neck. Subjects were required to have sufficient imaging (e.g., extending through the proximal neck) at both time points. Patients who underwent AAA repair (open or endovascular) prior to two years were excluded, either because (1) data were not available at two years or (2) if data were available, the authors believed that post-EVAR measurements would not accurately capture the natural disease course in these patients, as there is evidence that EVAR itself can cause dilation of the proximal aortic neck in the peri-operative period, possibly due to device or balloon inflation, imaging artifact from the metal attachment system, or inflammatory thickening of the aortic wall immediately post-procedure.[7] Males were included in NTA^3 CT if their baseline AAA MTD was between 3.5 and 5.0 cm, and females were included if their baseline AAA was between 3.5 and 4.5 cm.

Computed tomography measurements

Computed tomography analysis was performed on a commercial post-processing workstation (Aquarius Intuition, version 4.4.12; TeraRecon), using a manually corrected automated aortic centreline. Aortic neck diameter was measured outer wall to outer wall and perpendicular to the centreline (in the orthogonal view)[13] at four locations: at the first slice just distal to the distal ostium of the lowest significant renal artery (LRA), and 5, 10, and 15 mm distal to this location. Average neck diameter was calculated by the mean of these values. All neck diameter measurements were performed prospectively at baseline and two years by a single reader at a centralised core laboratory (AortaCore Aortic Imaging Lab, Madison, WI) who followed a standardised, validated protocol and was blinded to the treatment group. In a subset of 10 randomly selected subjects, the intra-observer intraclass correlation coefficient for neck diameter measurements performed by this reader was 0.96 (95% confidence interval 0.86—0.99).

Statistical analysis

Unpaired two tailed t test analysis was used to detect differences in measurements of neck diameters between subjects treated with doxycycline and those treated with placebo at baseline and two years with an intention to treat approach. *Post hoc* modified Bonferroni correction yielded an alpha level of .0125 for assessing the statistical significance of each individual t test performed at each component anatomical level (LRA, 5 mm, 10 mm, 15 mm).[14] Statistical analysis was completed using StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

RESULTS

Baseline characteristics

Randomisation for N-TA^{3}CT took place from May 2013 to January 2017 at 22 US clinical sites. Of the 261 subjects in the N-TA^{3}CT trial, 197 subjects were eligible for inclusion in the present analysis (Supplementary Figure S1) (96 treatment group subjects, 101 control group subjects.) There were 171 males and 26 females included in the study. Sixty-four patients were excluded based on lack of two year imaging. Twenty-two subjects underwent repair prior to two

year imaging (21 endovascular repair, one open repair; 13 doxycycline subjects, nine control subjects, $p = .49$) and were therefore excluded from the study and constituted a portion of the 64 aforementioned patients. Two subjects were repaired following two year imaging and were thus included in the analysis. There were no AAA ruptures. The baseline characteristics of the patient population are summarised in Table 1. The mean age of patients was 70.8 years old (standard deviation 7.4). Ninety-three per cent were current or former smokers. Common comorbidities included hypercholesterolaemia (80%), coronary artery disease (42%), cancer (30%), diabetes mellitus (24%), and chronic obstructive pulmonary disease (22%).

Table 2 summarises mean diameter at the four anatomical levels and their average, and mean change in neck diameter over two years in patients treated with doxycycline *vs.* placebo, in millimetres. There was no statistically significant difference in mean diameter at four anatomical levels or in average neck diameter, and there was no statistically significant difference in change in mean diameter at two years when using an alpha level of .0125 via the modified Bonferroni correction. In general, greater increase in mean diameter was observed at the more caudal levels for both treatment groups; a +0.3 mm and +0.5 mm increase in diameter was observed in control and treatment subjects, respectively at 15 mm below the LRA, compared with mean changes of −0.43 and 0.08 mm observed in control and treatment subjects, respectively at the level of the LRA. Sex specific results of these values can be found in Supplementary Tables S1 and S2. These demonstrated no significant differences by sex.

Figure 1 serves as a visual example of a subject randomised to treatment with doxycycline who demonstrated stable neck diameter at all four anatomical levels over two years.

DISCUSSION

This study adds to existing literature regarding the impact of doxycycline on AAA neck size, an important determinant of both EVAR eligibility and durability. Importantly, this is the largest sample size ever studied to detect aortic neck stabilisation in patients treated with doxycycline *vs.* placebo, and measurements were performed on standardly acquired, thin cut CT by an independent core laboratory analyst who demonstrated excellent reproducibility. Thus, beyond revealing the impact of doxycycline on neck diameter, the study offers high quality, longitudinal data regarding aortic neck behaviour.

Table 1. Baseline characteristics of the 197 subjects included in this analysis.

Characteristics	All subjects ($n = 197$)	Doxycycline ($n = 96$)	Control (n = 101)
Demographics			
Age — y	70.8 ± 7.4	70.6 ±7.4	70.9 ± 7.3
Sex			
Female	26 (13)	11 (11)	15 (15)
Male	171 (87)	85 (89)	86 (85)
Health status			
Smoking status			
Current	64 (32)	28 (29)	36 (36)
Former	120 (61)	62 (65)	58 (57)
Never	13 (7)	6 (6)	7 (7)
Hypercholesterolaemia	157 (80)	76 (79)	81 (80)
Coronary artery disease	83 (42)	38 (40)	45 (45)
Cancer	59 (30)	31 (32)	28 (28)
Diabetes mellitus	48 (24)	29 (30)	19 (19)
Chronic obstructive pulmonary disease	44 (22)	23 (24)	21 (21)
Family history of abdominal aortic aneurysm	39 (20)	22 (23)	17 (17)
Atrial fibrillation	25 (13)	11 (11)	14 (14)
Stroke	22 (11)	9 (9)	13 (13)
Congestive heart failure	14 (7)	8 (8)	6 (6)
Medication			
Statin	163 (83)	80 (83)	83 (82)
Antihypertensive			
β Blocker	104 (53)	52 (54)	52 (51)
Diuretics	66 (34)	32 (33)	34 (34)
Angiotensin converting enzyme inhibitor	65 (33)	34 (35)	31 (31)
Calcium channel blocker	48 (24)	21 (22)	27 (27)
Angiotensin receptor blocker	40 (20)	19 (20)	21 (21)
Aspirin or other antiplatelet			
Daily aspirin	140 (71)	66 (69)	74 (73)
Other antiplatelet	36 (18)	14 (15)	22 (22)

Data are presented as mean ± standard deviation or *n* (%).

Table 2. Maximum diameter over two years in patients treated with doxycycline *vs.* placebo at four anatomical levels, from the level of the lowest renal artery (LRA) distally in 5 mm increments, and the average of these values.

Maximum diameter − mm	All subjects($n = 197$)	Control($n = 101$)	Doxycycline($n = 96$)	Difference	p value
LRA					
Pre-enrolment	24.6 ± 3.7	24.6 ± 2.9	24.7 ± 4.4	−0.1 (−1.1—1.0)	.89
24 months	24.4 ± 4.0	24.1 ±2.8	24.7 ± 5.0	−0.6 (−1.7—0.5)	.31
Change at 24 months	−0.18 ± 1.6	−0.43 ±1.6	0.076 ± 1.5	−0.5 (−0.9 — −0.1)	.0232
5 mm below LRA					
Pre-enrolment	24.7 ± 4.1	24.6 ± 3.3	24.9 ± 4.8	−0.2 (−1.4—0.9)	.70
24 months	24.8 ± 4.5	24.6 ± 3.3	25.0 ± 5.5	−0.4 (−1.7—0.9)	.56
Change at 24 months	0.07 ± 1.5	−0.01 ± 1.5	0.15 ± 1.6	−0.2 (−0.6—0.3)	.47
10 mm below LRA					
Pre-enrolment	25.2 ± 4.4	25.0 ± 3.8	25.5 ± 5.0	−0.4 (−1.7—0.8)	.49
24 months	25.5 ± 5.1	25.2 ± 4.0	25.9 ± 6.1	−0.7 (−2.1—0.8)	.36
Change at 24 months	0.28 ± 2.0	0.16 ± 1.8	0.4 ± 2.3	−0.2 (−0.8—0.3)	.42
15 mm below LRA					
Pre-enrolment	26.0 ± 4.8	25.7 ± 4.2	26.2 ± 5.3	−0.4 (−1.8—0.9)	.52
24 months	26.3 ± 5.5	26.0 ± 4.6	26.6 ± 6.3	−0.6 (−2.2—0.9)	.43
Change at 24 months	0.37 ± 2.0	0.28 ± 1.7	0.46 ± 2.4	−0.2 (−0.8—0.4)	.53
Average neck diameter					
Pre-enrolment	25.1 ± 4.0	25.0 ± 3.3	25.3 ± 4.7	−0.3 (−1.4—0.8)	.61
24 months	25.2 ± 4.5	25.0 ± 3.4	25.6 ± 5.5	−0.6 (−1.8—0.7)	.38
Change at 24 months	0.13 ± 1.5	0.0004 ± 1.4	0.27 ± 1.7	−0.3 (−0.7—0.2)	.21

Data are presented as mean ± SD; 95% confidence intervals are reported for mean difference between the two treatment arms. *Post hoc* Bonferroni correction for change in diameter at 24 months at the level of the LRA, 5, 10, and 15 mm distal to this point yielded a significance level of .0125.

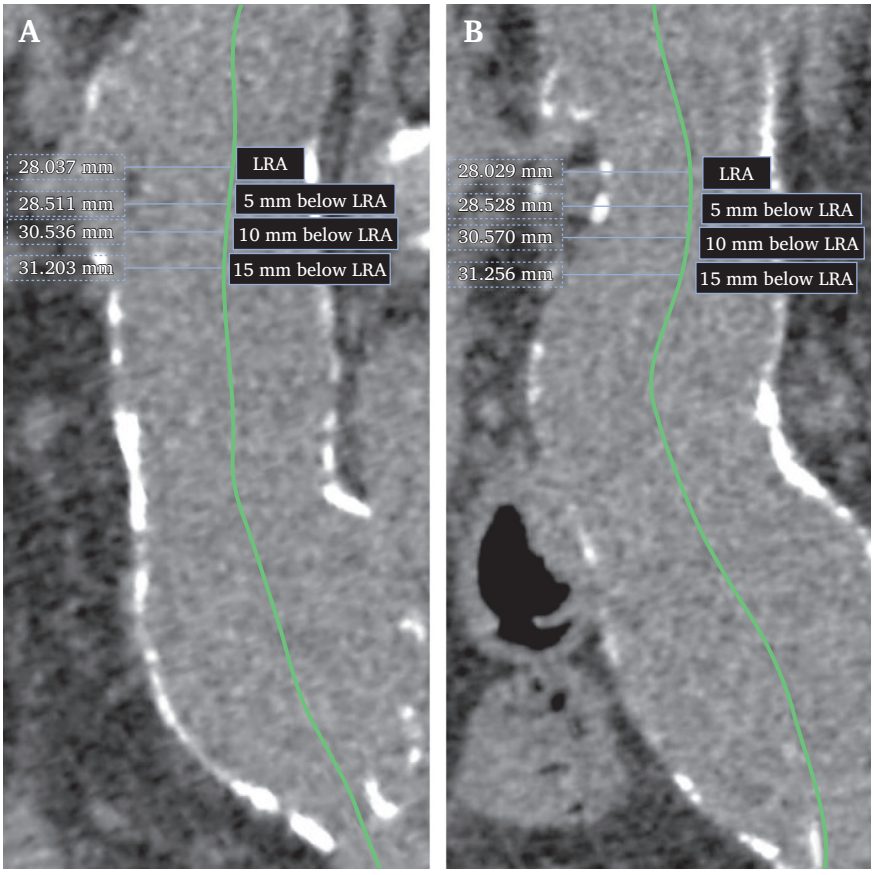

Figure 1. Example of a subject randomised to treatment with doxycycline whose neck diameter remained stable at all four anatomical levels (lowest renal artery [LRA] and 5, 10, and 15 mm below the LRA) over the two year study period. (A) Pre-enrolment and (B) at two years.

Aortic neck stabilisation is appealing for multiple reasons. Post-EVAR proximal aortic neck dilation has been estimated to affect nearly 25% of patients over a 15 month to nine year post-operative period, and is associated with increased risk of device migration, type Ia endoleak, and re-intervention.[15] Thus, ongoing aortic neck dilation post-EVAR plays a critical role in hindering treatment durability. Additionally, aortic neck diameter is the primary anatomical determinant of device eligibility for endovascular repair,[16] and therefore is a potential pharmacological target for pre-operative management of AAA to maintain eligibility for EVAR.

MMPs degrade elastin and collagen at the level of the tunica media, promoting both initiation and perpetuation of aortic wall expansion.[17] MMP-9 is the predominant MMP in aneurysmal disease and elevated circulating MMP-9 levels have been previously correlated with rupture risk[18] and risk of endoleak post-EVAR.[19,20] Among its many proposed mechanistic pathways, doxycycline has been associated with indirect inhibition of MMP function via zinc chelation.[21] Thus, indirect MMP-9 inhibition via doxycycline's anti-inflammatory properties has been a proposed means of medical management of AAA both before and after repair. Of note, this is contrasts with its antimicrobial properties, which have been previously associated with chlamydia pneumoniae eradication and subsequent AAA stabilisation.[22]

A randomised, double blind, placebo controlled trial of 44 subjects by Hackmann et al. in 2008 demonstrated that, in patients who underwent EVAR, doxycycline was associated with significantly reduced MMP-9 levels following six months of treatment compared with baseline. In addition, Hackmann et al. found that, in patients who developed endoleak, plasma MMP-9 increased in 83% of the placebo group compared with 14% of the doxycycline treated group. Beyond this, Hackmann et al. found that in 27 patients without endoleak who were treated with AneuRx or Excluder endografts, greater decreases in maximum aortic diameter and aortic neck dilatation were seen in the doxycycline group compared with placebo (13.3% $\pm$ 3.3 *vs.* 3.8% $\pm$ 3.0).[10] In contrast to Hackmann's findings, this study demonstrates that, in patients with unrepaired small AAA, doxycycline is not effective at stabilising neck size over a two year period, and therefore administration of doxycycline with the goal of stabilising the aortic neck is not supported by this study. However, it is imperative to note that the contrasting results may be attributable to the different patient populations studied (i.e., post-EVAR *vs.* native aneurysmal aorta).

The infrarenal aortic neck is not only an important determinant of EVAR device eligibility and durability, but has also been hypothesised to represent an early phase of aneurysm pathogenesis,[23] demonstrating mild inflammatory infiltration of the adventitia and mild degradation of the elastic media when compared with its distally dilated AAA on histology.[24] Even with a grossly non-dilated appearing neck, there is evidence that the infrarenal neck of an AAA is already demonstrating microscopic pathological change. This postulation may be plausibly supported by this study's findings that (1) neck diameter is larger more caudally (i.e., greater neck diameter at 15 mm distal to LRA compared with at the level of the LRA), and (2) neck size grows more rapidly caudally. That is, the closer the infrarenal aortic neck to the AAA, the more likely it is to mirror the radial growth seen in AAA pathophysiology. Conversely, the more cephalic sections of the aortic neck are smaller and dilate less rapidly, perhaps demonstrating an earlier stage of AAA pathogenesis. If it is thought that the proximal aortic neck is representative of early phase AAA pathogenesis, this study fails to demonstrate AAA pathogenesis is impeded by doxycycline.

Limitations

One limitation of this study was that intravenous contrast was not required in the N-TA^{3}CT study protocol, and neck thrombus and plaque could not be quantified, limiting their inclusion in the analysis. Additionally, it is feasible that the slow rate of neck change may be below the level of measurement detection over two years, as evidenced by clinically miniscule changes in average neck diameter detected in this study. Longer follow up and or sample size may be required to elucidate a statistically and clinically significant difference in stabilisation of the aortic neck. Similarly, although the authors propose that doxycycline mediated aortic neck stabilisation may occur via indirect competition of MMP-9 function, N-TA^{3}CT failed to demonstrate differences in MMP-9 levels between the doxycycline and control groups. However, in the longitudinal analysis, there was a significant decrease in log transformed C reactive protein (mg/L) in the doxycycline group over time, suggesting doxycycline had some anti-inflammatory impact. Finally, it is possible that exclusion of patients who were repaired prior to two years of follow up could bias the results via inadvertent exclusion of patients with faster growing necks. However, of the 22 patients repaired prior to two years, 19 were repaired prior to reaching the sex specific MTD indication for repair (most commonly due to symptomatic disease), suggesting against the notion that these patients had disproportionately larger aneurysmal disease when compared with their unrepaired counterparts. Beyond this, there was no statistically significant difference in repair rate by treatment group, again suggesting that doxycycline does not stabilise the aortic neck.

Conclusions

In patients with small, unrepaired AAA followed for two years, there was no statistically significant difference in infrarenal neck stabilisation between patients treated with doxycycline and patients treated with placebo. Both treatment arms demonstrated a larger neck diameter caudally as well as faster growth in more caudal segments of the aorta, though this growth remains small clinically.

CONFLICT OF INTEREST

L.K. is a consultant for Alucent Biomedical. J.N.M. is a cofounder and stockholder of Vessel Wave Technologies and Aquablade. B.K. serves on the WL Gore Scientific Advisory Board. A.P., S.O., B.R., W.B., B.T.B., and S.B. have no conflicts of interest to disclose.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvsvf.2023.05.011.

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