

# Effect of Tetracyclines on the Development of Vascular Disease in Veterans with Acne or Rosacea: A Retrospective Cohort Study

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## TO THE EDITOR

Tetracyclines are commonly used for the treatment of acne and rosacea. In addition to their antibacterial properties, tetracyclines are increasingly being studied for other properties, such as their anti-inflammatory properties (Jackson *et al.*, 1999; Meier, 2000; Sho *et al.*, 2004; Griffin *et al.*, 2005; Tessone *et al.*, 2006; Hackmann *et al.*, 2008; Romero-Perez *et al.*, 2008; Griffin *et al.*, 2010). One can hypothesize that these qualities may have secondary benefits and a protective effect on other organ systems. We sought to test the hypothesis that tetracyclines used in acne and rosacea patients may have secondary benefits on the cardiovascular system, specifically, a decreased odds ratio of developing vascular diseases.

After approval by the Institutional Review Board at the Miami Veterans Affairs Health System, we used the electronic medical records from the veterans integrated service network-8 (which includes the Veterans Affairs medical centers of Bay Pines, Miami, West Palm Beach, Tampa, North Florida/South Georgia, and San Juan) to perform a retrospective observational cohort study and identify patients with the diagnosis of acne or rosacea using the International Classifications of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes during the period of 1 July 2004 through 30 June 2010, allowing for at least 18 months of follow-up. We excluded any patient who had been diagnosed with vascular

disease before prescription of a tetracycline, or before the diagnosis of acne/rosacea. Demographic, clinic, and pharmacy data were extracted. Vascular disease was defined and identified using the ICD-9 codes for cardiovascular disease, cerebrovascular disease, atherosclerosis, and aortic aneurysm with or without rupture/dissection.

In a multiple logistic regression model, age, sex, and comorbidities (see Table 1) were included as covariates. The Hosmer–Lemeshow test was performed to assess goodness-of-fit. *P*-values were reported as two sided. Statistical analyses were performed using SAS software (Version 9.2, SAS Institute, Cary, NC).

In total, 13,847 patients matched our inclusion and exclusion criteria (Figure 1). Patients were further subdivided—to those with prior treatment with a tetracycline, and those without tetracycline treatment (control). Demographics can be found in Table 1. There were similar race profiles between control and treatment groups within both the acne and rosacea sets (data not shown). Similar rates of comorbidities were found between study and control groups (Table 1).

Of those rosacea patients who were treated with a tetracycline, 12.56% patients developed a new diagnosis of vascular disease compared with 17.15% of the control group. Overall, rosacea patients who were prescribed a tetracycline had an odds ratio of 0.69 for the development of vascular disease when compared with those not prescribed a

tetracycline (odds ratio 0.69 in the univariate model, 95% confidence interval (CI) 0.61–0.79, *P*<0.05; odds ratio 0.78 in the multivariate model, 95% CI 0.68–0.89, *P*<0.05) (Table 1).

Acne patients showed an odds ratio of 0.79 (95% CI 0.62–1.02) in a univariate model; however, the results were not statistically significant, and did not persist with the multivariate model.

The effect of treatment duration (<3 months, 3–12 months, >12 months of daily dosing with a tetracycline) was explored; however, the group sizes were too small to make meaningful conclusions (data not shown). Cumulative dose effect was not explored, nor was daily dosage.

A statistically significant decrease was found in the development of new aortic aneurysms in rosacea patients treated with doxycycline (*P*=0.007) (Table 1), although the number of cases was quite small. Other vascular diagnoses were not analyzed individually.

We found a potential association between the administration of tetracyclines and a decreased odds ratio for the development of vascular disease in veterans with rosacea. This study further contributes to the body of literature supporting an association between chronic low-grade inflammation and cardiovascular disease (Prodanowich *et al.*, 2005; Wang *et al.*, 2012). One can conjecture that the stabilization or inhibition of matrix metalloproteinases by tetracyclines has a beneficial effect on the vascular wall and/or calcifications in arteries.

We did not detect any benefit of tetracyclines in acne patients, possibly due to the inherent demographics of acne patients. The average age of our acne patients may be too young to

Abbreviations: CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; ICD-9, International Classifications of Diseases, Ninth Revision, Clinical Modification; MMP, matrix metalloproteinase

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**Table 1. Demographics, comorbidities, and outcomes**

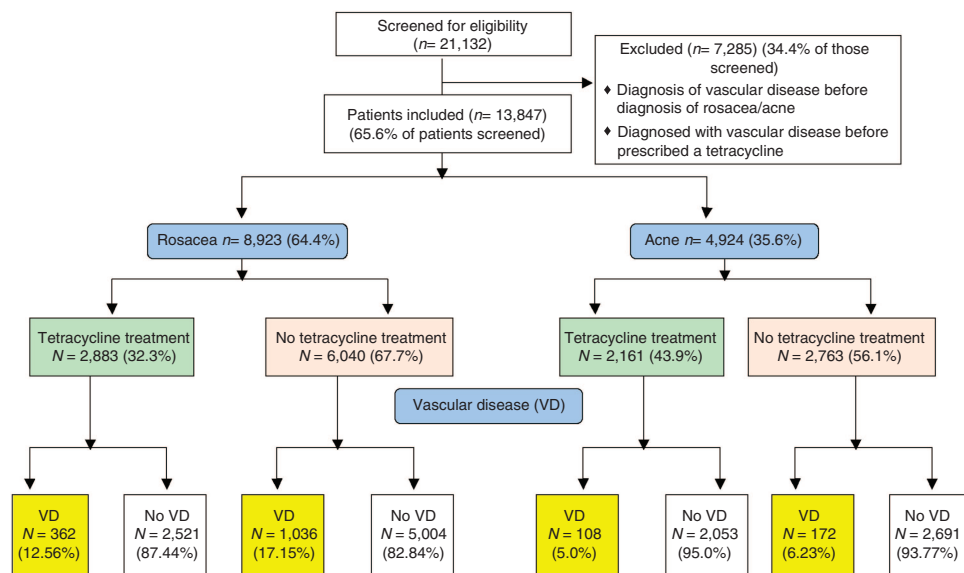
Demographics and comorbidities						
	Rosacea			Acne		
	Overall n = 8,923	Control n = 6,040	Treatment n = 2,883	Overall n = 4,924	Control n = 2,763	Treatment n = 2,161
Age (year), mean (SD)	66.86 (12.03)	67.78 (12.05)	64.95 (11.76)	44.82 (16.42)	46.49 (17.35)	42.70 (14.88)
Sex (male), n (%)	8,342 (93.49)	5,680 (94.04)	2,662 (92.33)	3,286 (66.73)	1,834 (66.38)	1,452 (67.19)
Diabetes, n (%)	761 (8.52)	490 (8.11)	271 (9.40)	245 (4.97)	137 (4.96)	108 (5.00)
Dyslipidemia, n (%)	1,950 (21.85)	1,327 (21.97)	623 (21.61)	895 (18.18)	509 (18.42)	386 (17.86)
Hypertension, n (%)	1,637 (18.34)	1,073 (17.76)	564 (19.56)	681 (13.83)	409 (14.80)	272 (12.59)
<b>Outcomes</b>						
Vascular Disease, n (%)	1,398 (15.67)	1,036 (17.15)	362 (12.56)	280 (5.69)	172 (6.23)	108 (5.00)
Aortic aneurysm, n (%)	189 (2.12)	145 (2.40)	44 (1.53)	26 (0.59)	15 (0.54)	14 (0.65)

Rosacea				Acne			
Model	Odds ratio	95% CI	P-value	Model	Odds ratio	95% CI	P-value
Univariate	0.694	0.610–0.789	<0.0001	Univariate	0.792	0.619–1.015	0.0655
Multivariate	0.775	0.678–0.885	0.0002	Multivariate	1.156	0.882–1.515	0.2952

Abbreviation: CI, confidence interval.

Multivariate model adjusted for covariates including age, gender, and comorbidities (diabetes, dyslipidemia, and hypertension).



**Figure 1. Flow diagram of study design.**

detect incipient or future vascular disease with our degree of follow-up.

Of note, the use of tetracyclines has garnered some disturbing attention in the last several years including increased risk of inflammatory bowel disease (Margolis *et al.*, 2010). A discussion of these risks is beyond the scope of this article, but is important to the understanding of tetracyclines (Margolis *et al.*,

2007; Sergentanis *et al.*, 2010). We contend that researchers may also need to explore the potential secondary benefits of tetracyclines.

Our study is a large review, however, due to its retrospective nature, care should be taken when interpreting our results. It would be premature to assume that there is a strong association between administration of tetracyclines

and the incidence of vascular disease. Further large-scale studies with rigorous attention to potential confounders are needed. Time from tetracycline exposure to cardiovascular disease was not factored into our analysis, nor was age-by-exposure interaction. By excluding previous vascular disease before tetracycline use, we may have selected a healthier group. However, as our primary

end point was to detect new diagnoses of cardiovascular disease, we felt that these exclusion criteria were necessary to calculate the incidence of disease.

Patient adherence cannot be assessed from pharmacy records. Other medications, family history, or lifestyle variables were not included in our analysis.

All patients who were prescribed a tetracycline, regardless of duration, were included. It is not possible to know whether the prescription was truly given for acne/rosacea versus an infection. There are data that rosacea itself may increase the risk of cardiovascular disease (Duman *et al.*, 2013), and it is possible that any indication for a tetracycline may perhaps positively affect the pro-inflammatory state of the rosacea patient.

In private practice, the use of low-dose (20 or 40 mg daily) doxycycline is commonplace in order to take advantage of the sub-antimicrobial dose that also provides an anti-inflammatory effect in rosacea. This formulation is not available at our facility, and most patients were prescribed between 50–200 mg daily.

Owing to sampling issues (three different medications in two different groups of patients, acne, and rosacea), we did not analyze the odds ratio for each of the tetracycline medications: tetracycline, doxycycline, and minocycline.

Finally, as our veteran population was predominantly male, our results may not be generalizable to a more heterogeneous population.

#### CONFLICT OF INTEREST

JD has received fees from Galderma Laboratories for consulting that was performed after the design and completion of this study.

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See related commentary on pg 2076

## New and Recurrent *SERPINB7* Mutations in Seven Chinese Patients with Nagashima-Type Palmoplantar Keratosis

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#### TO THE EDITOR

Hereditary palmoplantar keratodermas (PPKs) consist of a heterogeneous group

of hyperkeratotic disorders involving mainly the palms and the soles (Lucker *et al.*, 1994). Nagashima-type palmo-

plantar keratosis (NPPK, MIM615598) was initially described in Japanese literature as a mild form of *mal de Meleda* (MIM248300), which is one of the diffuse autosomal-recessive PPKs (Nagashima, 1977). Later, similar cases were reported both in Japanese and