Aortic Aneurysms

William Pearce, M.D.
Aortic Aneurysm: Mortality

By Age – Total vs Male

Age Group

40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89 90-94 95-99 ≥ 100

Total

Male
Hypothesis: Create a story to explain clinical observations which can be scientifically tested

- Age
- Genetic clustering
- Infra renal localization
- Histologic findings
- Smoking
Aortic Function

FORM FOLLOWS FUNCTION

Adapted from Boudoulas et al
Aortic Lamellar Units
ABFLEX™
THE RAPID ABDOMINAL DEVELOPMENT MACHINE!

Amazing TV Demonstration!
Martin Van Der Hoeven demonstrates with cement blocks how strong ABFLEX™ abs can be!

3 MINUTES A DAY TO PERFECT FLAT, FIRM ABS!

Easy Tension Adjustment
Individualize each workout to your fitness level.

FREE! Video & Fitness Guide
Included in package!
PDAY Project – Abdominal Aorta

Stained & Opened Half Aorta

29 y.o. White Male
Cholesterol = 334, LDL = 282, HDL = 52
PDAY Probability
Calcified Lesions
PDAY Abdominal Aorta

Raised Probability

The Ohio State University
AORTIC FLOW PATTERNS
Atherosclerotic Arterial Enlargement

Adapted from Zarins
PDAY : 440R0
Adjusted for Age, Race, Sex, Smoking

Hypertensive
N=16
Avg IEL Circ = 11.58
Avg Lesion Thk = .3987
Avg Medial Thk = .2033

Normal Control
N=14
Avg IEL Circ = 10.81
Avg Lesion Thk = .3094
Avg Medial Thk = .1910
Decline in Physiological Measurements with Age

- Basal Metabolic Rate
- Cardiac Index
- Glomerular Filtration Rate
- Vital Capacity
- Maximal Breathing Capacity

Percent Remaining

0 30 40 50 60 70 80 90 100

0 30 40 50 60 70 80 90
Aortic Aging

Year 1

Year 8

Year 12
Aortic Diameter and Aging

<table>
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<th>Diameter (mm)</th>
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<td>4</td>
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<td>12</td>
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<tr>
<td>13</td>
<td>6</td>
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</tbody>
</table>

**Female**

**Male**

INFRARENAL

Decade
Effects of Aging on Rat Aorta

Elastin/Collagen Ratio

Age (days)
FIRST AORTIC ANEURYSM REPAIR
The main feature, together with the destruction of the elastic tissue is the presence throughout the outer half of the aorta of masses of lymphocytic cells accompanying the vaso vasorum; these cells form concentric sheets but are also seen sometimes to follow the vessels at right angles to all layers of the wall.

In summary....This endarteritis and periartheritis would suggest an inflammatory process without any specific indication as to its nature.

Dubost 1951
AAA: Autoimmunity?

N=100 Patients    109 Controls

T-Cell Activation

CD 28

CD 80

CD 86

CTLA-4 Inhibitor

Ng/ml

150
125
100
75
50
25
0

121 103 135

90 106 *

91 *

AAA Controls

* indicates significant difference
Inflammatory Cytokines and AAA

IL1-β Concentration (pg/ml)

- Normal
- Occlusive
- AAA

0.4 1.3 2.4
Matrix Metalloproteinases: MMPs

- Matrix degradation
- Control of inflammation
- Role in apoptosis
- Release of matrix bound or surface bound cytokines and growth factors
MMP Expression in Aortic Tissue

Tamarina et al, 1997

mRNA/GAPDH mRNA (copy number)

Normal Aorta
AAA
*p < 0.05

MMP-1
MMP-2
MMP-9

mRNA Type

Tamarina et al, 1997
Inflammation and Immune Response

Over the past decade, there has been increasing evidence demonstrating a role for MMPs in normal immunity. However, it is now becoming apparent that MMP activity can contribute to the development of immunopathology. This paradox results from the fine line between normal MMP function and MMP host related tissue damage.

<table>
<thead>
<tr>
<th>MMP</th>
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<td>MMP-1</td>
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<tr>
<td>MMP-3</td>
<td>Coronary artery disease</td>
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<tr>
<td>5A/6A</td>
<td>AAA</td>
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<tr>
<td>5A/5A</td>
<td>Coronary aneurysms</td>
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<td>MMP-13v2</td>
<td>Aortic atherosclerosis in African Americans</td>
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</table>
Proteins That Comprise ECM and Potential MMP Cleavage

Collagen IV
Laminin 1
Laminin 5
Nidogen
Perlecans
Collagen XVIII
MMP
TGFβ bound to LAP and LTBP

Integrins
Dystroglycan
Cryptic Fragments and Growth Factors Released from the ECM by MMPs

- NC1α1 arresten
- NC1α 2 canstatin
- NC1α 3 tumstatin
- NC1, restin
- NC1, endostatin
- C-term, endorepellin
- Cryptic epitope

TGF-β
VEGF
TIMPs
MMPs
EDPs
Abdominal aneurysm
a time bomb for some

Dear Abby:

Two years ago, my husband’s sister had a sonogram to check for a possible gynecological problem. What the doctor discovered was an abdominal aortic aneurysm that was large enough for mandatory surgery. Her doctor told her to notify any siblings that they, too, should have a sonogram. The unexpected result of my husband’s examination stunned us all. Bill, too, had an abdominal aortic aneurysm! Bill was monitored for one year, until the aneurysm

And another plus is the fact that the test is painless and non-invasive. Thank you for a letter that is sure to be a lifesaver.

-- Abigail Van Buren

Dear Abby
Risk for AAA in Relatives

Salo et al. *Ann Int Med* 1999; 130:637
Linkage of Marfan syndrome and a phenotypically related disorder to two different fibrillin genes

Brendan Lee*, Maurice Godfrey*, Emilia Vitale*, Hisao Hori†, Marie-Gevenèviève Mattei, Mansoor Sarrafzad, Petros Tsimpouras†, Francesco Ramirez‖‡ & David W. Hollister∥†

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A Mutation in the Gene for Type III Procollagen (CCL3A1) in a Family with Aortic Aneurysms

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Department of Biochemistry and Molecular Biology, Jefferson Institute of Molecular Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania 19107

Abstract
Experiments were carried out to test the hypothesis that familial aortic aneurysms, whether thoracic or abdominal, are caused by mutations in the gene for type III procollagen (CCL3A1). One such mutation, identified in a family with thoracic and abdominal aortic aneurysms, causes a recurrent de novo missense mutation in the fibrillin gene.

Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene

Harry C. Diets*, Garry R. Cutting*, Reed E. Pyeritz, Cheryl L. Massion, Lynn Y. Sakaia, Glen M. Corson, Erik G. Puffenberger, Ada Hamoshi, Elizabeth J. Nanthakumar, Sheila M. Currin, Gall Stetten†, Deborah A. Meyers†, and Clark R. Acarano

Genetic Variants of Collagen III and Abdominal Aortic Aneurysm

Janet T. Powell*, Jane Adamson†, Shane T. R. MacSweeney‡, Roger M. Greenhalgh§, Steven E. Humphries**, and Adriano Henney†

Departments of *Surgery and †Biochemistry, ‡Claring Cross and Westminster Medical School, London, and §Claring Cross
Insulin Research Centre, London, U.K.

Collagens provide the tensile strength of the aortic wall. Variations in collagen structure are recognized in Ehlers-Danlos syndrome type IV and could also be associated with a predisposition to aortic aneurysm. The frequency of some genetic variants of type III collagen, present in the normal population, can be detected by restriction enzyme digestion of genomic DNA from peripheral blood. The frequency of these genetic variants in type III atheroma was compared to that in aortic aneurysm patients. The frequency of the minor allele was significantly higher in aortic aneurysm patients (n = 70) compared to patients with normal aortic diameter (n = 70), p < 0.05. The presence of the minor allele was also associated with a higher aortic diameter in patients with aortic aneurysm (1.27 cm) compared to patients with normal aortic diameter (1.17 cm), p < 0.05. These results indicate that genetic variants of type III collagen may influence the tensile properties of the aortic wall and that mutations in the type III collagen gene may be associated with aortic aneurysms.

Key Words: Aortic aneurysm; Collagen.
MARFAN SYNDROME AND FIBRILLIN

FIRST PLANET OUTSIDE OUR SOLAR SYSTEM
Schematic representations of the domains of the fibrillin-1 protein and approximate location of the first 100 mutations documented to cause MFS (asterisks)

Dysregulation of TGF-β activation contributes to pathogenesis in Marfan syndrome

Enid R. Neptune1,2, Pamela A. Frischmeyer2, Dan E. Arking2, Loretha Myers2, Iracie E. Bunton3, Barbara Gayraud4, Francesco Ramirez4, Lynn Y. Sakai5 & Harry C. Dietz2,6

Marfan syndrome is an autosomal dominant disorder of connective tissue caused by mutations in fibrillin-1 (encoded by FBN1 in humans and Fbn1 in mice), a matrix component of extracellular microfibrils. A distinct subgroup of individuals with Marfan syndrome have distal airspace enlargement, historically described as emphysema, which frequently results in spontaneous lung rupture (pneumothorax; refs. 1–3). To investigate the pathogenesis of genetically imposed emphysema, we analyzed the lung phenotype of mice deficient in fibrillin-1, an accepted model of Marfan syndrome4. Lung abnormalities are evident in the immediate postnatal period and manifest as a developmental impairment of distal alveolar septation. Aged mice deficient in fibrillin-1 develop destructive emphysema consistent with the view that early developmental perturbations can predispose to late-onset, seemingly acquired phenotypes. We show that mice deficient in fibrillin-1 have marked dysregulation of transforming growth factor-β (TGF-β) activation and signaling, resulting in apoptosis in the developing lung. Perinatal antagonism of TGF-β attenuates apoptosis and rescues alveolar septation in vivo. These data indicate that matrix sequestration of cytokines is crucial to their regulated activation and signaling and that perturbation of this function can contribute to the pathogenesis of disease.

Mice homozygous with respect to a centrally deleted Fbn1 allele (Fbn1<sup>tm1Rnm</sup>), herein called Fbn1<sup>tm1Rn</sup>; ref. 4) die at postnatal day (PD) 7–10 from aortic dissection and rupture, recapitulating the vascular phenotype of Marfan syndrome4. At PD9, we observed a graded increase in distal airspace caliber in Fbn1<sup>tm1Rnm</sup> and Fbn1<sup>tm1Rn</sup>/Fbn1<sup>tm1Rn</sup> mice compared with their wild-type (Fbn1<sup>tm1Rn</sup>/+) littermates (Fig. 1a,b). Fbn1<sup>tm1Rn</sup> mice had rare secondary alveolar septae (Fig. 1c), but their proximal airway caliber and vasculature appeared grossly normal. There was no inflammation or overt tissue damage. Calculation of mean linear intercepts (Lm, ref. 5), a measure of the distance between alveolar structures, at PD1, PD4 and PD9 showed progressive distal airspace enlargement in the mutant mice, apparent from PD1 (Fig. 1a,b). Ratios of lung weight to body weight at PD3 were consistent in mice of all three genotypes (data not shown), arguing against overt lung hypoplasia. Thus, the early lung phenotype associated with deficiency in fibrillin-1 is most consistent with a

---

**Fig. 1** Lung histopathology and morphometry of mice deficient in fibrillin-1. a, Lung sections from wild-type (+/+), Fbn1<sup>tm1Rn</sup>/+ (−/+) and Fbn1<sup>tm1Rn</sup>/Fbn1<sup>tm1Rn</sup> (−/−) littermates at PD1, PD4 and PD9. A marked...
Losartan, an AT1 Antagonist, Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome

Jennifer P. Habashi,†‡ Daniel P. Judge,† Tammy M. Holm, Ronald D. Cohn, Bart L. Loeys, Timothy K. Cooper,† Loretha Myers, Erin C. Klein, Guosheng Liu, Carla Calvi,‡ Megan Podowski,‡ Enid R. Neptune,‡ Marc K. Halushka,‡ Djahida Bedja,‡ Kathleen Gabrielson, Daniel B. Rifkin, Luca Carta, Francesco Ramirez,§ David L. Huso,§ Harry C. Dietz†‡‡

Aortic aneurysm and dissection are manifestations of Marfan syndrome (MFS), a disorder caused by mutations in the gene that encodes fibrillin-1. Selected manifestations of MFS reflect excessive signaling by the transforming growth factor-β (TGF-β) family of cytokines. We show that aortic aneurysm in a mouse model of MFS is associated with increased TGF-β signaling and can be prevented by TGF-β antagonists such as TGF-β-neutralizing antibody or the angiotensin II type 1 receptor (AT1) blocker, losartan. AT1 antagonism also partially reversed noncoronary manifestations of MFS, including impaired alveolar septation. These data suggest that losartan, a drug already in clinical use for hypertension, merits investigation as a therapeutic strategy for patients with MFS and has the potential to prevent the major life-threatening manifestation of this disorder.

MFS is a systemic disorder of connective tissue caused by mutations in FBN1, the gene encoding fibrillin-1 (1). As a principal component of the extracellular matrix microfibril (2,3), fibrillin-1 was initially thought to play primarily a structural role in connective tissue. Several lines of evidence support an additional role as a regulator of the cytokine TGF-β (4,5). Mice homozygous for a hypomorphic Fbn1 allele have impaired pulmonary alveolar septation associated with increased TGF-β signaling that can be prevented by perinatal administration of a polyclonal TGF-β neutralizing antibody (NAb) (5). Similarly, myxomatous thickening of the cardiac outflow valves in mice harboring a Fbn1 missense mutation is attenuated by perinatal systemic administration of TGF-β NAb (6).

Aortic root in Fbn1/Jc1039G/+ mice undergoes progressive dilatation, evident as early as 2 weeks of age. By 7 weeks of age, the aortic root in the mutant mice is larger than that in wild-type mice (1.82 ± 0.14 mm versus 1.59 ± 0.11 mm, respectively; P < 0.05). This size difference becomes more pronounced with age (aortic root at 8 months, 2.47 ± 0.33 mm versus 1.82 ± 0.11 mm; P < 0.0001).

Histologic analysis of 14-week-old Fbn1/Jc1039G/+ mice revealed aberrant thickening of the aortic media with fragmentation and disarray of elastic fibers (fig S1). In addition, Fbn1/Jc1039G/+ mice showed increased collagen deposition, which is an indirect marker of increased TGF-β signaling (fig S1) (9,10). Phosphorylation and subsequent nuclear translocation of Smad2 (pSmad2), which are induced by TGF-β signaling (11), are markedly increased in the aortic root in Fbn1/Jc1039G/+ mice.
Mutations in Transforming Growth Factor-β Receptor Type II Cause Familial Thoracic Aortic Aneurysms and Dissections

Hariyadarshi Pannu, PhD; Van Tran Fadulu, MS; Jessica Chang; Andrea Lafont, BS; Sumera N. Hasham, PhD; Elizabeth Sparks, MS; Philip F. Giampietro, MD, PhD; Christina Zaleski, MS; Anthony L. Estrera, MD; Hazim J. Safi, MD; Sanjay Shete, PhD; Marcia C. Willing, MD, PhD; C.S. Raman, PhD; Dianna M. Milewicz, MD, PhD

Background—A genetic predisposition for progressive enlargement of thoracic aortic aneurysms leading to type A dissection (TAAD) is inherited in an autosomal-dominant manner in up to 19% of patients, and a number of chromosomal loci have been identified for the condition. Having mapped a TAAD locus to 3p24–25, we sequenced the gene for transforming growth factor-β receptor type II (TGFBR2) to determine whether mutations in this gene resulted in familial TAAD.

Methods and Results—We sequenced all 8 coding exons of TGFBR2 by using genomic DNA from 80 unrelated familial TAAD cases. We found TGFBR2 mutations in 4 unrelated families with familial TAAD who did not have Marfan syndrome. Affected family members also had descending aortic disease and aneurysms of other arteries. Strikingly, all 4 mutations affected an arginine residue at position 460 in the intracellular domain, suggesting a mutation “hot spot” for familial TAAD. Despite identical mutations in the families, assessment of linked polymorphisms suggested that these families were not distantly related. Structural analysis of the TGFBR2 serine/threonine kinase domain revealed that R460 is strategically located within a highly conserved region of this domain and that the amino acid substitutions resulting from these mutations will interfere with the receptor’s ability to transduce signals.

Conclusion—Germline TGFBR2 mutations are responsible for the inherited predisposition to familial TAAD in 5% of these cases. Our results have broad implications for understanding the role of TGF-β signaling in the pathophysiology of TAAD. (Circulation. 2005;112:513-520.)

Key Words: aneurysm ■ aorta ■ genetics ■ dissection ■ receptors, transforming growth factor beta

Aneurysms and dissections are the major diseases affecting the aorta and are a leading cause of morbidity and mortality in the United States.1 The most common location inherited in an autosomal-dominant manner and is caused by mutations in the FBN1 gene on chromosome 15q.2 FBN1 encodes fibrillin-1, a large glycoprotein that is a component
Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm

BASIC RESEARCH STUDIES

Identification of a genetic variant associated with abdominal aortic aneurysms on chromosome 3p12.3 by genome wide association

James R. Elmore, MD,* Melissa A. Obmann, DO,* Helena Kuivaniemi, MD, PhD, b,c
Gerard Tromp, PhD, b,d Glenn S. Gerhard, MD,* David P. Franklin, MD,* Amy M. Boddy, b and
David J. Carey, PhD,* Danville, Pa; and Detroit, Mich

Objective: The goal of this project was to identify genetic variants associated with abdominal aortic aneurysms (AAAs).

Methods: A genome wide association study was carried out using pooled DNA samples from 123 AAA cases and 112 controls matched for age, gender, and smoking history using Affymetrix 500K single nucleotide polymorphism (SNP) arrays (Affymetrix, Inc., Santa Clara, Calif). The difference in mean allele frequency between cases and controls was calculated for each SNP and used to identify candidate genomic regions. Association of candidate SNPs with AAA was confirmed by individual TaqMan genotype assays in a total of 2096 cases and controls that included an independent replication sample set.

Results: A genome wide association study of AAA cases and controls identified a candidate AAA-associated haplotype on chromosome 3p12.3. By individual genotype analysis, four SNPs in this region were significantly associated with AAA in cases and controls from the original study population. One SNP in this region (rs7635818) was genotyped in a total of 502 cases and 736 controls from the original study population (P = .017) and 448 cases and 410 controls from an independent replication sample (P = .013; combined P value = .0028; combined odds ratio [OR] = 1.33). An even stronger association with AAA was observed in a subset of smokers (391 cases, 241 controls, P = .00041, OR = 1.80), which represent the highest risk group for AAA. The AAA-associated haplotype is located ~200 kbp upstream of the CNTN3 gene transcription start site.

Conclusion: This study identifies a region on chromosome 3 that is significantly associated with AAA in 2 distinct study populations. (J Vasc Surg 2009;49:1525-31.)

Clinical Relevance: Genotype data can be used to identify individuals at increased genetic risk for AAA. Ultimately this genetic information may lead to improved diagnosis and better understanding of the pathophysiology of AAAs.
The immunoprivileged elastic media may provide a site for persistence of pathogens or self antigens leading to chronic vascular disease, a process regulated by IFN-g actions on both somatic and hematopoietic cells. These concepts have significant implications for understanding immune responses contributing to or controlling chronic inflammatory diseases of the great vessels.

Albert J. Dal Canto, Paul E. Swanson, Andrew K. O’Guin, Samuel H. Speck, and Herbert W. Virgin

J Clin Invest 2001; 107:R15-R22
Abdominal Aortic Aneurysms: RA
Abdominal Aortic Aneurysms: HLA

Inflammatory AAA
Degenerative AAA
Controls

Percentage

NS

DR B1*02
DR B1*04

AAA AND LOWER EXTREMITY AMPUTATIONS
AORTIC FLOW PATTERNS
Mean Wall Shear Stress at Rest and Mild Exercise

Stanford SCCOR in AAA

- **SCCOR = Specialized Center of Clinically Oriented Research**

- **Purpose:**
  Test the ability of lower extremity exercise to reduce AAA risk, modify biologic markers of disease and limit small aneurysm progression

- **Long term research objective:**
  To identify, validate and apply effective non-surgical therapies to treatment and prevention of AAA disease
Effects of Exercise Training in Patients With Abdominal Aortic Aneurysm

PRELIMINARY RESULTS FROM A RANDOMIZED TRIAL

Jonathan N. Myers, PhD; Julie J. White, BS; Balasubramanian Narasimhan, PhD; Ronald L. Dalman, MD

OBJECTIVE: No effective medical therapy exists for early abdominal aortic aneurysm (AAA) disease. Lower extremity exercise improves aortic hemodynamics and reduces inflammation, but the safety and efficacy of exercise training in AAA disease is unknown. As an interim analysis of our prospective, randomized, longitudinal trial of exercise for AAA suppression, we investigated whether subjects with early disease could safely achieve target metabolic and hemodynamic goals.

METHODS: One hundred eight participants were randomized to exercise training (EX) or usual care (UC). EX subjects participated in a combination of in-house and home exercise training, with efforts directed toward moderate daily exercise participation. Comparisons were made between EX and UC subjects who completed 1 year of follow-up (n = 26 and 31, respectively, mean age 72 ± 8 years). EX and UC groups were compared for safety, cardiopulmonary exercise test responses, weekly energy expenditure, and biometric indices.

RESULTS: No paradoxical increase in AAA growth rate or adverse clinical events occurred as a consequence of exercise training. EX participants expended an average of 2259 ± 1207 kcal/wk and increased exercise capacity (42% increase in treadmill time, 24% increase in estimated metabolic equivalents, P = .01 and .08 between groups, respectively). EX participants demonstrated a significant reduction in C-reactive protein and tended to reduce waist circumference and waist-to-hip ratio (P = .06 and .07, respectively).

CONCLUSIONS: Preliminary analyses suggest that exercise training is well tolerated and sustainable in small AAA subjects over 1 year. Despite age and comorbidities, exercising AAA subjects achieve meaningful exercise targets and significantly modify activity-dependent variables.

KEY WORDS
abdominal aortic aneurysm
exercise therapy
oxygen uptake

Author Affiliations: Division of Cardiology, Veterans Affairs Palo Alto Health Care System, Palo Alto; Department of Cardiology (Dr Myers), Department of Surgery (Ms White and Dr Dalman), and Department of Health, Research, and Policy (Dr Narasimhan), Stanford University, Stanford, California.

The authors performed this study on behalf of the Stanford AAA SCCOR investigators.

Correspondence: Jonathan Myers, PhD, Veterans Affairs Palo Alto Health Care System, Cardiology 111C, 3801 Miranda Ave, Palo Alto, CA 94304 (dmr993@aol.com).

Clinicaltrials.gov identifier: NCT00349947
DOI:10.1097/HCR.0b013e3181eb2db
OBESITY AND AORTIC ANEURYSMS

- Obesity, smoking increase AAA growth
- “Hypertension” and hip circumference protective
- Relationship of central obesity, resistin production to AAA risk.
- Obesity and diabetes linked through “metabolic syndrome” – influence of insulin resistance alone minimal in absence of other features.
AAA: Surgical and Endovascular Repair
Best Medical Management

- Aspirin
- Statins
- Blood pressure control
## Medical Management

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<th>Effect on AAA growth</th>
<th>Level of evidence</th>
<th>Class of recommendation</th>
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<tr>
<td>Propanolol</td>
<td>no inhibition</td>
<td>A</td>
<td>III</td>
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<td>inhibition</td>
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<td>C</td>
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Baxter, Circulation
Comparison of Rat Aorta Following Treatment with Doxycycline or Saline Solution

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<th>Day 7</th>
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</table>

* indicates significant difference.
Doxy and Change in Aneurysm Size

Baseline Aneurysm Diameter (mm) vs. Expansion of the Aneurysm at 18 Month Follow-up (mm)

- Placebo
- Doxycycline

Non invasive treatment of AAA
N-TA$^3$ CT

- Tim Baxter
- Robert Thompson
- Michael Terrin
- Jon Matsumura
- John Curci