

A Perspective on Natural History and Survival in Nonoperated Thoracic Aortic Aneurysm Patients

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Abstract

There are many questions that remain unanswered in the understanding of the natural history of thoracic aortic aneurysm (TAA). This review will critically appraise the current published evidence on the natural history of TAA in nonoperated patients and their present rates of survival.

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Key Words

Natural history · Aorta · Aortic aneurysm

Introduction

Thoracic aortic aneurysm (TAA) represents an important component of vascular disease due to the particularly lethal nature of this disease [1]. It is widely accepted that without intervention, medical or surgical, TAA carries a poor prognosis. The bleak long-term prognosis of TAA underpins the critical importance of understanding precisely the natural history of the disease. Such understanding is crucial to making precise diagnostic, management, and prevention plans. Furthermore, such understanding is imperative, as it needs to be imparted on patients, allowing them to make a well-informed decision and provide consent regarding their management plan. Knowledge of the natural history is critical when planning elective surgery in order to weigh the significant risk of major

surgery against the risk of aneurysm progression. This is particularly pertinent considering that, after surgical aneurysm repair, survival rates comparable to that of a matched general population can be achieved [2].

We aim to demonstrate in this review the published evidence pertaining to survival among nonoperated or nonintervened thoracic aortic aneurysm cohorts.

Literature Review

Literature Search Strategy

Electronic searches were performed on PubMed and Cochrane databases with no limits placed on dates. Search terms included natural history, thoracic aortic aneurysms, aneurysm size, risk factors, survival rates, medical therapy, aneurysm growth, dissection, rupture, and mortality. Search terms were charted to MeSH terms and combined using Boolean operations, and also used as key words. Papers were selected on the basis of title and abstract. The reference lists of selected papers were reviewed to identify any relevant papers that might be suitable for inclusion in the study.

Selection Criteria

Research papers were not excluded based on study design except for case reports. Comments, opinions, or editorials were not included in our selection, so as to provide an unbiased view. Papers were



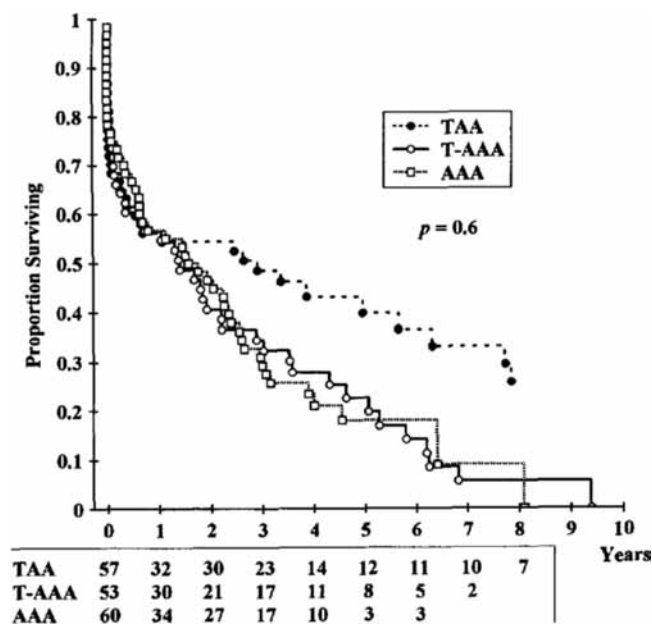


Figure 1. Kaplan-Meier cumulative survival displaying the dismal prognosis of unoperated patients with thoracic aortic aneurysms (TAA), thoraco-abdominal aneurysms (T-AAA), and abdominal aortic aneurysms (AAA). From Perko et al. [4].

selected based on providing primary end points of death, rupture, or dissection and/or information regarding aortic aneurysm growth. Papers were not excluded based on patient population age.

Survival

An Overview. There is unarguable evidence that a diagnosis of TAA carries with it a dismal prognosis. This is well described by Crawford and DeNatale [3], in an observational study of unoperated thoraco-abdominal aneurysm patients published in 1986. This observation has since been repeated in much larger cohorts that also include TAAs of the ascending and descending portions of the aorta. This is visibly demonstrated in Figure 1, a Kaplan-Meier plot displaying the starkly poor 10-year survival in a group of 170 patients from 1984 to 1993 [4], which compares TAAs, thoraco-abdominal aneurysms, and abdominal aortic aneurysms.

A report of 107 patients with TAAs attending the Mayo Clinic between 1945 and 1955 describes 1- and 5-year survival rates of 87% and 50%, respectively [5]. It is pertinent to consider that these observations were reported more than 5 decades ago, and advances in conservative management may have improved prognosis, although even this is currently debated. The advent of large databases, specifically designed for

thoracic aortic aneurysms, has allowed for more recent estimates of survival. Coady et al. [6] report overall survival in 230 patients at 1 and 5 years from diagnosis to be 85% and 64% respectively, during the period 1985 to 1996. To date, this database has now recruited 721 patients and reports that 5-year survival in medically treated patients is approximately 66% [7].

What are the specific pertinent factors that we need to consider when dealing with an aortic aneurysm?

Etiology. The prevailing consensus, reflected in the most recent guidelines for thoracic aortic disease, cites medial degeneration as the primary causative factor for the majority of TAAs [8]. Historically, atherosclerosis was credited as the main cause for aortic aneurysms, which was based on findings from postmortem examinations [9,10]. Although atherosclerotic lesions are commonly associated with thoracic aneurysms, typically they are preceded by medial degeneration [1]. In the past, the majority of cases could be attributed to syphilitic infection; however, with the modern era of screening and antibiotics, this is now a rarity.

Classically, Marfan syndrome has been the most extensively studied connective tissue disorder in relation to thoracic aortic disease. It is well documented that approximately 50-80% of these patients will develop aortic dilation. Because of this predictable progression, Marfan syndrome has been used to extrapolate clinical findings and practice to TAA of different etiologies [2,11]. Recently, these observations have been challenged, in part due to the obvious differences in etiology and varied clinical findings; it is now realized that substantial variation exists among aneurysms of different etiologies. Because patients with Marfan syndrome and other genetic diseases related to TAA often exhibit symptoms earlier in their course, this has allowed for study of the natural history in those disease groups. Because of this, earlier surgical intervention is advocated for Marfan's disease and other genetic syndromes compared to TAA of other etiologies, as aneurysms in these patients tend to rupture or dissect earlier [12].

Coady et al. [13] have reported an extensive database of approximately 1200 patients who were diagnosed with TAA in Connecticut. Their analysis of this database identified 21% of this cohort who had a first degree relative with known or likely aortic aneurysm, in the absence of a known connective tissue syndrome (affecting multiple organ systems). Among these familial patients, an autosomal dominant pattern of inheritance, with incomplete penetrance, was

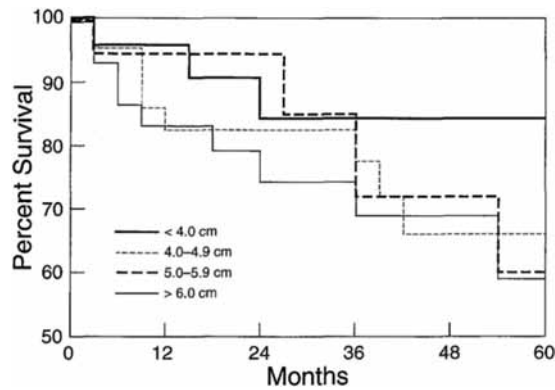


Figure 2. Kaplan-Meier cumulative survival for 5-year survival in TAAs of varying size between 4 and 6 cm. From Coady et al. [6].

displayed. The Yale group notes that the actual percentage of inheritance is likely to be higher, as these results were based on family interview and are subject to bias due to nonimaged family members.

In the absence of connective tissue disease syndrome, current evidence points toward a strong inherited genetic phenotype of accelerated medial degeneration as the primary culprit for TAA. However, there are many risk factors that contribute to formation of a TAA. Therefore, the likelihood that this is a multifactorial disease is the consensus of most papers.

Size of Aneurysm. TAA size is currently utilized as the primary marker for surgical indication in asymptomatic patients. The Yale group was among the first to provide evidence-based data supporting aortic size as a predictor of rupture and mortality [6]. Their initial work encompassed clinical and radiological data of 370 patients with TAAs from 1985 to 1997. This produced a striking graph depicting how survival significantly decreases over time with increasing aortic aneurysm diameter (Fig. 2). Please note that small aneurysms take years to produce mortality: this is a virulent but indolent disease. Furthermore, the incidence of rupture and dissection as a function of initial aneurysm size increases with greater aneurysm diameter (Fig. 3). Statistical analysis reveals odds of rupture or dissection to be 8.84 times greater for an aneurysm of 6-6.9 than that of an aneurysm of 4.0-4.9 cm. Critically, this paper demonstrates how aneurysm size significantly relates to probability of rupture, dissection, and death. These data have since been the foundation of current recommended guidelines for surgi-

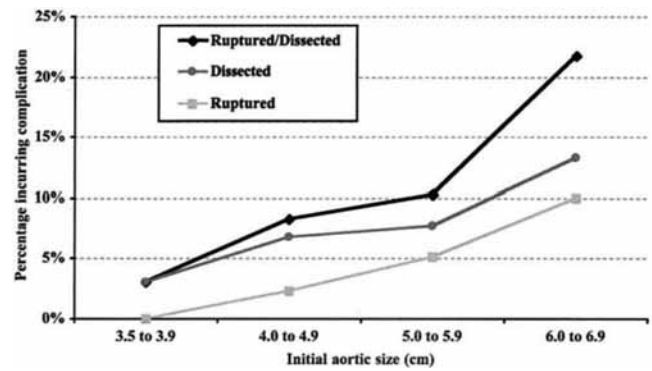


Figure 3. Cumulative incidence of rupture and/or dissection displayed as a function of initial aortic size. From Davies et al. [7].

cal intervention based on size, and these evidence-based paradigms are used internationally [8].

Other groups as well have published results pertaining to aneurysm size, morbidity, and mortality which show similar results, strengthening the evidence in favor of using size as a predictor of rupture or dissection [4,5]. Perko et al. [4] report a 5-fold increase in cumulative hazard of rupture in aneurysms greater than 6 cm compared to those below this threshold, and a 66% probability of rupture. Further analysis of size, from the Yale group, reveals a statistically significant increase in the incidence of rupture, mortality, and dissection with increasing size [14].

Certainly, there is powerful evidence that initial measured aortic size accurately predicts prognosis with regard to mortality, rupture, and dissection. Furthermore, documented analysis shows these risks increase with increasing aortic size, and maximal risk is realized in aneurysms > 6 cm. Analysis from the Yale database in 2002, that includes data prospectively collected from 1600 patients, demonstrates that even in aneurysms categorized to the smallest diameter (3.5 cm-3.9 cm) have a yearly risk of rupture, dissection, or death of 7.2% (see Fig. 7) [15], the majority representing dissection rather than rupture. Rupture is reported at a 0% rate in aortic sizes of 3.5-4.0 cm [15].

However, size as a model of prediction of the natural history is not perfect. It could be argued that information derived from large groups and data sets do not accurately predict the behavior of the individual patients. The ideal would be a move toward a personalized medical model, however to achieve this, the complete understanding of the natural history of the disease is a necessity.

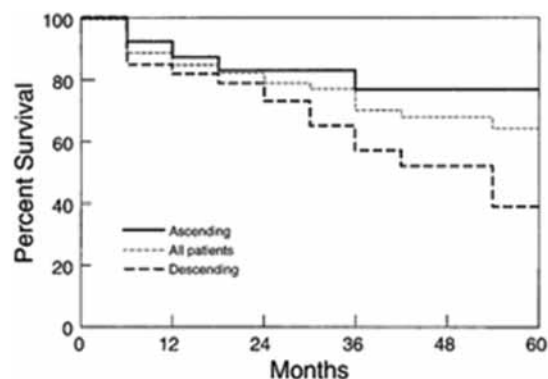


Figure 4. Kaplan-Meier cumulative survival displaying 5-year survival for patient suffering from ascending and descending thoracic aortic aneurysms. From Coady et al. [6].

Location. The thoracic aorta is a complicated structure that has been shown in mechanical ex vivo modeling to display different characteristics on both a macroscopic and microscopic level in different anatomical locations along the aorta [16,17]. Clinically, aneurysms located in the ascending, descending, and thoraco-abdominal aorta vary in terms of prevalence, management, and prognosis. Elefteriades and Farkas [2] differentiate two different diseases, separated at the ligamentum arteriosum. Ascending aortic aneurysms are rarely calcified, almost never contain thrombus, and are not as strongly correlated with traditional arteriosclerotic risk factors. On the other hand, descending and thoraco-abdominal aneurysms are almost invariably calcified, contain generous thrombus, and correlate well with traditional arteriosclerotic risk factors.

It is recognized that descending aneurysms are less prevalent than ascending aneurysms, but are associated with a poorer prognosis, starkly demonstrated in Figure 4 [6]. The Yale group report 5-year survival in ascending and descending aneurysms as 77% and 39% respectively, in a cohort of 153 patients. In this study the prevalence of ascending and descending aortic aneurysms was 64% and 24%, respectively. Other groups report similar figures and a similar difference in survival among ascending and descending aortic aneurysms [18]. The postulated reasons why descending aneurysms are more deadly than ascending aneurysms are speculative and not conclusively proven.

A further critical observation of aneurysm location regards the mean aortic diameter for rupture. Coady et al. [6] report significantly different probabilities in the complications from aneurysms with similar aortic

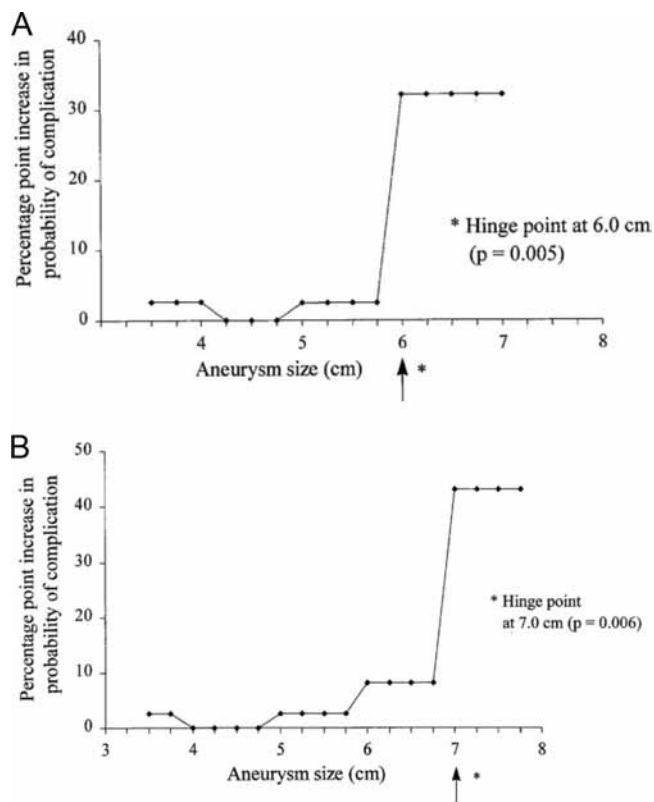


Figure 5. The percentage risk of complications for (A) ascending and (B) descending aortic aneurysms according to aneurysm size. From Coady et al. [6].

sizes in the ascending and descending aorta. They describe these sizes for which the risk dramatically increases as “hinge points,” which are 6 cm and 7 cm in the ascending and descending aorta, respectively (Fig. 5A and 5B). This observation has influenced recent aortic aneurysm surgical guidelines insofar as it is recommended to operate on ascending and descending aneurysms at different sizes [8].

Thus, location of an aortic aneurysm plays a decisive role in the natural history of the disease. There is a significant difference in the prognosis of ascending and descending aortic aneurysms. Furthermore, the ascending aorta has a susceptibility to rupture at smaller diameters in comparison to the descending aorta. However, it is pertinent to consider aortic arch involvement, which has not yet been discussed. Involvement of the arch is not uncommon in TAA disease, and considering its added complexity, it is natural to question whether aortic arch involvement can influence the natural history of the disease. This is a

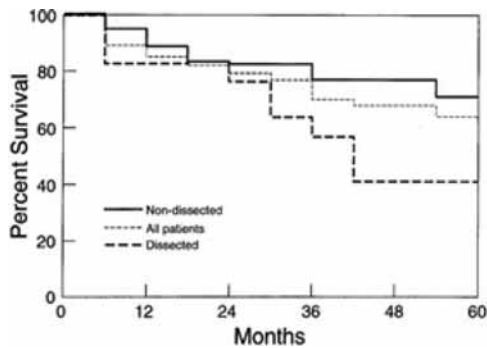


Figure 6. Kaplan-Meier cumulative survival demonstrating 5-year survival in TAA patients with or without a dissection present [6].

question that has not been thoroughly investigated, and our future research will address this.

Dissection. The presence of an aortic dissection negatively impacts prognosis in TAAs, as demonstrated in the Kaplan-Meier survival curves reported by Coady et al. (Fig. 6) [6]. Dissection can present itself in either an acute or chronic fashion, and also in two locations (ascending and descending): these distinctions all herald different prognoses. The International Registry of Acute Aortic Dissection (IRAD) is able to provide insight into these differences. Acute Type A dissections incurred an in-hospital mortality, in those not surgically treated, of 58%. Acute Type B dissection medically managed yielded an in-hospital mortality of 10.7% [19]. Chronic dissections have not been thoroughly researched, but evidence suggests that chronic dissections are quite vulnerable to progression, via additional dissection, enlargement, and aneurysmal dilatation, rupture, and death [20–23]. Future clinical investigation from our center will examine chronic behavior of the dissected aorta more fully.

In the context of aortic size, dissection holds an interesting position. It is true that an aortic size greater than 6.0 cm carries a much greater risk of dissection than diameters below that level. However, unlike rupture, which positively correlates with increasing aortic size, dissection does not hold entirely true in this concept. In fact, Elefteriades and Farkas [2] observed a 2.2% yearly risk for dissection in aneurysms between 3.5 and 4.0 cm, which only increased to 3.6% in those greater than 6 cm (Fig. 7). It is well known that, on occasion, dissection can indeed occur at small sizes.

Trimarchi et al. [24] used the IRAD database to look at 613 patients with acute Type B aortic dissections between 1996 and 2009. In this study the mean aortic

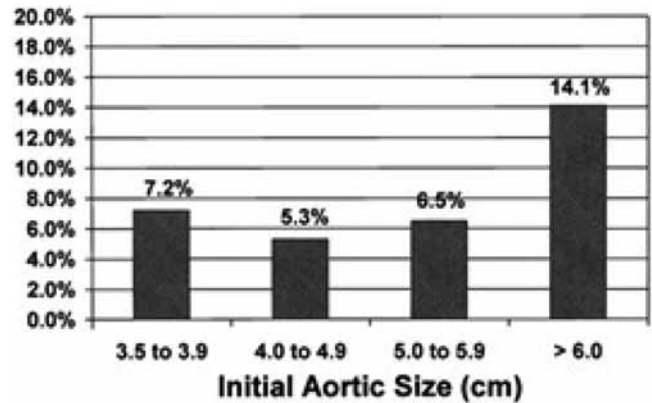


Figure 7. Cumulative risk of rupture, dissection, or death graphically represented as a function of initial aortic size. From Elefteriades et al. [15].

size at time of dissection was 4.1 cm and, furthermore, only 18.4% of patients in this cohort had an aortic diameter equal to or greater than 5.5 cm, the current recommended surgical intervention size. However, the study reports a mortality rate of 6.6% and 23.0% in aortic diameters less than 5.5 cm and greater than 5.5 cm, respectively ($P < 0.001$). This paper further demonstrates that risk of dissection is not entirely dependent on aneurysm size. However, the IRAD study had no information regarding the denominator of patients at risk with small aneurysm. Because of the bell-curve distribution of aortic size, many millions of patients have aortas in the 4- to 5-cm range, so that the actual likelihood of dissection is indeed small [2]. Thus, the IRAD study recommended no change from current intervention criteria.

Interestingly, a report of 100 consecutive acute descending aortic dissections, presenting between 1988 and 1998, revealed the mean aortic size at the time of dissection to be 5.05 cm [25].

Growth Rate. TAA growth rate is an important factor to consider in the natural history of the disease. Figure 3 demonstrates that with increasing aortic size, the risk of rupture, dissection, or death is increased. Accurate predictions of aneurysm growth would significantly add to the surgeon's armamentarium to predict the opportune time for surgical intervention. Such ability would enhance decision making, which is currently based on current indications of aneurysm size [8].

Calculation of growth rate exhibits controversy in the aortic world [26]. In particular, many studies ignore the fact that measurements vary about a mean, and that specific aortic measurements may be lower than a

prior measurement in the same patient. To discard such measurements leads to an erroneously high calculated rate of growth. Accordingly, some experts argue that such measurements should not be discarded. Such issues contribute to the much varied reported aneurysm growth rates in different centers [2,26].

Bonser et al. [10] described a mean aneurysm expansion rate of 1.43 mm/yr. This expansion rate was significantly different by anatomical location of the aneurysm and aneurysm size. The ascending aorta experienced the lowest expansion rate, with the highest rate of expansion observed in the midportion of the descending aorta. In all segments, increasing aortic size was associated with increasing rate of aneurysm expansion. Aneurysm growth was not affected by the presence of a dissection in this study. Hirose et al. [27], in Japan, observed in a case series of 82 TAAs that aneurysms of the arch grew at a faster rate than at any other location (0.56 cm/yr, $n = 34$).

Other quoted rates of aneurysm growth vary between 0.07 and 2.0 cm per year, but on average are about 1 mm per year [6,10,26,28]. TAA growth rate is often described as indolent, and thus it is recommended that asymptomatic TAAs that have yet to reach the appropriate size for intervention be imaged yearly (or even less frequently). However, it is generally accepted that rapid expansion of TAAs is a criterion for surgical intervention. Clinical practice tells us that these patients are likely to suffer an acute aortic dissection or rupture, although documented evidence supporting this is limited [1,29].

Risk Factors. There is increasing recognition that numerous modifiable and nonmodifiable risk factors contribute, not only to the development of TAAs, but also to the risk of rupture of established TAAs, as well as to the rate of growth of an aneurysm. Bonser et al. [10] evaluated 87 TAA patients who underwent serial imaging at their clinic. Univariate analysis revealed that the presence of thrombus, transient ischemic attack (TIA)/stroke, smoking, or peripheral vascular diseases were all factors that statistically accelerated aneurysm growth. The median difference of expansion varies from 0.82 to 2.10 mm/yr according to risk factors, with TIA/stroke causing the greatest increase in growth. Further analysis in this study reveals factors that have no effect on aneurysm growth, including sex, dissection, calcification, β -blockers, ischemic heart disease, or hypertension. It is interesting to see that β -blockade and hypertension have no effect

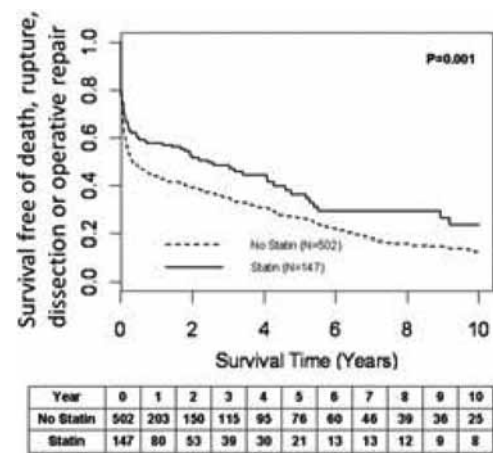


Figure 8. Kaplan-Meier survival demonstrating survival free of death, rupture, dissection, or operative repair in TAA patients who were prescribed a statin and those who were not. From Jovin et al. [32].

on aneurysm growth, although this should be interpreted with caution due to the small number of patients. It should be noted that this study looks at aneurysm growth but does not assess risk of rupture or death. The study begs the question: does rupture occur earlier in patients when these risk factors are present?

Large-scale prospective controlled trials, specifically designed to assess impact of risk factors on aneurysmal growth, have not been performed. Hypertension prevails as a modifiable risk factor that can be stringently controlled in TAA patients [8]. This stems mainly from work with Marfan patients, where β -blockade and angiotensin receptor blockade significantly reduce the rate of aortic dilation [30,31]. Although studies prospectively analyzing smoking and TAAs have not been performed, it is reasonable to advise smoking cessation because of its significant links with hypertension and atherosclerosis.

Statin use was recently evaluated by the Yale group [32], who examined 649 patients, among whom 147 were taking statins at first presentation, compared to 502 who were not. Analysis revealed a statistically significant improved freedom from death, rupture, or dissection in patients taking statins compared to those who were not, depicted in Figure 8.

What's on Medical Management?

Medical management in TAAs is the mainstay treatment in asymptomatic aneurysms that do not reach the required size for surgical intervention. The main

objectives of medical management are to reduce aneurysm growth, risk of rupture or dissection, and ultimately death. Thus, medical management can play a pivotal role in modifying the natural history of TAAs. There is good evidence to show that statin therapy does not increase risk of growth, but rather significantly reduces risk in the long term (Fig. 8) [32].

β -Blocker therapy enjoys its position as the drug of choice in the medical management of TAAs. The evidence underpinning this stems from studies of Marfan patients and mechanical modeling of the aorta in relation to blood pressure. However, recently, it has become increasingly recognized that this evidence is not applicable to the majority of TAAs that are degenerative in origin. Currently, no randomized controlled trials exist assessing this, which is understandable considering the lethality of the disease; ethically, it would be challenging to conduct such a trial. However, a recent meta-analysis of β -blocker therapy in TAAs of Marfan patients concluded that there was no clinical benefit [33]. The study included 802 patients over 6 studies; however, it lacked high-quality randomized trials in its analysis, reducing the power of the results. Bonser et al. [10] describe β -blocker therapy and hypertension to have no significant effect on aneurysm growth. Again, this must be interpreted carefully, considering that in their study, only a small group of patients were not taking β -blockers, and of these, all were having their blood pressure controlled with other medications.

β -Blocker trials in TAA are limited, and currently, the aneurysm world can only glimpse the potential benefits of β -blockers by assessing clinical outcomes of patients who are unable to take β -blockers due to adverse effects. Genoni et al. [34] retrospectively evaluated 71 patients with medically treated chronic Type B aortic dissection, and of these, 51 were prescribed β -blockers, and the remaining 20 were prescribed other antihypertensives. In this study, freedom from subsequent aortic operation was 80% and 47% in those prescribed β -blockers and those prescribed other antihypertensives, respectively ($P < 0.001$); the study also found that aortic aneurysm growth was significantly reduced in the β -blocker therapy group.

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Conclusion

Understanding the natural history of a disease is critical in managing patients, and this review demonstrates particularly why this is of such importance in TAAs. However, there is continuing debate and need for further investigation to characterize disease progression in TAAs. However, some facts remain accepted about TAAs: first, that untreated TAAs remain a deadly disease with a very poor prognosis; second, that prognosis varies with TAA location in either the ascending or descending aorta; third, that increasing aneurysm size correlates with increasing aneurysm growth, risk of rupture and risk of death; and, finally, that a dissection in the presence of a TAA heralds a poor prognosis.

Many controversies remain. The aortic arch has not been evaluated with respect to aneurysm growth or risk of complications: whether small size adequately prevents dissections in small TAAs; or what constitutes optimal medical therapy. Researching the natural history of TAAs in humans poses ethical and methodological issues. Much evaluation is based on retrospective database analysis, which is currently providing novel insights into this disease, particularly as these databases grow. However, observational findings still do not rank highly within the hierarchy of evidence. Furthermore, the natural history of TAA in unoperated patients can only be deduced from a very small minority of patients. This includes those patients who decline surgery, those who unexpectedly suffer a complication with a small aneurysm diameter, and those whose aneurysm activity precedes recognition and consequent surgical and medical management. There are many questions that remain unanswered and will require careful research to be solved. However, the aortic surgery subspecialty is growing at an exponential rate (as is the rate of aneurysm disease), and the near future will see many exciting advances [2].

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Cite this article as: Bashir M, Fok M, Hammoud I, Rimmer L, Shaw M, Field M, Harrington D, Kuduvalli M, Oo A. A Perspective on Natural History and Survival in Non-operated Thoracic Aortic Aneurysm Patients. *Aorta* 2013;1(3):182–189. DOI: <http://dx.doi.org/10.12945/j.aorta.2013.13-043>