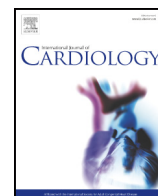




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Expert consensus recommendations on the cardiogenetic care for patients with thoracic aortic disease and their first-degree relatives

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ABSTRACT

Background: Thoracic aortic aneurysm (TAA) is a potentially life-threatening disorder with a strong genetic component. The number of genes implicated in TAA has increased exponentially over the last decade. Approximately 20% of patients with TAA have a positive family history. As most TAA remain asymptomatic for a long time, screening of at risk relatives is warranted to prevent complications. Existing international guidelines lack detailed instructions regarding genetic evaluation and family screening of TAA patients. We aimed to develop a consensus document to provide medical guidance for all health care professionals involved in the recognition, diagnosis and treatment of patients with thoracic aortic disease and their relatives.

Methods: A multidisciplinary panel of experts including cardiologists, cardiothoracic surgeons, clinical geneticists and general practitioners, convened to review and discuss the current literature, guidelines and clinical practice on genetic testing and family screening in TAA.

Results: There is a lack of high-quality evidence in the literature. This consensus statement, based on the available literature and expert opinions, summarizes our recommendations in order to standardize and optimize the cardiogenetic care for patients and families with thoracic aortic disease. In particular, we provide criteria to identify those patients most likely to have a genetic predisposition, and discuss the preferred modality and frequency of screening in their relatives.

Conclusions: Age, family history, aortic size and syndromic features determine who is advised to have genetic testing as well as screening of first-degree relatives. There is a need for more prospective multicenter studies to optimize current recommendations.

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1. Introduction

Thoracic aortic aneurysm (TAA) is an abnormal, usually progressive widening of one or multiple segments of the aorta within the thoracic cavity. This consensus statement focuses on patients with aneurysms involving the aortic root and/or ascending aorta without concomitant aortic valve disease, and on thoracic aortic dissections (Stanford type

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A and B). This includes patients with thoracic aortic disease as part of a connective tissue disorder. Aortic dilatation in patients with repaired or uncorrected congenital heart disease, e.g. bicuspid aortic valve (BAV), tetralogy of Fallot, truncus arteriosus or after the Ross or arterial switch operation, is not included in this consensus document.

Most patients with TAA are asymptomatic. TAA is usually found accidentally during imaging studies for other purposes or upon screening of relatives. TAA can, if left untreated, lead to aortic dissection, rupture or sudden death. Approximately 20% of patients with TAA have a positive family history. Familial TAA is often inherited in an autosomal dominant pattern with incomplete penetrance and variable expressivity [1]. Despite advancing genetic knowledge and sequencing technologies, only one quarter of families with TAA receive a molecular diagnosis, suggesting further locus heterogeneity. Hence, a negative genetic test result does not exclude a genetic predisposition. Patients with TAA are more likely to develop aneurysms elsewhere in the arterial tree. However, the number of studies addressing this issue is limited. Approximately one quarter of patients with TAA have a concomitant abdominal aortic aneurysm (versus 5% in the general population) [2], and 10% a concomitant intracranial aneurysm (versus 1–2% in the general population) [3]. Relatives of patients with TAA also have an increased risk for aneurysms beyond the thoracic aorta [1].

The purpose of this document is to provide medical guidance for all health care professionals involved in the recognition, diagnosis and treatment of patients with thoracic aortic disease and their relatives. This consensus statement focuses on the cardiogenetic aspects of care in thoracic aortic disease including the indications for genetic testing and guidelines for the cardiovascular screening of relatives. For more information on the indications for treatment and the various treatment options, the authors refer to the latest guidelines of the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) [4,5].

2. Methods

The National Working Group on BAV & TAA was established in April 2015 at the 3rd Aortic Symposium in Rotterdam, The Netherlands, and gathers experts with a shared interest in improving the cardiogenetic care for patients with thoracic aortic disease. Members were actively recruited from various disciplines and health care institutions, in order to achieve a broad representation of the field. For a complete list of all members of the working group and their affiliations, please see the electronic supplement. The aim of this working group was to develop consensus recommendations in order to standardize and optimize care for patients and families with TAA.

We first discussed and agreed upon the definition of TAA. Following a national inventory of the major topics among cardiologists and clinical geneticists, three clinical questions were formulated: What factors are associated with an increased likelihood of a genetic predisposition for TAA? What genetic tests should be offered for efficient and cost-effective detection of mutations predisposing to TAA? What cardiovascular screening of relatives should be recommended? Relevant literature was evaluated to answer these questions and to formulate concept recommendations. These recommendations were then discussed at three plenary meetings held between October 2015 and January 2017, and were distributed via email to receive input from all working group members. A concept version of this document was provided to the Netherlands Heart Institute (formerly known as ICIN), the Working Group Congenital Cardiology of the Netherlands Society of Cardiology (NVVC), the Netherlands Association for Cardio-Thoracic Surgery (NVT) and the chairman of the Dutch General Practitioners' Expert Group on Cardiovascular Diseases (HartVaathAG). After the comments were processed, the consensus document was approved by all members of the working group.

3. Results

3.1. Definition

The definition of TAA has been the subject of considerable debate among clinicians and researchers for decades. In the international literature, different sets of normal reference values for aortic measurements are provided. Except for the aortic root, these values are often based on small studies. The expected normal aortic diameters depend on age, gender, and body surface area. In adults, an aortic diameter of 40 mm or more is generally considered dilated [4,6]. In adults with short stature

and in children, a smaller size can already be considered dilated. Calculating Z-scores (number of standard deviations from the predicted mean) is a helpful way to correlate aortic diameters to body size and to track aortic growth over time. There are several online tools available (e.g. www.parameterz.org and www.marfan.org) to calculate Z-scores using published reference data [7,8]. An aortic diameter Z-score ≥ 2.0 in adults and ≥ 3.0 in children is considered enlarged [8,9]. Above the 95th percentile for height, the aortic diameter does not increase linearly but seems to reach a plateau [10]. In patients with large body size, the Z-score seems to underestimate the aortic root dilatation and is therefore unreliable. In adult women with Turner syndrome, the use of aortic size index is preferred [11].

We recommend to use an absolute threshold of 40 mm for the definition of aortic dilatation. In adults with short stature and in children, we recommend to use a Z-score of ≥ 2.0 and ≥ 3.0 , respectively, in order to adjust for small body size. In adult women with Turner syndrome, aortic dilatation is defined as aortic size index > 2.0 cm/m².

3.2. Factors increasing the likelihood of a genetic predisposition for TAA

3.2.1. Aortic size

Although there is no scientific evidence for this contention, we assume that the contribution of strong genetic factors is larger in patients with more severe disease, e.g. an aortic size ≥ 45 mm. Of course, the presence of other risk factors such as age and hypertension also needs to be considered (as summarized in Section 3.2.2). We expect that non-genetic factors are the major contributors to TAA below 45 mm. Patients with an aortic diameter between 40 and 45 mm should be judged on a case-by-case basis, e.g. depending on age, body size, family history and configuration of the aorta (e.g. a pear-shaped aortic root).

3.2.2. Traditional cardiovascular risk factors

Ageing and hypertension are important risk factors for developing TAA [12]. In our experience, the chance of finding a disease-causing mutation significantly decreases at older age, unless the medical or family history provides further clues (see below). Familial disease tends to occur at relatively younger age [1,13]. A genetic cause should therefore be suspected in patients with thoracic aortic disease diagnosed before the age of 50 years, irrespective of the presence of hypertension, and patients diagnosed between 50 and 60 years without hypertension. There is no convincing association with other traditional cardiovascular risk factors. Tobacco use and dyslipidemia may contribute to *expansion* (but not *formation*) of TAA, and aortic dissection [14–16]. Diabetes mellitus is not clearly associated with thoracic aortic disease [17]. Some studies even suggest a negative association [18]. In contrast to aneurysms of the descending thoracic or abdominal aorta, atherosclerosis is relatively infrequent in ascending TAA [15]. The presence of hypertension does not exclude a genetic etiology: hypertension can also be a feature of shared underlying biological processes [19–21].

3.2.3. Positive family history

Family history is a simple yet powerful tool to recognize a genetic disorder in a family, and should therefore be part of the medical record of every TAA patient. In TAA patients with a “positive” family history of TAA or a related disorder an underlying genetic cause is very likely. To our knowledge, there is no single, generally accepted definition of a ‘positive’ family history. A positive family history is most commonly defined as having at least one first-degree relative (parents, siblings or children) with a thoracic aortic aneurysm or dissection. Considering the small size of modern families, the reduced penetrance of hereditary thoracic aortic disease, and the association with aneurysms along the arterial tree (especially abdominal and intracranial aneurysms), we believe this definition should be broadened here. We suggest to define a positive family history as having at least one first- or second-degree relative with (1) a thoracic aortic aneurysm or dissection, (2) an aneurysm or dissection elsewhere in the arterial tree, diagnosed below 60

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