SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Study participants and baseline characteristics assessment

All participants were recruited from the University of Ottawa Heart Institute's Aorta Clinic between. Patients were excluded from the study if they had a previous surgical repair of the aorta, suffered an acute aortic syndrome, a history of aortic valve replacement, aortic stenosis with a systolic mean gradient >20 mmHg, worse than moderate aortic regurgitation, permanent atrial fibrillation or flutter, previous carotid endarterectomy or stenting, or previous lower extremity bypass (all of which could impair the accuracy of non-invasive hemodynamic assessment). Baseline characteristics were assessed at enrollment. Patients were asked about their previous medical history and smoking status through a standard questionnaire. Weight was measured in kilograms (kg) using a standardized digital scale and height was assessed using a stadiometer in meters (m). From this, body mass index (BMI) was calculated as kg/m^2. Body surface area (BSA) was calculated using the Gehan method[35]. Blood pressure measurements were taken using a digital sphygmomanometer while the patient was laying supine, three times, with two-minute intervals between readings. The average from the three readings was recorded. TAA etiology was classified as heritable (hTAA) if caused by heritable conditions such as bicuspid aortic valve, Marfan's syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, etc; or degenerative (dTAA) if occurring in the presence of hypertension or other cardiovascular risk factors and in the absence of known heritable conditions.

Measurement of arterial age

Arterial age was estimated using published validated equations based on aortic stiffness and brachial blood pressure. The gold standard to measure aortic stiffness is carotid-femoral wave velocity (cfPWV)[19]. Trained and experienced sonographers conducted the study, and all measurements were obtained with patients laying supine in a darkened room with controlled temperature. To minimize effects from exogenous sources, twelve hours prior to study, patients were asked to avoid any medications with vasoactive properties, alcohol, tobacco and caffeine.

cfPWV was assessed by arterial tonometry. Transit distances were obtained from the carotid tonometry site to the manubrium sternum and from the manubrium sternum to the femoral artery which estimated aortic path length (*D*) according to the subtraction method. The time (*t*) between the onset of carotid and femoral waveforms was determined from tonometry of the carotid and femoral arteries with simultaneous ECG recordings. This was reported as the mean from at least 10 consecutive cardiac cycles. cfPWV was calculated as *D/t* (m/s), where *D* is distance in meters and *t* is the time interval in seconds. Reproducibility of this assessment has been shown to be excellent, with correlation coefficients above 0.90[36]. For example, within-observer variability for cfPWV has been shown to be very low (0.07 ± 1.17 m/s).

Brachial blood pressure readings were spaced 2 minutes apart and averaged over 3 times. Blood pressure was measured with patients lying supine in a dark room with controlled

temperature. An electronic sphygmomanometer was used. A microphone over the right brachial artery was applied with the user listening with headphones, to enhance accuracy of the measurements (Non-Invasive Hemodynamics, NIHem – Cardiovascular Engineering Inc. Norwood, MA, USA). Average brachial systolic (SBP) and diastolic (DBP) blood pressure readings were obtained. MAP was calculated as [(2 * DBP) + SBP] / 3.

The above values were inputted into validated equations to calculate arterial age which are shown below:

If optimal blood pressure (BP): $\sqrt{\frac{\boldsymbol{cfPWV}-5.55}{0.00083}}$

If normal BP: $\sqrt{\frac{\boldsymbol{cfPWV}-5.69}{0.00099}}$

If high-normal BP: $\sqrt{\frac{\boldsymbol{cfPWV}-5.91}{0.00105}}$

If grade 1 hypertension (HTN): $\sqrt{\frac{\boldsymbol{cfPWV}-6.17}{0.00118}}$

If grade 2-3 HTN: $\sqrt{\frac{\boldsymbol{cfPWV}-5.73}{0.00085}+669.89610}\quad-25.88235$

Assessment of aneurysm size and growth rates

TAA size was determined at baseline with one of three validated imaging modalities recommended as per guidelines for surveillance of TAA[5]: transthoracic echocardiogram (TTE), gated computed tomography (CT) or gated magnetic resonance imaging (MRI). Aneurysm size was documented by using the portion of the aorta with the widest diameter as per the imaging studies. Maximum aneurysm size was calculated at the time of enrollment and then repeated

at the last follow-up visit. To optimize consistency, efforts were made to use identical imaging modalities throughout follow-up (concordant imaging). When the baseline imaging modality was not subsequently repeated, a different imaging modality was used to measure the aorta in follow-up (discordant imaging). The specific protocols for each imaging modality is stated below.

Transthoracic Echocardiography

For participants undergoing imaging with transthoracic echocardiography, images were obtained using either a Philips iE33, Philips EPIQ or GE Vivid7 ultrasound machine with a cardiac probe. Images of the aortic root were obtained at the level of the mid-sinuses of Valsalva in a left parasternal long axis view. The ascending aorta was also measured in left parasternal long axis (PLA) view, in addition to a modified left PLA view which was obtained from one interscostal space above the standard PLA imaging site. This allowed for better delineation of the mid-ascending aorta. A right PLA view was used as needed in order to provide supplemental information. The aorta size was measured at the level of the root and the widest portion of the ascending aorta, in diastole, using a leading edge to leading edge technique as per published guidelines[37].

Computed Tomography

A Siemens Flash CT scanner (Siemens Inc., Erlangen, Germany) was used to obtain images. For smaller patients, with a lung width that was smaller than the field of view, a high-pitch ECG-triggered technique was used with automated kVp selection (which was based on patient size

and quality reference mAs of 500) and 60 cc Omnipaque 350 was injected through an antecubital fossa vein at 4 cc/sec. For participants that were larger, a prospective ECG-triggered axial sequential image acquisition was performed using 100-120 cc Omnipaque 350 at 4 cc/sec. An image was obtained after 10 seconds following the injection bolus in the ascending aorta reaching 100. The image was obtained during an inspiratory breath hold. In terms of the flash and axial sequential techniques, a 0.6 mm scan thickness with a rotation speed of 0.28 sec and pitch of 3.2 was used. For reconstruction of the images, a 0.6 mm thick mediastinal image was made in the axial plane and a 2 mm reconstruction image in the coronal and sagittal oblique planes. Picture Archiving Computer System (PACS) was used to analyze the images in detail. Sagittal and coronal images were used to obtain the double-oblique measurements of the following: sinuses of Valsalva [three measurements made from cusp to opposite commissure (1)], sinotubular junction, ascending aorta, aortic arch, proximal, mid and distal descending aorta. An inner-edge to inner-edge technique was used for making measurements.

Magnetic Resonance Imaging

The machine used for MRI images was a 1.5T scanner (Siemens Aera) using a 32-channel phased-array body coil with standard Black Blood HASTE spin-echo sequences in the axial planes, from the apex of the lung to the diaphragm, with cardiac gating and phase reordering with respiration (TE:43 msec, field of view: 45 cm, slice thickness: 6 mm, interslice gap: 1 mm). Specifically, ECG-gated 3-D SSFP images of the thoracic aorta were obtained in the sagittal oblique plane with the following imaging parameters [FOV 400 × 400 mm^2, matrix size 302 × 302, slice thickness 1.3 mm (no interpolation), leading to a true voxel size of 1.3 × 1.3 × 1.3

mm^3, flip angle (FA) 90°, bandwidth 967 Hz/pixel, TE 1.1 ms, repetition time (TR) 2.3 ms, 60 segments, parallel imaging (GRAPPA;R=2) and 24 integrated reference lines]. If it was felt that the image quality obtained was suboptimal, 5 ml Gadavist® 0.1 mmol/kg (Bayer Healthcare Pharmaceuticals Inc.;Wayne, NJ) was automatically injected at 2 mL/sec via a power injector (Medrad, Inc. USA; Warrendale, Pa) (after a scan delay determined by test-bolus injection of 1 mL of total weight-based dose of contrast medium and a timing formula). 15 consecutive sagittal oblique T1w 3D datasets (TR/TE 2.8/1.2 ms; FA 25°; slices 64; matrix 231 × 320; spatial resolution 1.9 × 1.6 × 2.1 mm^3, effective temporal resolution 1.6 s) were acquired using the TWIST sequence and parallel imaging technique (GRAPPA; R = 2) and then a 3-D spoiled gradient-echo sequence [repetition time, 3.2 to 3.4 ms; echo time, 1.1 to 1.3 ms, GRAPPA acceleration factor, 2; mean voxel size, 1 × 0.9 ×1.3 mm (no interpolation), average time of acquisition, 17 ± 2.5 sec (range,12.8–21.8 sec)] will be done before and after injection. TeraRecon software was used to analyze the images. To obtain measurement of TAA, the internal diameter of the aorta at its widest part, in diastole, perpendicular to the axis of blood flow was used, according to published guidelines[37].