Peak wall stress as a prognostic indicator of Abdominal Aortic Aneurysm rupture risk

Thesis submitted by

Tejas Pratap Singh, MBBS, MPH, GradDipAnatomy

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3. Golledge J, Singh TP. Effect of blood pressure lowering drugs and antibiotics on abdominal aortic aneurysm growth: a systematic review and meta-analysis. Heart. 2021 Sep 1;107(18):1465-71.

4. Singh TP, Moxon JV, Iyer V, Gasser TC, Jenkins J, Golledge J. Comparison of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms. British Journal of Surgery. 2021 Jun;108(6):652-8.

5. Singh TP, Moxon JV, Gasser TC, Golledge J. Author response to: Peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms. British Journal of Surgery. 2021;108(7):e256-e.

6. Singh TP, Moxon JV, Gasser TC, Golledge J. Systematic Review and Meta-Analysis of Peak Wall Stress and Peak Wall Rupture Index in Ruptured and Asymptomatic Intact Abdominal Aortic Aneurysms. Journal of the American Heart Association. 2021 Apr 20;10(8):e019772.

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Abstract

Abdominal aortic aneurysm (AAA) is an important vascular disease that affects approximately 20 million people. Annually, AAA rupture is responsible for approximately 200,000 deaths worldwide. Open or endovascular surgical repair are currently the only treatments available for AAA rupture however surgery has a number of limitations including poor durability and requirement for re-intervention. Recent meta-analyses, which pooled data from previous randomised controlled trials, suggest that there are no medical treatments, which can significantly reduce AAA progression or the risk of events (AAA rupture or repair) in individuals with small AAAs. All previous trials have tested the effects of medications through examining their efficacy in limiting the increase in maximum AAA diameter (referred to as AAA growth). Estimation of AAA diameter is subject to significant measurement error, which is estimated to be similar to the annual change in AAA size. Furthermore, AAA diameter is also an imperfect measure of AAA rupture risk, since some large AAAs remaining intact throughout a patient's lifetime, while some small AAAs rupture. In view of these limitations of using AAA diameter, use of alternative surrogate measures of AAA rupture risk are needed to more effectively stratify patients for AAA events and enable better assessment of the efficacy of potential AAA drugs.

There is interest using in using biomechanical estimates of wall stress to estimate the prognosis of individuals with AAAs. The maximum tensile stress within the AAA wall (peak wall stress, PWS) and the ratio between wall stress and the local aortic wall strength (i.e. peak wall rupture index, PWRI) are two widely reported biomechanical measures which can estimate AAA rupture risk. Both PWS and PWRI can be measured non-invasively from routinely conducted computed tomography angiography (CTA) scans using semi-automated methods that can be performed in a timely manner. It is unclear however whether PWS and

PWRI confer useful prognostic information independent of diameter and whether these measures can be used to predict the risk of future AAA events among individuals with small AAAs. Furthermore, the effect of drug treatments on PWS and PWRI has not been assessed in prior clinical trials.

The aims of this research were: 1) investigate whether aortic peak wall stress (PWS) and peak wall rupture index (PWRI) is greater in ruptured than asymptomatic intact AAAs of similar diameter; 2) perform a systematic review and meta-analysis of all prior case control studies investigating the differences between PWS and PWRI between individuals with ruptured and asymptomatic intact AAAs; 3) Assess whether PWS/PWRI can independently predict the risk of future AAA events (AAA rupture or repair) among patients with small AAAs; 5) Assess whether a commonly used blood pressure lowering medication can reduce the PWS/PWRI of small AAAs. A series of studies were conducted to achieve the above aims.

Collectively, the findings from the systematic review and meta-analysis conducted as a part of this research suggested that aortic PWRI, but not PWS, was greater in individuals with ruptured than asymptomatic intact AAAs of similar AAA diameter. Important and novel findings from this research include the results from a prospective observational investigation which suggested that PWRI and PWS can independently predict the risk of future AAA events among patients with small AAAs after adjusting for diameter and other risk factors. Furthermore, for the first time, a randomized controlled trial was conducted where the effect of a commonly used blood pressure lowering agent (telmisartan) on aortic PWS/PWRI was assessed. Findings from this study suggested that telmisartan limits the rate of increase in PWS/PWRI of small AAAs by reducing blood pressure. The findings commensurate previous

reports that high blood pressure is associated with an increased risk of AAA rupture in individuals with small AAAs.

Further research is required to validate the findings from this project in other populations and identify clinically relevant cut-off values of PWS and PWRI, which may accurately predict AAA rupture risk.

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List of Abbreviations

Abbreviation	Name
AAA	Abdominal aortic aneurysm
ABR	Dimensionless ratio of wall stress and wall strength
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
AT1	Angiotensin 1
BP	Blood pressure
cm3	Cubic centimeter
CART	Classification and regression tree analysis
CVD	Cardiovascular disease
CHD	Coronary heart disease
COV	Coefficient of variation
COPD	Chronic obstructive pulmonary disease
CI	Confidence intervals
CT	Computed tomography
CTA	Computed tomography angiography
DBP	Diastolic blood pressure
DICOM	Digital Imaging and Communications in Medicine
HR	Hazard ratio
IHD	Ischaemic heart disease
iAAAs	Asymptomatic intact abdominal aortic aneurysm
rAAAs	Ruptured abdominal aortic aneurysm
ICC	Intraclass correlation coefficient

ILT	Intra-luminal thrombus
IQR	Inter quartile range
kPa	kilopascals
Mm	Millimeters
mmHg	Millimetre of mercury
MPa	Megapascals
MRI	Magnetic resonance imaging
N/cm^2	Newton Per Square Centimeter
NOAC	Non-Vitamin K antagonist oral anticoagulants
NRI	Net reclassification index
NR	Not reported
PAD	Peripheral artery disease
PWS	Peak wall stress
PWRI	Peak wall rupture index
OR	Odds Ratio
ROI	Region of interest
RBWH	Royal Brisbane and Women's Hospital
SBP	Systolic blood pressure
SD	Standard deviation
SMD	standardised mean difference
FEA	Finite element analysis
TEDY	Efficacy of Telmisartan to Slow Growth of Small Abdominal Aortic Aneurysms: A Randomized Clinical Trial

VIF	Variance inflation factor
3D	Three-dimensional

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Preface

This thesis comprises of seven chapters, four of which were originally composed as research articles for peer review. The research findings have been presented in a similar format within this thesis with minor modifications to enable consistent reporting and formatting throughout. The published research articles related to this thesis can be found in Appendix E.

Chapter 1. Introduction and outline of research

1.1 Background

Abdominal aortic aneurysm (AAA) refers to a focal weakening and dilatation of the abdominal aorta[1] which is estimated to affect approximately 20 million people worldwide.[2] The most widely accepted definition of AAA is a maximum infra-renal abdominal aortic diameter of ≥ 30mm on abdominal imaging (e.g. ultrasonography, computed tomography or magnetic resonance imaging).[1, 3] The main complication from an AAA is aortic rupture, which is responsible for approximately 200,000 deaths worldwide.[1, 2] Open or endovascular surgical repair are the only available treatments for AAA and there have been no medical treatments found to be effective at limiting AAA growth or rupture.[1] Surgical repair has recognised limitations however and has not been shown to reduce mortality in individuals with small AAAs (<55mm in men and <55mm in female).[4, 5] Based on evidence from four previous randomised controlled trials, individuals with small AAAs are generally managed conservatively with regular surveillance.[6-9]

1.2 Epidemiology of abdominal aortic aneurysm

The recognised risk factors for AAA include old age, male sex, smoking, family history of AAA and history of other cardiovascular disease, hypertension and dyslipidaemia.[1] Diabetes has been associated with a decreased prevalence of AAA.[1, 10] The prevalence of AAA is variable and related to the population age structure, ethnicity and possibly world region.[1, 10] Aortic rupture is the main complication from AAA, which frequently leads to fatal bleeding into the retroperitoneum and abdomen.[1] The maximum AAA diameter is strongly associated with the risk of AAA rupture (Table 1.1).

Table 1.1. Estimated annual risk of rupture based on AAA diameter.

AAA diameter (cm)	Estimated rupture risk (%)
<5.5	<1%
5.5-5.9	1-11
6.0-6.9	11-22
>7	>30

The large majority of participants included in the investigations[6, 11, 12] were male.[6, 7, 12]

Adapted from Rutherford's vascular surgery 8th editition.[13]

1.3 Pathogenesis of abdominal aortic aneurysm

Current knowledge of AAA pathogenesis is based on animal models and histological and molecular analysis of human tissue samples of the abdominal aorta. There are a number of mechanisms suggested to be of relevance to AAA pathogenesis. These have been summarised in Table 1.2

Table 1.2 Proposed mechanisms contributing to AAA pathogenesis.

Mechanism	Relationship with AAA pathogenesis
Inflammation[1]	Chronic aortic inflammation may lead to the weakening of the aortic media and vascular smooth muscle apoptosis, secondary to proteolytic enzymes, free radicals and cytokines.
Atherothrombosis[14]	Excessive positive aortic remodelling in response to atherosclerosis may lead to changes in vascular smooth muscle cells and promote matrix remodelling enzymes. Intimal expansion as a result of atherosclerosis may cause loss of medial vascular smooth muscle cells leading to thinning of the medial and disintegration of the aortic wall.
Inherited factors[15, 16]	Population based twin studies have estimated the heritability of AAA to be 70-77%.
Haemodynamic factors[1, 17]	Experimental models suggest that stiffening of the aorta may contribute to elevated wall stress, which is thought to contribute to the development of an AAA.

1.4 Risk factors for AAA growth and rupture among individuals with small AAAs

A pooled analysis of 15, 475 individuals (from 18 different studies) with small AAAs published by the RESCAN collaborators provides insight into the risk factors for AAA growth and rupture.[18] The data included in that meta-analysis underwent comprehensive quality assessment prior to amalgamation of the datasets.[18] A summary of the reported risk factors for AAA growth and rupture have been summarised in Table 1.3.

Table 1.3 Risk factors for AAA growth and rupture among individuals with small AAAs.

Risk factor	Effect on AAA growth	Effect on AAA rupture
Age	Nil	↑
Female sex	Nil	↑
Current smoking	↑	↑
High blood pressure	Nil	↑
Diabetes	↓	Nil

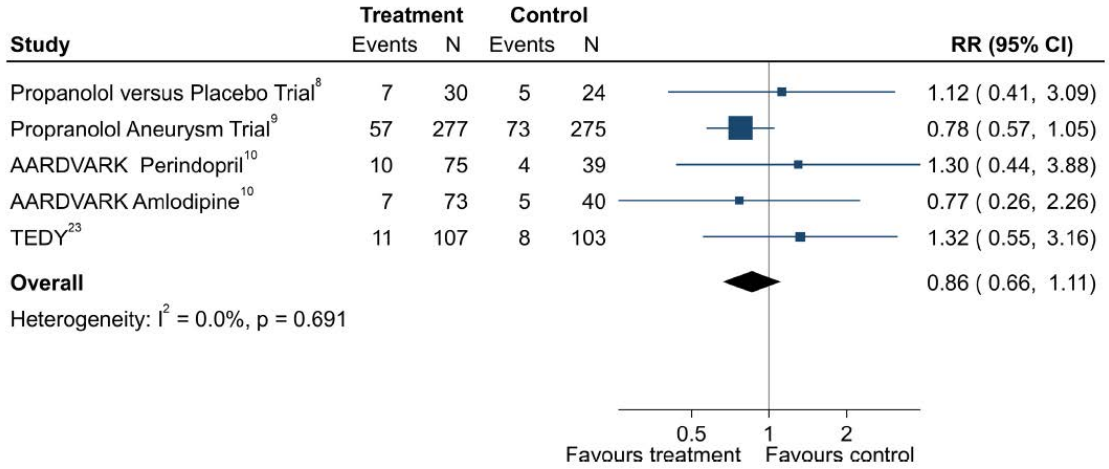
Adapted from Sweeting et al. (2012).[18]

The findings of that study suggested that the risk factors for AAA growth and rupture are distinct.[18] For example, age, female sex and high blood pressure were reported to be associated with an increased risk of AAA rupture, but were not associated with AAA growth.[18] Another more recent meta-analysis reported that high blood pressure is not associated with AAA growth.[19]

1.5 Medical treatments investigated for small abdominal aortic aneurysms

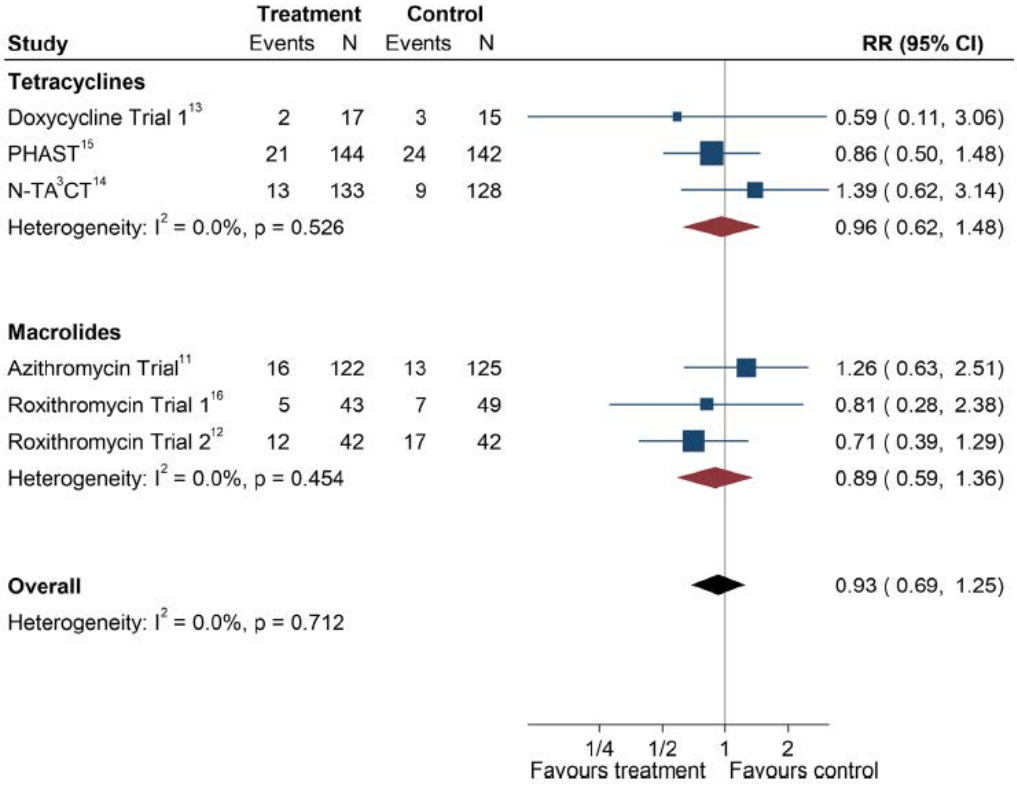
A number of randomised controlled trials have investigated the efficacy of potential drug treatments in limiting AAA growth or clinically relevant AAA events (i.e. rupture or AAA repair). There is currently no proven drug treatment for small AAAs. A recent meta-analysis of previous randomised control trials performed by Golledge and Singh[16] (Figures 1.1 and 1.2) suggested that neither blood pressure lowering agents or antibiotics reduce the risk of clinically important AAA events (i.e rupture or repair).

Figure 1.1 Forest plot summarising the effect of blood pressure-lowering agents AAA-related clinical events (repair or rupture) in prior randomised controlled trials.



Adapted from Golledge and Singh[16]

Figure 1.2 Forest plot summarising the effect of antibiotics on AAA related clinical events (repair or rupture) in randomised controlled trials.



Adapted from Golledge and Singh[16]

1.6 Limitations of maximum diameter and the need for surrogate measures of AAA rupture risk

While maximum AAA diameter is the preferred measure for estimating the rupture risk of an AAA and selecting patients for surgical repair, this measurement has many important limitations. Firstly, there is considerable intra-observer and inter-observer variability in the assessment of diameter.[3] Secondly, the annual growth rate of small AAAs is slow and is comparable to the measurement error associated with measuring AAA diameter from established surveillance methods including ultrasound and computed tomography imaging.[3] Furthermore, there is substantial variability in the methods used to estimate AAA diameter across different institutions. This includes estimating diameter from different imaging planes

(coronal and sagittal), orientations (orthogonal and axial), and cursor placement (outer-to-outer, leading edge-to-leading edge, or inner-to-inner wall).[3] Importantly, approximately 1-2% of small asymptomatic AAAs rupture per year (UK small aneurysm trial)[6] and some large AAAs remain stable during a patient's lifetime[8], indicating that maximum AAA diameter is an imperfect estimate of AAA rupture risk. Given the high risk of mortality from rupture, risks and expenses associated with AAA surgery, more accurate surrogate measures for rupture risk are required.

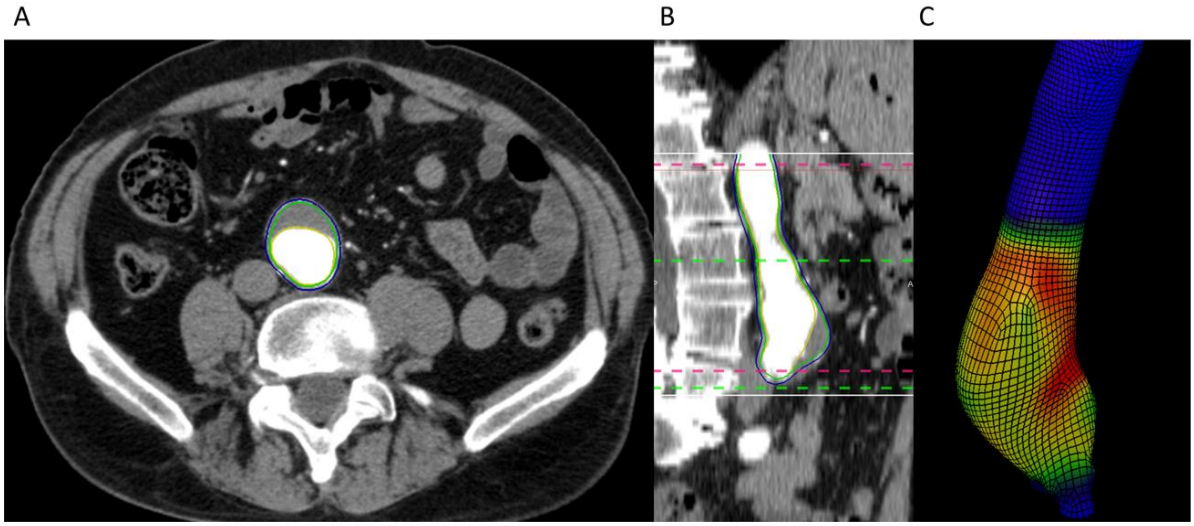
1.7 Biomechanics of abdominal aortic aneurysm rupture

There has been considerable interest in using biomechanical principles to explain and predict AAA rupture.[3, 20] From a biomechanical engineering perspective, AAA rupture is thought to occur when the mechanical stress (i.e forces per unit area) acting on the aneurysmal aortic wall exceeds the ability of the wall to endure the mechanical stress (i.e wall strength).[1, 21] A number of biomechanical measures have been studied in the context of AAA including AAA surface area, aortic tortuosity, intra-luminal thrombus volume, vessel wall properties, finite element analysis (FEA) and computational fluid dynamics.[22] All these measures are non-invasive and can be estimated from routinely conducted surveillance imaging (e.g computed tomography or ultrasound) for AAA.

FEA is the most widely studied biomechanical technique in the context of AAA. Interfaces developed for FEA of AAAs are user-friendly, time-efficient and semi-automatic, enabling health professionals with limited engineering background to utilise this technology.[23] Three-dimensional models generated by FEA (Figure 1.3) can be used to estimate the peak tensile strength arising within the AAA wall (peak wall stress, PWS). PWS is dependent on AAA morphology, intra-luminal thrombus and the blood pressure at which the three-dimensional

model is pressurised. A previous meta-analysis of case-control studies performed by Khosla and colleagues reported that PWS is greater in symptomatic or ruptured AAAs compared to intact AAAs.[24] There were a number of limitations of that systematic review including the inclusion of symptomatic AAAs with ruptured AAAs in one group, significant differences in AAA diameter between intact and ruptured or symptomatic AAAs, small sample sizes of the individuals studies, and limited validation of the methods used to estimate PWS.[24] It therefore remains unclear whether PWS is significantly different in ruptured than asymptomatic intact AAAs, and whether this difference is independent of diameter.

Figure 1.3 Example of a three-dimensional (3D) segmentation produced using finite element analysis on the computed tomography image of an AAA.



A and B represent the axial and sagittal views of the AAA. C represents the three-dimensional segmentation produced using finite element analysis on a CT scan of an AAA. The red areas of the model indicate areas of high peak wall stress.

Furthermore, since the publication of that systematic review and meta-analysis[24] a number of studies have investigated the utility of another biomechanical measure, the peak wall rupture index (PWRI), which estimates the ratio between maximum wall stress and estimated local

wall strength.[23] For this measurement, the local wall strength AAA wall strength is estimated using a statistical model incorporating intra-luminal thrombus, AAA diameter and sex.[23, 25] Wall strength values related to the variables included in this model are estimated from tensile testing of human AAA wall specimens, assuming a constant wall thickness, as described previously.[26] Due to the integration of wall strength in the measurement, PWRI has been proposed by some to be a superior marker of AAA rupture risk than PWS.[27] However, studies comparing PWRI between ruptured and asymptomatic intact AAAs are limited and have reported conflicting findings.[27, 28] There is no systematic review and meta-analysis that has compared PWRI in ruptured and asymptomatic intact AAAs of similar diameter.

Importantly, there is a lack of observational studies assessing the association between baseline PWS and PWRI with the future risk of clinically important AAA events (i.e AAA rupture or repair) among individuals with small AAAs (maximum orthogonal aortic diameter of ≥30 and ≤50 mm), who have a low risk of AAA rupture. Such data is required to assess whether PWS and PWRI can predict the risk of future AAA events amongst people with a low risk of AAA rupture. If PWS and PWRI can accurately predict the risk of AAA events, these measures may be used to assess the effectiveness of drug treatments hypothesized to limit AAA rupture. To our knowledge, no previous randomised controlled trial has examined the effects of a drug treatment on aortic PWS and PWRI.

1.8 Primary research questions

Acknowledging the gaps in prior research the following research questions were examined in this thesis:

Question 1: Is PWS a reproducible measurement and is PWS and PWRI greater among patients with ruptured than asymptomatic intact AAAs of similar diameter ?

Question 2: What are the findings of other investigations that have compared PWS and PWRI among patients with asymptomatic intact and ruptured AAAs of similar diameter? What does a pooled analysis of all prior studies comparing PWS and PWRI between ruptured and asymptomatic AAAs suggest?

Question 3: Is baseline PWS and PWRI associated with an increased risk of future AAA events (rupture or repair) among individuals with small AAAs ?

Question 4: Can a commonly used blood pressure lowering medication reduce the PWS and PWRI of individuals with small AAAs ?

1.9 Outline of thesis

To address the research questions, this thesis is presented by publication and contains 7 chapters; an introduction, one systematic review and meta-analysis, a general methods section, three original research investigations and a discussion. Each chapter contains a preface that summarises the manuscript contained within the chapter and its relevance to the thesis. A brief outline of each chapter has been presented in Table 1.4

Table 1.4 Brief outline of thesis and relevant publications.

Chapter number	Title	Aim	Relevant publications
1	Introduction and outline of research	To review the epidemiology of AAA, previous drug trials for AAA, limitations of aortic diameter in the estimation of rupture risk and the biomechanics of AAA.	Golledge J, Singh TP. Effect of blood pressure lowering drugs and antibiotics on abdominal aortic aneurysm growth: a systematic review and meta-analysis. Heart. 2021 Sep 1;107(18):1465-71 Golledge J, Moxon JV, Singh TP, Bown MJ, Mani K, Wanhainen A. Lack of an effective drug therapy for abdominal aortic aneurysm. Journal of internal medicine. 2020 Jul;288(1):6-22.
2	General methods for finite element analysis	To outline the methods by which the biomechanical measures PWS and PWRI are computed and assessment of the reproducibility of PWS.	Singh TP, Moxon JV, Iyer V, Gasser TC, Jenkins J, Golledge J. Comparison of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms. British Journal of Surgery. 2021 Jun;108(6):652-8.

3	Comparison of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms	To investigate whether PWS and PWRI is different among individuals with intact and ruptured AAAs with a similar aortic diameter.	Singh TP, Moxon JV, Iyer V, Gasser TC, Jenkins J, Golledge J. Comparison of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms. British Journal of Surgery. 2021 Jun;108(6):652-8.
4	Systematic review and meta-analysis of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms	To pool the results of all prior case control studies (including the study reported in Chapter 3) that have compared PWS and PWRI among patients with asymptomatic intact and ruptured AAAs.	Singh TP, Moxon JV, Gasser TC, Golledge J. Systematic Review and Meta-Analysis of Peak Wall Stress and Peak Wall Rupture Index in Ruptured and Asymptomatic Intact Abdominal Aortic Aneurysms. Journal of the American Heart Association. 2021 Apr 20;10(8):e019772.
5	Association between aortic peak wall stress and peak wall rupture index with abdominal aortic aneurysm related events	To assess whether baseline PWS and PWRI can predict the risk of future AAA events (rupture and repair).	Under review

6	Effect of telmisartan on the peak wall stress and peak wall rupture index of small abdominal aortic aneurysms: An exploratory analysis of the TEDY trial	To assess whether a commonly prescribed blood pressure lowering agent (telmisartan) can significantly reduce the PWS and PWRI of patients with small AAAs.	Under review
7	Discussion and recommendations	To summarise the findings of the studies reported in this thesis and discussion on the implications of the work for future research and clinical practise.	Nil

Chapter 2. General methods for finite element analysis

This chapter describes the methods used to perform finite element analysis (FEA) and compute measures of peak wall stress (PWS) and peak wall rupture index (PWRI). FEA was performed using the commercially available software A4 Research 5.0; VASCOPS, Graz, Austria.[23, 29] This program and the outlined methods have been used in Chapters 3, 4 and 5.

2.1 Finite element analysis

FEA is a computerised method, which can predict how an object reacts to different types of physical effects including forces, fluid flow, heat and vibrations.[30] The finite element method involves breaking down complex geometries with unclear structural behaviour into an assembly of small geometrical units (finite element mesh) with known structural behaviour.[30, 31] By using complex mathematical modelling, computerised systems can predict how the finite element mesh may react to different dynamic loadings.[31] This method has been extensively used to solve complex structural analysis problems by engineers.[30, 31]

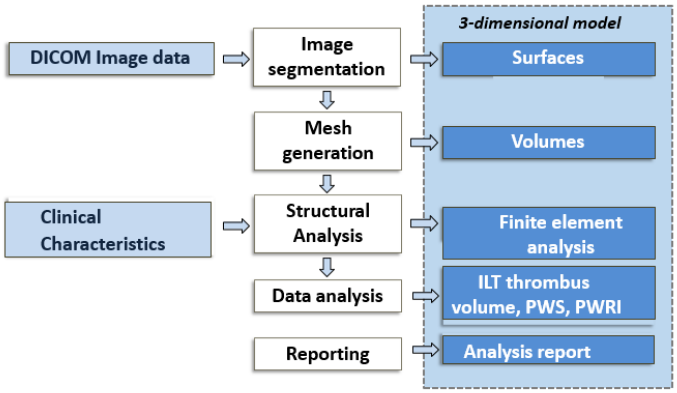
More recently, FEA has been used for patient risk stratification and operative planning in a number of medical specialities including orthopaedics, cardiovascular medicine and maxillofacial surgery.[32, 33] FEA has also been proposed to be a useful method of estimating the rupture risk of an abdominal aortic aneurysm (AAA).[23] FEA can non-invasively estimate the maximum tensile stress within the AAA wall (PWS) and the maximum ratio between wall stress and the estimated local wall strength (PWRI) using computed tomography angiography (CTA) scans that are routinely performed to assess the prognosis of people with AAAs.[23, 29] PWS and PWRI can be estimated in a semi-automated way, enabling clinicians without engineering backgrounds to perform FEA in a time efficient manner. The software that will be used in the current thesis is the A4 Research 5.0;

VASCOPS, Graz, Austria.[23, 29] The subsequent sections will present the interface of the software, steps to undertake FEA and report the reproducibility of PWS.

2.2 Workflow of A4 Research 5.0

The workflow of the A4 Research 5.0 software is summarised in Figure 1. Briefly, medical imaging data from a CTA scan (DICOM, Digital Imaging and Communications in Medicine) is imported into the A4 Research 5.0 software and a three dimensional model of a patients AAA is then generated using a semi-automated technique. Following this, a finite element mesh is generated and estimates of PWS and PWRI are generated by inputting clinical characteristics.

Figure 2.1 Summary of the workflow of the A4 Research 5.0.



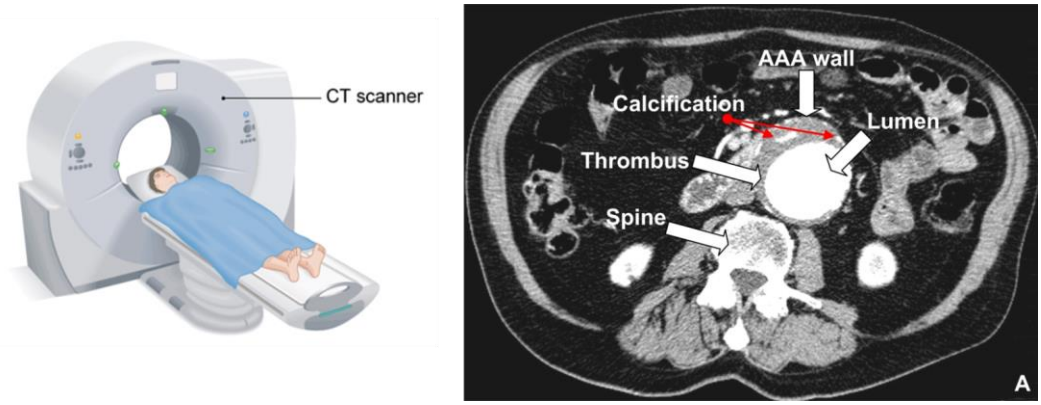
2.3 FEA steps and PWS/PWRI estimation

The following section will detail the steps by which PWS and PWRI are computed.

Step 1: Import CT scan of patient with AAA

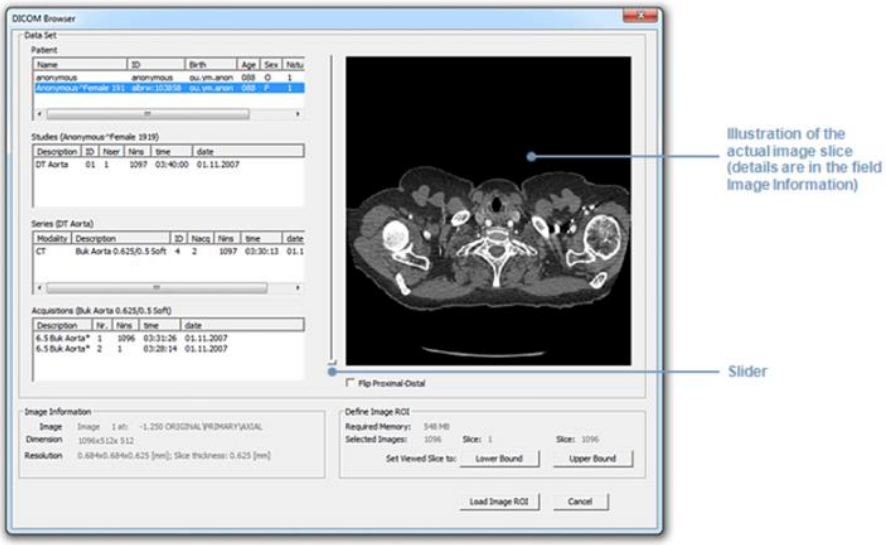
A CTA scan of a patient with an AAA is obtained (Figure 2.2).

Figure 2.2 Patient undergoing a CTA and an axial view of the patient's AAA.



The DICOM images from the CTA are then uploaded into a workstation and imported into the A4 Research 5.0 software (Figure 2.3).

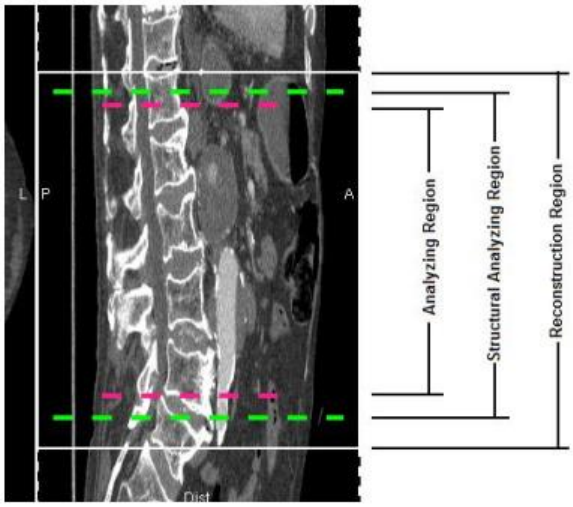
Figure 2.3 Importing DICOM images from a CTA scan of a patient with an AAA



<u>Step 2: Selecting a region of interest (ROI).</u>

A ROI is selected, which included the region marked by the slice inferior to the origin of the lowest renal artery (excluding accessory arteries) to the slice superior to the aortic bifurcation (Figure 2.4).

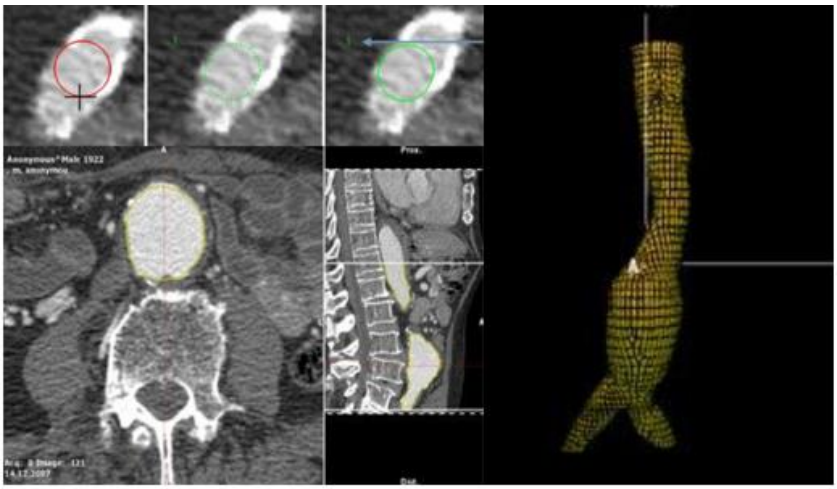
Figure 2.4 Selection of a ROI.



Step 3: Capture luminal surface using control polygon tool

A control polygon is inserted into the lumen to initiate the segmentation of the lumen of the AAA (Figure 2.5).

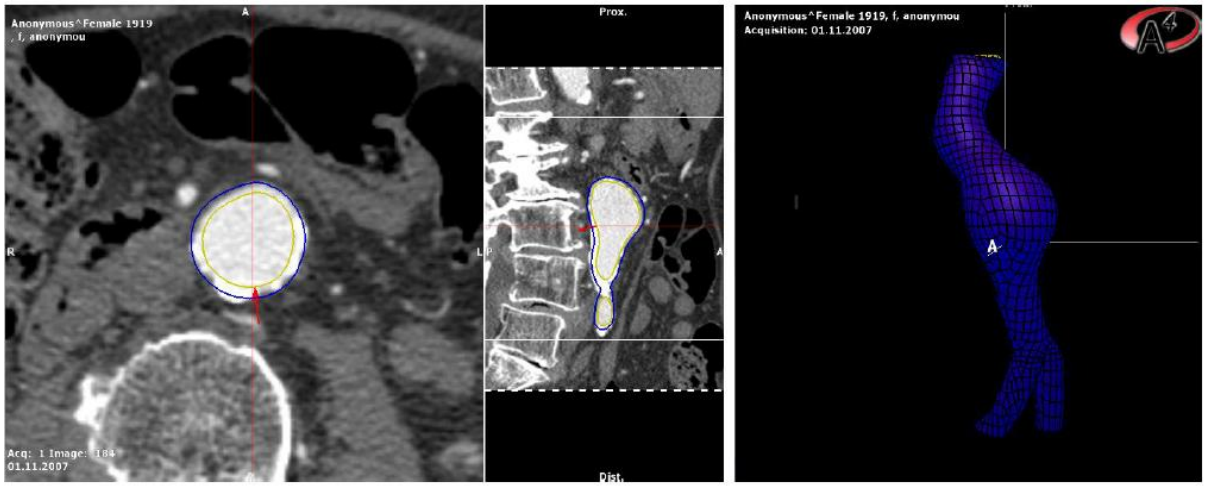
Figure 2.5 Closed polygon tool (yellow) capturing the luminal surface of the AAA (left) and three-dimensional segmentation of the luminal surface of the AAA (right).



Step 4: Capture exterior surface using control polygon

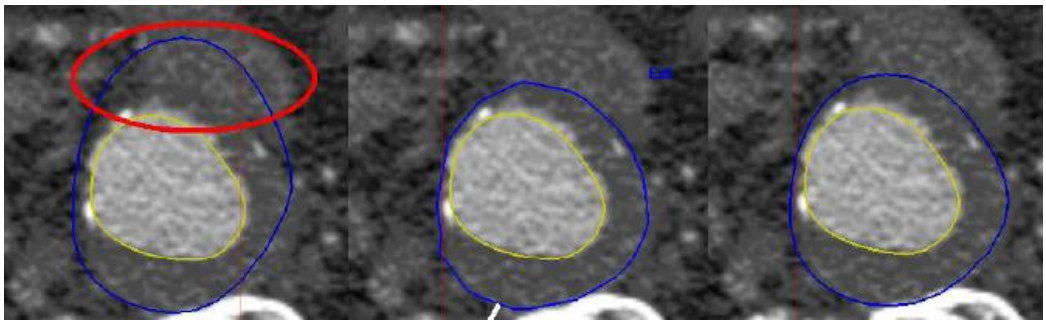
Similarly, to Step 3, a control polygon is created to capture the exterior surface of the AAA (Figure 2.6).

Figure 2.6 Closed polygon tool (blue) capturing the exterior surface of the AAA (left) and three-dimensional segmentation of the exterior surface of the AAA (right).



Both steps 3 and 4 are semi-automated and require a minimum of one closed polygon in once slice to be manually inserted by the user. At times, there may be an inaccurate estimation of the luminal or exterior surface. If this occurs, this can be manually corrected by the operator by insertion of more closed polygons at different slices when required (Figure 2.7).

Figure 2.7 Example of inaccurate estimation of the exterior surface (left; highlighted by the red circle) and creation of more accurate closed polygon capturing the exterior surface (middle) and re-segmentation of the exterior surface (right).

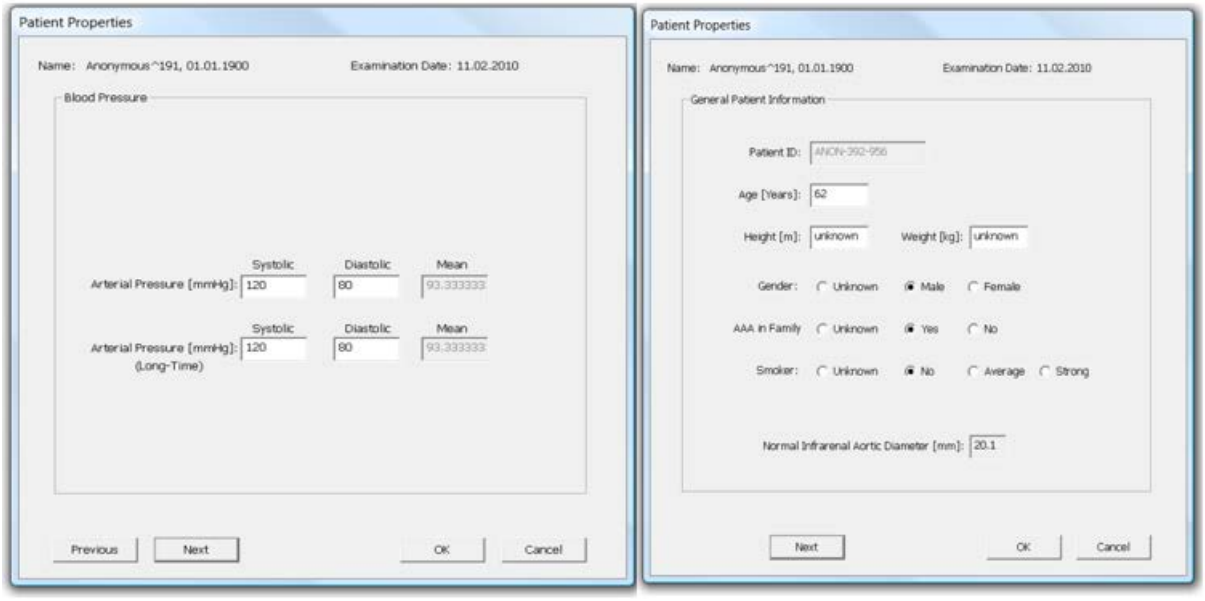


<u>Step 5: Inputting patient characteristics</u>

Patient characteristics are inputted into the software (Figure 2.8). These include blood pressure, age, gender, weight, height family history and smoking history (if known). Of these,

blood pressure, gender and family history of AAA are the most important.[23] The inputted blood pressure is used to pressurise the three dimensional model to compute PWS. Gender and family history of AAA are used to estimate the AAA wall strength. AAA wall strength is estimated using a statistical model incorporating intra-luminal thrombus thickness, AAA diameter, gender and family history of AAA as previously described.[23, 26, 34] If gender or family history of AAA are unknown, these variables are omitted from the model. Wall strength values related to the variables included in this statistical model were estimated from tensile testing of human AAA wall specimens, as described previously.[25, 34]

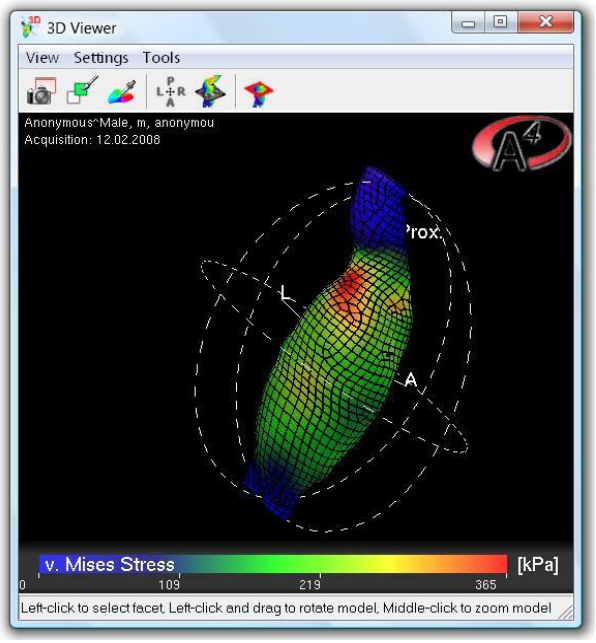
Figure 2.8 Inputting of patient characteristics.



Step 7: Perform FEA

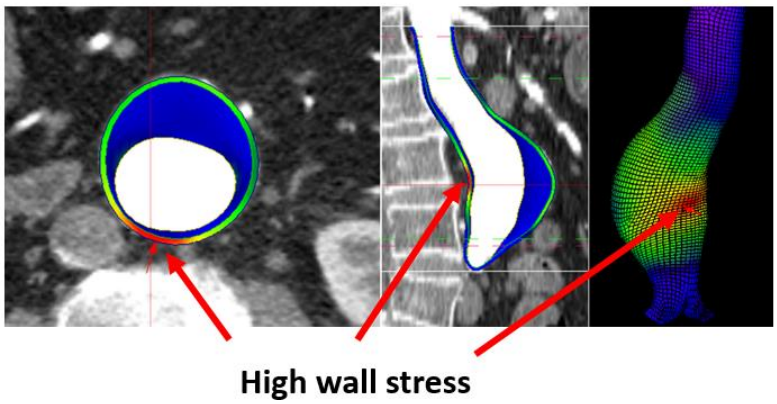
The 3D model is processed into a hexahedral finite element mesh (Figure 2.9) to prevent volume locking of incompressible solids. FEA meshes are required to comprise more than 7000 finite elements to ensure accuracy of the FEA calculations. Low-quality meshes are optimised by the mesh refinement tool.

Figure 2.9 Finite element mesh of the AAA.



Areas of high aortic wall stress are indicated by the red elements and areas of low aortic wall stress are indicated by the blue segments (Figure 2.10).

Figure 2.10 Finite element mesh of the AAA and corresponding areas of high wall stress in axial and sagittal planes.



<u>Step 8: Computation of PWS and PWRI</u>

After the structural analysis, biomechanical measurements are computed (Figure 2.11).

Figure 2.11 Computation of geometrical and biomechanical properties.

```
      Geometrical Properties:
-----------------------------------------------
Max. Exterior AAA Diameter                    = 56.7(56.5) [mm]
Max. Luminal AAA Diameter                     = 35.5 [mm]
Max. ILT Thickness                            = 31.1 [mm]
Tot. Vessel Volume                            = 189.3 [cm3]
Tot. Lumen Volume                             = 56.8 [cm3]
Tot. ILT Volume                               = 109.2 [cm3]

       Mechanical Properties:
  Note that the mechanical properties do only apply to abdominal aortic a
  and for all other vascular bodies these parameters must not be consider
-----------------------------------------------
Considered Spherical Radius for Averaging     = 5.00 [mm]
Considered Average Nodes    for Averaging     = 65
FE-mesh:                                      = 29377 nodes 23871 elements

Max. v. Mises Stress in the AAA Wall (PWS)    = 204.4 [kPa]
Mean v. Mises Stress in the AAA Wall          = 95.50 ±23.57 [kPa]
Max. Rupture Risk Index in the Wall (PWRI)    = 0.519
Rupture Risk Equivalent Diameter (RRED)       = 59.1 [mm]
Mean Rupture Risk Index in the Wall           = 0.3 ±0.1
Max. v. Mises Stress in the AAA ILT           = 35.9 [kPa]
Mean v. Mises Stress in the AAA ILT           = 7.2 ±2.6 [kPa]
Max. Rupture Risk Index in the ILT            = 0.6 []
Mean Rupture Risk Index in the ILT            = 0.1 ±0.0
```

The PWS estimates the maximum tensile stress subjected to the aortic wall based on AAA morphology and blood pressure (kilopascals, kPa).[23] PWRI estimates the maximum ratio between wall stress and the estimated local aortic wall strength.[23, 26]

2.4 Methods to assess reproducibility of PWS

The intra-observer reproducibility of estimates of PWS was evaluated through assessment of a group of randomly selected CTA scans from 10 patients with asymptomatic intact AAAs and 10 patients with ruptured AAAs. The CTA scans were examined on two separate occasions by the same observer 48 hours apart. Concordance correlation coefficient and coefficient of variation, were calculated. Bland and Altman's method was used to estimate mean difference and 95% confidence intervals (CI).[35]

2.5 Results of reproducibility assessment for PWS

The coefficient of variations for repeatability of PWS for asymptomatic and ruptured AAAs were 2.7% and 4.3% respectively (Table 2.1). Bland-Altman plots (Figure 2.12 and 2.13) suggested that differences in PWS estimates between readings were similar across the range of PWS.

Table 2.1 Intra-observer reproducibility of PWS

Group	Mean Difference	Concordance correlation coefficient (95% CI)	Coefficient of variation (COV)
Intact AAAs (n=10)			
Maximum axial diameter (mm)	0.4	0.997 (0.988, 0.999)	1.8%
Peak Wall Stress (kPa)	2.4	0.982 (0.933, 0.995)	2.7%
Ruptured AAAs (n=10)			
Maximum axial diameter (mm)	0.1	0.966 (0.892, 0.989)	3.2%
Peak wall Stress (kPa)	0.6	0.976 (0.933, 0.991)	4.3%

kPa, Kilopascals; CI, confidence intervals.

Figure 2.12 Intact AAAs: Bland-Altman plot of difference in peak wall stress (PWS) against the mean AAA PWS of two independent measurements from one observer.

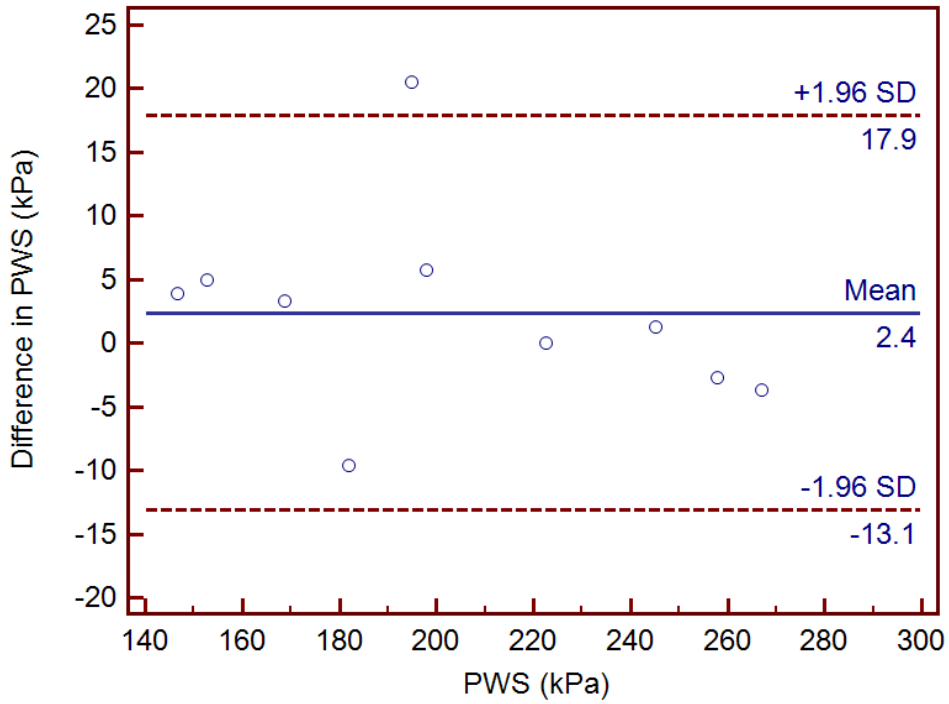
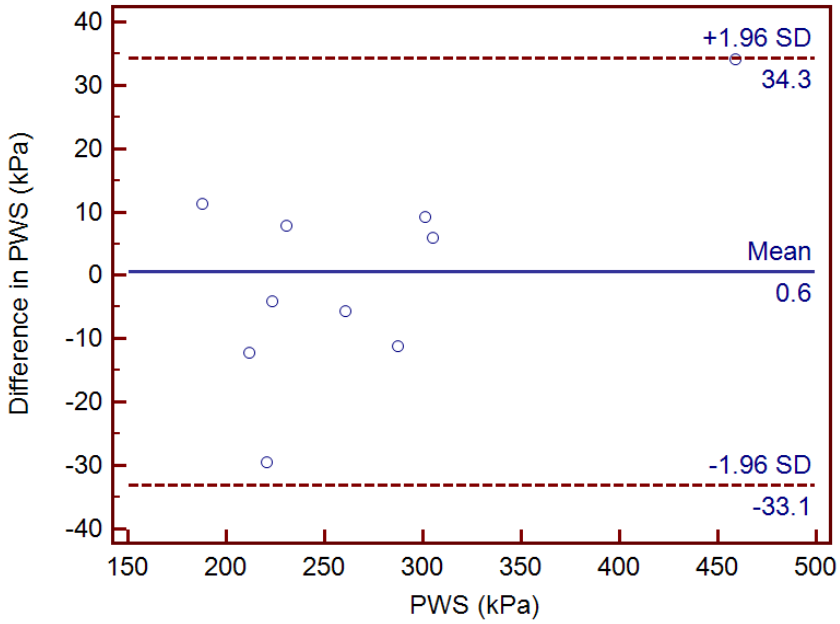


Figure 2.13 Ruptured AAAs: Bland-Altman plot of difference in peak wall stress (PWS) against the mean AAA PWS of two independent measurements from one observer.



2.6 Other software available to estimate PWS

It is important to acknowledge that a number of other software other than A4 Research 5.0 are available which can compute PWS. These have been summarised in Table 2.2. The A4 Research 5.0 software was used in the research contained within this thesis. This software was selected due to its semi-automated methods of conducting FEA, ability to calculate PWS/PWRI without the requirement for additional software, user-friendly interface that enables clinicians without engineering backgrounds to easily use the software.[23, 29]

Table 2.2 Currently available software for estimating aortic wall stress.

Software	**Measures computed**	**Important considerations**
A4 Research 5.0; VASCOPS[23]	PWS and PWRI	Commercially available; Semi-automated methods;

		One software needed to estimate PWS/PWRI
ABAQUS v.6.5 (Hibbit, Karlsson and Sorensen, Inc, Pawtucket, RI)[36]	PWS	This software has not been specifically designed to compute PWS of AAAs; Not semi-automated; This software is required to compute aortic wall stress in other platforms (e.g BioPARR)
BioPARR (Intelligent Systems for Medicine Laboratory and Vascular Engineering Laboratory, The University of Western Australia)[37]	RPI (rupture potential index), ABR (a dimensionless ratio of wall stress and wall strength)	This platform requires an additional software including ABAQUS, 3D slicer and Paraview; Not semi-automated.
SEPRAN (Sepra, Delft, the Netherlands)[38]	PWS	This software can only be used for wall stress analysis. Three-dimensional models are created in other soft wares.
ANSYS (v 5.3, ANSYS, Houston, Pa)[39]	PWS	This software can only be used for wall stress analysis. Three-dimensional models

		are created in other softwares.

Chapter 3. Comparison of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms

This chapter has been adapted from the below publication:

Singh TP, Moxon JV, Iyer V, Gasser TC, Jenkins J, Golledge J. Comparison of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms. British Journal of Surgery. 2021 Jun;108(6):652-8.

3.1 Preface

In this chapter, the findings of a case-control study comparing PWS and PWRI among ruptured and asymptomatic intact AAAs is presented. This study addresses a number of limitations of previous case-control studies as highlighted in Chapter 1 and utilised FEA methods as described in Chapter 2.

3.2 Abstract

Background: Previous studies have suggested that finite element analysis (FEA) can estimate the rupture risk of an abdominal aortic aneurysm (AAA), however the value of biomechanical estimates over measurement of AAA diameter alone remains unclear. This study aimed to compare peak wall stress (PWS) and peak wall rupture index (PWRI) in participants with ruptured and asymptomatic intact AAAs.

Methods: The repeatability of semi-automated methods of estimating aortic PWS and PWRI from computed tomography scans was assessed in 20 participants. PWS and PWRI were estimated in 25 people with ruptured AAAs and 50 people with asymptomatic intact AAAs matched by orthogonal diameter on a 1:2 basis. Spearman's correlation coefficient assessed

the association between PWS, PWRI and AAA diameter. Logistic regression analyses assessed the independent associations between PWS and PWRI with AAA rupture.

Results: Median orthogonal diameter was similar in ruptured and intact AAAs (82.3 (inter-quartile range 73.5-92.0) vs 81.0 (73.2-92.4) mm, p=0.906). Median PWS were 286.8 (220.2-329.6) and 245.8 (215.2-302.3) kPa in ruptured and intact AAAs respectively (p=0.192). PWRI was not significantly different in the two groups (p=0.982). PWS and PWRI were positively correlated with orthogonal diameter (p<0.001). Participants with high PWS, but not PWRI, were more likely to have a ruptured AAA after adjusting for potential confounders (Odds ratio, OR 5.84, 95% confidence intervals, CI 1.22-27.95, p=0.027). This association was not maintained in all sensitivity analyses.

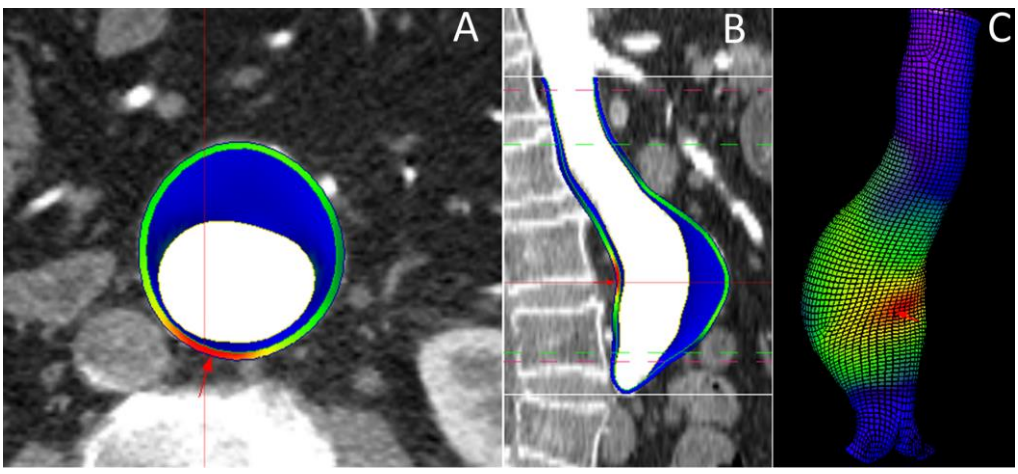
Conclusion: This study suggested that high aortic PWS had an inconsistent association with greater odds of AAA rupture in patients with large AAAs.

3.3 Introduction

Abdominal aortic aneurysm (AAA) is estimated to be responsible for about 200,000 deaths per year worldwide.[1, 2] AAA rupture is thought to occur when the haemodynamic forces on the aortic wall exceed the aortic wall strength.[1, 24] Maximum AAA diameter is the main measure used to predict the risk of AAA rupture and inform patient management. Small asymptomatic AAAs (<55mm diameter in men and <50mm in women) are generally managed conservatively based on evidence from previous randomised control trials.[6-9] Some small AAAs rupture[40] and some large AAAs remain stable during a patient's lifetime,[8] suggesting aortic diameter is not a perfect measure to estimate AAA rupture risk and requirement for surgery. Given the risks and expense associated with AAA repair, more effective approaches are needed to select patients for surgery in order to avoid unnecessary interventions.[1]

Biomechanical imaging analyses can be performed non-invasively by applying methods such as finite element analysis (FEA) to computed tomography (CT) images to estimate AAA rupture risk.[24, 41] Recently developed interfaces are user-friendly, time efficient and semi-automatic, enabling clinicians with non-engineering backgrounds to utilise this technology.[23, 29] Peak wall stress (PWS) is an estimation of the maximum mechanical tensile stress that arises in the AAA wall (Figure 3.1). A previous meta-analysis reported that PWS is greater in symptomatic or ruptured AAAs compared to intact AAAs,[24] although the results were confounded by differences in maximum diameter between the groups. Subsequent studies have also had a mismatch in aortic diameter between ruptured and intact AAAs,[24, 41] and other design weaknesses, such as a small sample size[41] and limited validation of the methods used to estimate PWS.[42, 43] It therefore remains unclear whether high PWS is associated with AAA rupture independent of aortic diameter. Furthermore, recent studies have reported that peak wall rupture index (PWRI)[41], which represents the ratio between maximum wall stress and wall strength, may be superior to PWS in estimating rupture risk of AAAs.[27] In order to address some of the limitations of these previous investigations, this study aimed to compare PWS and PWRI in ruptured and asymptomatic intact AAAs from participants with matched aortic diameter.

Figure 3.1 Three dimensional segmentation of an AAA using finite element analysis.



A and B represent the axial and sagittal views of the AAA. C represents the three dimensional segmentation produced using finite element analysis on a CT scan of an AAA. The red arrow indicates areas of high peak wall stress. The blue and green area represents intra-luminal thrombus and exterior wall of the AAA respectively.

3.4 Methods

3.4.1 Study design

This was a retrospective case control study in which cases with ruptured AAAs were matched 1:2 with controls with asymptomatic intact AAAs. Maximum anterior-posterior AAA diameter was matched between cases and controls to within 2mm. Ethics and governance approvals were obtained from the Human Research Ethics Committees of the Royal Brisbane and Women's Hospital (RBWH) and the Townsville Hospital and Health Services (HREC/11/QRBW/198; SSA/11/QTHS/159).[44]

3.4.2 Participants

Participants were retrospectively selected from databases maintained at the RBWH and The Townsville University Hospital.[44] AAA was defined as maximum orthogonal diameter ≥30 mm. AAA rupture was defined as blood within the retroperitoneum or peritoneum identified by CT imaging by a consultant vascular specialist.[45] Participants with asymptomatic intact AAAs were individuals who had an incidental finding of an AAA and were referred to a vascular specialist for management. For inclusion in the study a CT angiogram suitable for FEA was required. Patients with juxta-renal or thoracic-abdominal aneurysms or massive contrast extravasation (in the case of rupture) were excluded.[46] Participants either had to have a ruptured AAA or an asymptomatic intact AAA at the time the CT was performed. Patients with symptomatic intact AAAs or who had undergone previous AAA repair were excluded.

3.4.3 Cardiovascular risk factors

These were obtained from existing databases and patient records.[44, 47, 48] Clinical characteristics collected included age, sex, hypertension, diabetes, ischaemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), smoking and current medications. Smoking classification was based on smoking history, defined as ever or never smoked. Medications collected included aspirin, other anti-platelet agents, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), statin and metformin. Hypertension, diabetes, IHD, stroke and COPD were defined as history of diagnosis or treatment for these conditions.[47]

3.4.4 CT acquisition

A 64 slice multi-scanner (Philips, North Ryde, NSW) was used to obtain contrast-enhanced CT images at 3mm intervals under a set acquisition protocol as previously described.[45, 49] Ultravist 300 contrast (100ml; Bayer, Wayne, NJ) was administered intravenously using a previously validated automatic injection driver system (MEDRAD, Warrendale, Pa).[45, 49-51] The CT imaging was triggered when the Hounsfield unit (HU) at the center of the aorta reached 130 after the injection of the contrast.[45]

3.4.5 Assessment of AAA morphology

A Philips MxView Visualisation Workstation was used to estimate maximum aortic diameter by following a previously validated protocol.[50, 51] A region of interest (ROI) was selected, which was restricted to the slice inferior to the origin of the lowest renal artery (excluding accessory arteries) to the slice superior the aortic bifurcation. This ROI was viewed to identify areas of maximal diameter and multiple measurements were taken using electronic callipers. Anterior-posterior outer-to-outer orthogonal diameters were estimated by tracing

the lumen of the infrarenal aorta and measuring perpendicular to this axis. The measurement was recorded to the nearest 0.1mm.[44, 52] The reproducibility of this method has been reported to be high (coefficient of variation <4%).[51]

3.4.6 Biomechanical analyses

FEA was performed using a semi-automated technique with a commercially available program (A4 Research 5.0, VASCOPS GmbH, Graz, Austria).[23, 29] Firstly, the CT image was acquired using the hospital Picture Archiving and Communicating System and the AAA region was selected for analysis. Next, a ROI from the infrarenal aorta to the iliac bifurcation was selected and a three-dimensional (3D) reconstruction of the AAA created. Manual modifications of the vessel wall and lumen were performed where necessary using the closed polygon tool. This was commonly required in ruptured AAA cases. The 3D model was then processed into a hexahedral mesh to prevent volume locking of incompressible solids. FEA meshes were required to be >7000 finite elements to ensure accuracy of the FEA calculations. Low quality meshes were optimised by mesh refinement. The model was adjusted for patient-specific and geometrical factors.[25, 53] Specifically, the mechanical properties of intra-luminal thrombus (ILT) and the AAA wall were described by isotropic material models.[25] AAA wall elasticity was modelled with an Yeoh-type strain energy function,[54] whilst the ILT was modelled with an Ogden-type strain energy function which accounts for the proportional decrease in ILT stiffness from the luminal to abluminal layer[53] as reported in previous in-vitro testing.[25] AAA wall strength distribution was estimated using a statistical model incorporating ILT thickness, AAA diameter, gender and family history of AAA.[25] Wall strength values related to these variables were estimated from tensile testing of human AAA wall specimens as previously described.[25, 55] The AAA FEA model was pressurised by inputting blood pressure, which in turn estimated the mechanical stress on the aortic wall.[23 25,

[55] The current study used a standardized blood pressure of 140/80 mmHg for the main analysis and sensitivity analyses were performed using a lower (120/70 mmHg) and higher (160/90 mmHg) blood pressure. The geometrical properties calculated included total vessel volume (cm^3) and total ILT volume (cm^3). The biomechanical measures estimated were PWS and PWRI.[23, 41] PWS estimated maximum tensile stress applied on the aortic wall based on AAA morphology and blood pressure. PWRI represented the maximum ratio between wall stress and the estimated local wall strength.[46]

3.4.7 Assessment of intra-observer reproducibility

The intra-observer reproducibility of estimates of PWS was evaluated through assessment of a group of randomly selected CT scans from 10 patients with asymptomatic intact AAAs and 10 patients with ruptured AAAs. The CT scans were examined on two separate occasions by the same observer 48 hours apart. Concordance correlation coefficient and coefficient of variation, were calculated. Bland and Altman's method was used to estimate mean difference and 95% confidence intervals.[35]

3.4.8 Sample size estimation

The sample size calculation was based on a previous study that compared PWS in participants with symptomatic or ruptured and asymptomatic intact AAAs at standardised blood pressure.[43] In that study, patients were not matched for diameter but differences in aortic diameter were not significant. The estimated mean PWS was 1.11 ± 0.51 and 0.67 ± 0.30 Megapascals (MPa) in symptomatic or ruptured and asymptomatic AAAs respectively. In order to demonstrate a similar difference in PWS at power of 90% (alpha 0.05), it was estimated that at least 15 ruptured AAA cases and 31 intact AAA controls were required. Sample size calculations were performed using G*Power (Version 3.1.9.6).[56] To allow for

scans in which there were technical difficulties in estimating PWS, 25 participants with a ruptured and 50 with an intact AAA were included.

3.4.9 Statistical analysis and adjusted analysis

Data were not normally distributed when assessed using Q-Q plots and the Kolmogorov-Smirnov test. Pearson chi-squared and Mann Whitney U-tests were used for comparing variables between the two groups. Spearman's correlation coefficient was used to assess the association between PWS and PWRI with AAA diameter. To assess the relationship between low and high PWS and PWRI with rupture, patients were stratified into low (≤275 kPa) and high (>275 kPa) PWS groups, and low (≤ 0.910) and high (> 0.910) PWRI groups. Patients were stratified into these groups based on the approximate median PWS and PWRI of the cohort using methods previously described.[57] A further analysis was also performed using PWS or PWRI as a continuous variable and reported per increase in PWS or PWRI of approximately the standard deviation (SD) in the population. Multivariable logistic regression was performed to examine the independent associations between PWS or PWRI, and ruptured AAA, adjusting for potential confounders[18] or variables that were found to be significantly different between asymptomatic intact AAAs and ruptured AAAs. The variables adjusted for were age, sex, smoking, orthogonal diameter, IHD, hypertension, diabetes and ARB prescription. Statistical significance was assumed at $p<0.05$. All analyses were performed using STATA version 16.1 (StataCorp, College Station, Texas, USA).

3.4.10 Sensitivity analysis

Sensitivity analyses were conducted to assess the robustness of the results. To account for potential under or overestimation of PWS and PWRI due to the use of a single blood pressure value (140/80 mmHg), PWS and PWRI were also estimated using low and high blood

pressures (120/70 mmHg and 160/90mmHg). Another analysis examined the differences in PWS and PWRI between ruptured and intact AAAs in male patients only in order to account for the over-representation of women in the participants with ruptured AAAs in the cohort.

3.5 Results

3.5.1 Clinical characteristics

25 patients with ruptured AAAs and 50 with asymptomatic intact AAAs were included (Table 3.1). Patients with ruptured AAAs were more likely to be female compared to patients with asymptomatic intact AAAs (28% vs 6%, p=0.008). There were no significant differences in median age and prevalence of smoking, diabetes and IHD between groups (Table 3.1). Patients with ruptured AAAs were more likely to be prescribed an ARB.

Table 3.1. Characteristics of patients with asymptomatic intact and ruptured AAAs in diameter matched group of patients.

	Intact AAA (n=50)	**Ruptured AAA (n=25)**	**p-value**
Age	74 [66-77]	74 [67-78]	0.380
Male sex	47 (94%)	18 (72%)	**0.008**
Smoking	47 (94%)	21 (88%)	0.338
Diabetes	9 (18%)	3 (13%)	0.548
IHD	26 (52%)	9 (38%)	0.242
Hypertension	33 (66%)	18 (75%)	0.434
Stroke	5 (10%)	0 (0%)	0.109
COPD	12 (24%)	3 (13%)	0.265

Aspirin	27 (54%)	13 (52%)	0.870
Other anti-platelet	12 (24%)	3 (12%)	0.221
ACEi	21 (42%)	5 (20%)	0.059
ARB	4 (8%)	10 (40%)	**0.001**
Statin	31 (62%)	13 (52%)	0.407
Metformin	1 (2%)	1 (4%)	0.612

AAA, abdominal aortic aneurysm; IHD, ischemic heart disease; COPD, Chronic obstructive pulmonary disease; ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker. Smoking as defined as patients that were current or ex-smokers. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test. Nominal data are presented as number (%) and were compared using Pearson's $\chi 2$ test. P-values highlighted in bold indicate significant differences.

3.5.2 Intra-observer reproducibility

The coefficient of variations for repeatability of PWS for asymptomatic and ruptured AAAs were 2.7% and 4.3% respectively. Bland-Altman plots suggested that differences in PWS estimates between readings were similar across the range of PWS (Appendix A, supporting information).

3.5.3 PWS and PWRI

Maximum orthogonal aortic diameter was similar in both groups (Table 3.2). PWS was greater in ruptured AAAs than asymptomatic intact AAAs although the difference was not statistically significant [286.8 (220.2-329.6) vs 245.8 (215.2-302.3), p=0.192). PWRI was not

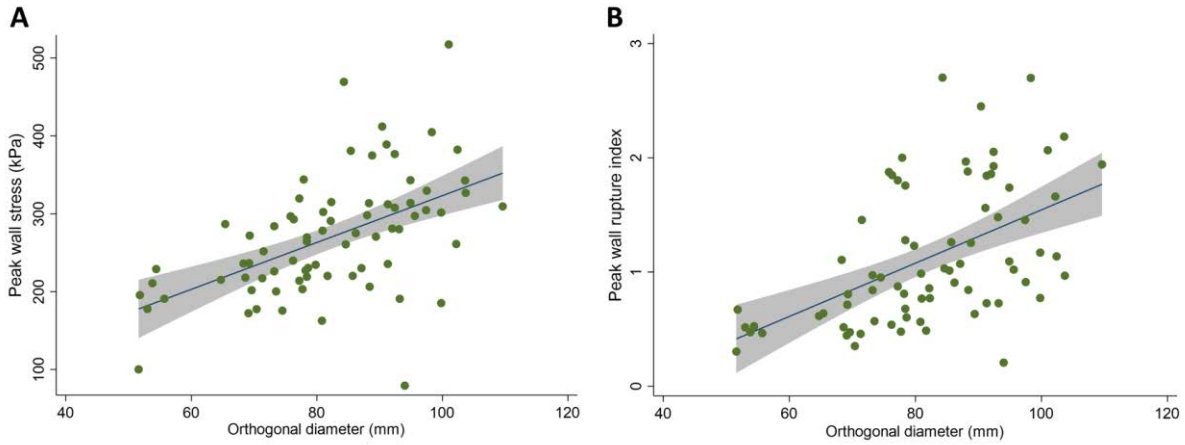
significantly different between groups (Table 3.2). PWS ($r=0.56$, $p<0.001$) and PWRI ($r=0.56$, $p<0.001$) were positively correlated with aortic diameter (Figures 3.2a and 3.2b).

Table 3.2 Estimated PWS and PWRI in asymptomatic intact and ruptured AAAs.

	Intact AAA (n=50)	**Ruptured AAA (n=25)**	**P-value**
Maximum orthogonal diameter (mm)	81.0 [73.2-92.4]	82.3 [73.5-92.0]	0.906
Total vessel volume (cm^3)	342.7 [200.6-526.8]	302.9 [224.6-466.3]	0.866
ILT volume (cm^3)	143.0 [91.2-237.1]	171.4 [44.5-223.8]	0.597
PWS (kPa)	245.8 [215.2-302.3]	286.8 [220.2-329.6]	0.192
PWRI	0.97 [0.68-1.46]	0.91 [0.57-1.85]	0.982

AAA, abdominal aortic aneurysm; PWS, peak wall stress; PWRI, peak wall rupture index; ILT, intra-luminal thrombus. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test.

Figure 3.2 Correlation between peak wall stress, peak wall rupture index and orthogonal diameter.



Correlation between PWS, PWRI and orthogonal diameter illustrated in Figures 3.2a and 3.2b respectively. The grey region represents 95% confidence intervals. PWS ($r=0.58$, $p<0.001$) and PWRI ($r=0.56$, $p<0.001$) was positively correlated with maximum axial diameter.

3.5.4 Adjusted analysis

Patients were grouped into low (≤275 kPa) and high (>275 kPa) PWS. Univariate logistic regression suggested that high PWS was not significantly associated with ruptured AAA (Odds ratio [OR] 1.91, 95% confidence intervals [CI] 0.72-5.04, p=0.192). After adjusting for potential confounders, participants with a high PWS were 5-times more likely to have a ruptured AAA compared to patients with a low PWS (OR 5.84, 95% CI 1.22-27.95, p=0.027) (see Table 3.3). High PWRI was not significantly associated with AAA rupture in the logistic regression analyses. Secondary analyses using PWS or PWRI as continuous variables suggested no significant association with AAA rupture in either univariate or multivariate analyses (Table 3.3).

Table 3.3 Logistic regression analysis examining the association of high PWS and PWRI with AAA rupture.

	Odds Ratio	**95% CI**	**P-value**
PWS			
Unadjusted analysis			
PWS †	1.23	0.76-2.00	0.394
PWS ≤ 275 kPa	(reference)		
PWS > 275 kPa	1.91	0.72-5.04	0.192
Adjusted analysis*			
PWS †	1.76	0.87-3.58	0.117
PWS ≤ 275 kPa	(reference)		
PWS > 275 kPa	5.84	1.22-27.95	**0.027**
PWRI			
Unadjusted analysis			
PWRI †	1.20	0.75-1.94	0.445
PWRI ≤ 0.910	(reference)		
PWRI > 0.910	0.92	0.35-2.41	0.870
Adjusted analysis*			
PWRI †	1.90	0.83-4.33	0.127
PWRI ≤ 0.910	(reference)		
PWRI > 0.910	0.89	0.21-3.70	0.869

*Adjusted for age, sex, smoking, orthogonal diameter, Ischaemic heart disease, hypertension, diabetes and Angiotensin II receptor blocker prescription. † Odds ratios expressed per 1

3.5.5 Sensitivity analyses

PWS and PWRI was similar between both the asymptomatic intact and ruptured AAA groups when computed at low and high blood pressures (Appendix A, Table 2). After adjusting for potential confounders, participants with a high PWS were more likely to have a ruptured AAA compared to patients with a low PWS at both low (OR 4.67, 95% CI 1.05-20.62, p=0.042) and high (OR 4.99, 95% CI 1.11-22.47, p=0.036) blood pressures (Appendix A, Table 3). The sensitivity analysis involving male participants only (n=65) showed similar findings to the main analysis (Appendix A, Tables 4 and 5).

3.6 Discussion

The main analysis in this study found that patients with high PWS were approximately 5 times more likely to have a ruptured AAA compared to patients with lower PWS after adjusting for important confounding factors. The result was robust when PWS was computed at high and low blood pressures, however there was no significant association between PWS and AAA rupture when continuous values were used in the logistic regression. No consistent relationship between PWRI and AAA rupture was found.

There are a number of design strengths of the current investigation when compared to previously published studies[24, 41, 43, 58, 59] Differences in diameter between ruptured and asymptomatic intact AAAs were not accounted for in many prior studies.[24, 43, 58, 59] In the current study, ruptured and asymptomatic intact AAAs were matched for diameter. A number of other steps were taken in order to reduce bias, such as the use of a standardised blood pressure and repeatable methods to estimate orthogonal AAA diameter and biomechanical measurements.[41] Furthermore, the number of patients included in the study were based on an a priori sample size estimate. These factors support the reliability of the findings.

AAA diameter is an imperfect measure to identify which patients should undergo surgery.[1, 3] AAA repair carries a substantial risk of peri-operative complications and some patients will require reinterventions.[1, 3] The findings of this study demonstrate a potential benefit of using PWS as a surrogate marker of AAA rupture risk to help identify which patients should be considered for surgery. There are however many limitations of this technology which need to be addressed, before it could be integrated in clinical practise. Firstly, there is no standardised approach to conducting FEA and many methods have been reported although few have been validated.[24, 41] Wall strength may be more important than wall stress in the pathogenesis of AAA rupture, however there is currently no accurate method of non-invasively measuring this.[60] Magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography may provide useful information regarding the biology of the AAA wall,[60, 61] however it is unlikely that there will be a wide uptake of such imaging modalities in clinical practice. The FEA method employed in the current study utilised patient-specific factors to estimate wall strength.[25, 53] We used the median values of PWS or PWRI to categorise participants with low and high PWS or PWRI. Further validation of the FEA method in larger populations is required to help define clinically useful cut-offs for PWS. Finally, the diameter of asymptomatic intact and ruptured AAAs included in this study were large and the results may not be generalizable to smaller AAAs.[41] Estimating PWS and PWRI in small AAAs could potentially help identify AAAs that are more likely to rupture that may benefit from closer surveillance, although this is yet to be investigated in a large observational study. There are some limitations of this investigation. Although a significant association between high PWS and AAA rupture was identified, confidence intervals were wide, which is reflective of the small sample size. The number of patients included in the current study was however larger than previous investigations.[27-29, 36, 62] The design of the current study required intact and ruptured AAAs to be matched for diameter, which resulted in the exclusion of

some large AAAs in which diameter matched asymptomatic intact AAAs could not be found. Secondly, this study included patients with CT scans performed after rupture and it is possible that the biomechanical forces prior to rupture were different.[45] Furthermore, the participants with ruptured AAA included need to be suitable for the FEA software used which excluded patients with massive contrast extravasation.[46] In the current study a standardised blood pressure was used and it is possible that PWS and PWRI was under or overestimated in some patients. We performed a sensitivity analysis in which PWS and PWRI were computed at low and high blood pressures to account for this limitation. Although both groups were balanced in terms of medical co-morbidities, confounding due to an unmeasured risk factor cannot be excluded. We were unable to match for sex due to difficulties in identifying the required number of female patients with asymptomatic intact AAAs that matched in diameter with the female patients who had a ruptured AAA. We attempted to address this limitation by adjusting for sex in the multivariate logistic regression as well as performing a sensitivity analysis restricted to male participants only. Finally, this study included participants recruited from centres in Queensland, Australia and the generalisability of the results needs to be confirmed in independent cohorts from other states and countries.

In conclusion, the findings of this study suggest that PWS may be useful in predicting the risk of AAA rupture independent of maximum aortic diameter.

Chapter 4. Systematic review and meta-analysis of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms

This chapter has been adapted from the below publication:

Singh TP, Moxon JV, Gasser TC, Golledge J. Systematic Review and Meta-Analysis of Peak Wall Stress and Peak Wall Rupture Index in Ruptured and Asymptomatic Intact Abdominal Aortic Aneurysms. Journal of the American Heart Association. 2021 Apr 20;10(8):e019772.

4.1 Preface

In this chapter, the results of Chapter 3 and all other prior case-control studies comparing PWS and PWRI between ruptured and asymptomatic intact AAAs are pooled in a meta-analysis. This systematic review and meta-analysis addresses a number of limitations of a previous meta-analysis as discussed in Chapter 1. The search for this systematic review was repeated in November 2021 in preparation for this thesis. No additional studies were found that could be included in this systematic review.

4.2 Abstract

Background: Prior studies have suggested aortic peak wall stress (PWS) and peak wall rupture index (PWRI) can estimate the rupture risk of an abdominal aortic aneurysm (AAA), but whether these measurements have independent predictive ability over assessing AAA diameter alone is unclear. The aim of this systematic review was to compare PWS and PWRI in participants with ruptured and asymptomatic intact AAAs of similar diameter.

Methods: Web of Science, Scopus, Medline and The Cochrane Library were systematically searched to identify studies assessing PWS and PWRI in ruptured and asymptomatic intact AAAs of similar diameter. Random-effects meta-analyses were performed using inverse variance-weighted methods. Leave-one-out sensitivity analyses were conducted to assess the robustness of findings. Risk of bias was assessed using a modification of the Newcastle-Ottawa scale and standard quality assessment criteria for evaluating primary research papers.

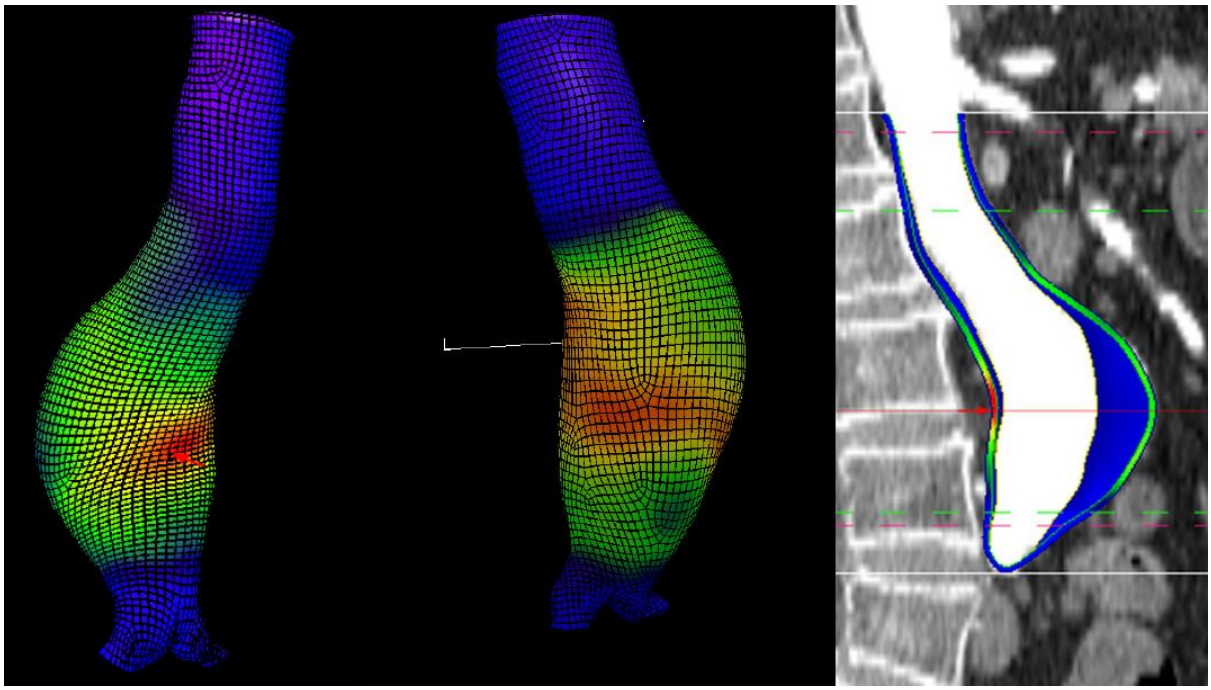
Results: Seven case-control studies involving 309 participants were included. Meta-analyses suggested that PWRI (standardised mean difference, SMD 0.42, 95% confidence intervals, 95% CI 0.14, 0.70, p=0.004) but not PWS (SMD 0.13, 95% CI -0.18, 0.44, p=0.418) was greater in ruptured than intact AAAs. Sensitivity analyses suggested that the findings were not dependant on the inclusion of any single study. The included studies were assessed to have a medium to high risk of bias.

Conclusions: Based on limited evidence, this study suggested that PWRI, but not PWS, is greater in ruptured than asymptomatic intact AAAs of similar maximum aortic diameter.

4.3 Introduction

Abdominal aortic aneurysm (AAA) rupture is estimated to be responsible for 200,000 deaths annually worldwide.[1, 2] AAA rupture is thought to occur when the haemodynamic forces exceed the aortic wall strength.[1, 24] In clinical practise, maximum AAA diameter is the main measure used to estimate rupture risk and select patients for elective repair.[1] Current guidelines recommend elective repair of asymptomatic large AAAs (maximum aortic diameter ≥50mm in women and ≥55mm in men).[1, 40, 63] Approximately 1-2% of small asymptomatic AAAs rupture each year[40] and some large AAAs remain stable during a patient's lifetime[8], suggesting that diameter is an imperfect measure of rupture risk. Biomechanical imaging may provide a more precise means to estimate AAA rupture risk and select patients for repair. Finite element analysis (FEA) can non-invasively estimate the maximum tensile stress within the AAA wall (peak wall stress; PWS) and the maximum ratio between wall stress and the estimated local wall strength (peak wall rupture index; PWRI).[24] Semi-automated systems have been developed to enable clinicians without engineering backgrounds to perform FEA using computed tomography (CT) scans that are routinely performed to assess people with AAA (Figure 4.1).[24, 64] Thus, it would be feasible to use PWS and/or PWRI in clinical practice if these measures were shown to be independent predictors of AAA rupture. Currently, however, the value of measuring PWS and PWRI over simply measuring maximum AAA diameter is unclear.

Figure 4.1 Examples of three-dimensional (3D) segmentation produced using finite element analysis from computed tomography images of AAA patients.



The red areas indicate areas of high aortic wall stress.

Previous meta-analyses[24, 65] have suggested that PWS is greater in patients with ruptured than intact AAAs, however, the generalisability of this finding is unclear owing to a number of limitations. These included lack of adjustment or matching for aortic diameter[24], inclusion of symptomatic AAAs mixed with ruptured AAAs[65] and small sample sizes.[41] These limitations have been addressed in more recent studies which have been reported after the publication of the most recent meta-analysis, suggesting that higher quality data is now available for an updated meta-analysis. Furthermore, PWRI has been suggested by one[27], but not another study[28], to be a superior measure of rupture risk than PWS. No meta-analysis comparing PWRI in ruptured and intact AAA has been reported.[24, 65] The aim of this systematic review and meta-analysis was to provide an up to date pooled analysis of prior studies that compared PWS and PWRI in patients with ruptured and asymptomatic intact AAA of similar diameter.

4.4 Methods

4.4.1 Literature search and inclusion criteria

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[66] A study protocol for this systematic review was designed (Appendix B, Supplementary File 1) and was not preregistered with any database. A literature search was performed using the following databases: Web of Science (via ISI Web of Knowledge; 1965), Scopus (1966), Medline (via OvidSP, 1966) and The Cochrane Library to identify case-control studies investigating PWS in patients with ruptured and diameter matched asymptomatic intact AAAs. The following search terms were applied: “peak wall stress” OR “peak wall rupture index” OR “rupture potential index” AND “abdominal aortic aneurysm”. The search was performed in November 2021 without language restrictions by one author (TPS). Reference lists of primary articles and reviews were searched to increase the yield of relevant publications. Titles and abstracts were screened to identify relevant studies. If the suitability of an article was uncertain, the full text was reviewed. For inclusion in the meta-analysis studies needed to have compared PWS or PWRI in asymptomatic intact AAAs and ruptured AAAs of similar diameter (within 3mm mean difference between groups). Studies in which it was not possible to separate symptomatic from ruptured AAAs were excluded.

4.4.2 Data extraction and risk of bias of the included studies

Data were extracted from included studies independently by three authors (TS, JM and JG). The following data were collected: Sample sizes for the ruptured and intact AAA group, study design, software used to perform FEA, PWS and PWRI estimates, AAA diameter, risk factors (including age, sex, smoking history, hypertension, diabetes, ischaemic heart disease [IHD], stroke, chronic obstructive pulmonary disease [COPD]) and systolic blood pressure. If

relevant data were not reported in the publication, the corresponding author was contacted for this information. The risk of bias was assessed independently by three authors (TS, JM and JG). A quality assessment tool was designed to assess the risk of bias of the included studies adapted from two previously reported tools (Newcastle-Ottawa scale and Standard quality assessment criteria for evaluating primary research papers).[67, 68] A number of additional aspects of the included studies relevant to this systematic review were also assessed including: criteria used to define AAA rupture; method used to estimate PWS and PWRI and reproducibility reported; use of a standardised blood pressure in PWS and PWRI calculations (i.e. use of a single blood pressure measurement for all participants or omission of blood pressure in calculations); inclusion of CT scan prior to or after rupture (for ruptured cases); matching for AAA diameter between asymptomatic intact and ruptured cases; matching for other confounding variables. The overall risk of bias assessed within each study was assessed as low, medium or high based on predefined criteria. Details regarding the quality assessment criteria can be found in Appendix B, Table 1.

4.4.3 Data synthesis

Meta-analysis was performed using inverse variance-weighted methods [69] in order to calculate standardised mean differences (SMD) with 95% confidence intervals (CI). PWS outcome data were converted from Newton Per Square Centimeter (N/cm^2) to kilopascal (kPa) where required.[36] Due to anticipated inter-study heterogeneity in methods and biomechanical analyses, SMDs were calculated using random-effects models.[70] Inter-study heterogeneity was assessed using the I^2 index and values <25%, between 25-75% and >75% were considered to represent low, moderate and high heterogeneity, respectively.[71] If PWS and PWRI were computed at a standardised blood pressure (i.e. same BP for all participants) this value was used in the meta-analysis. One study calculated PWS and PWRI using a

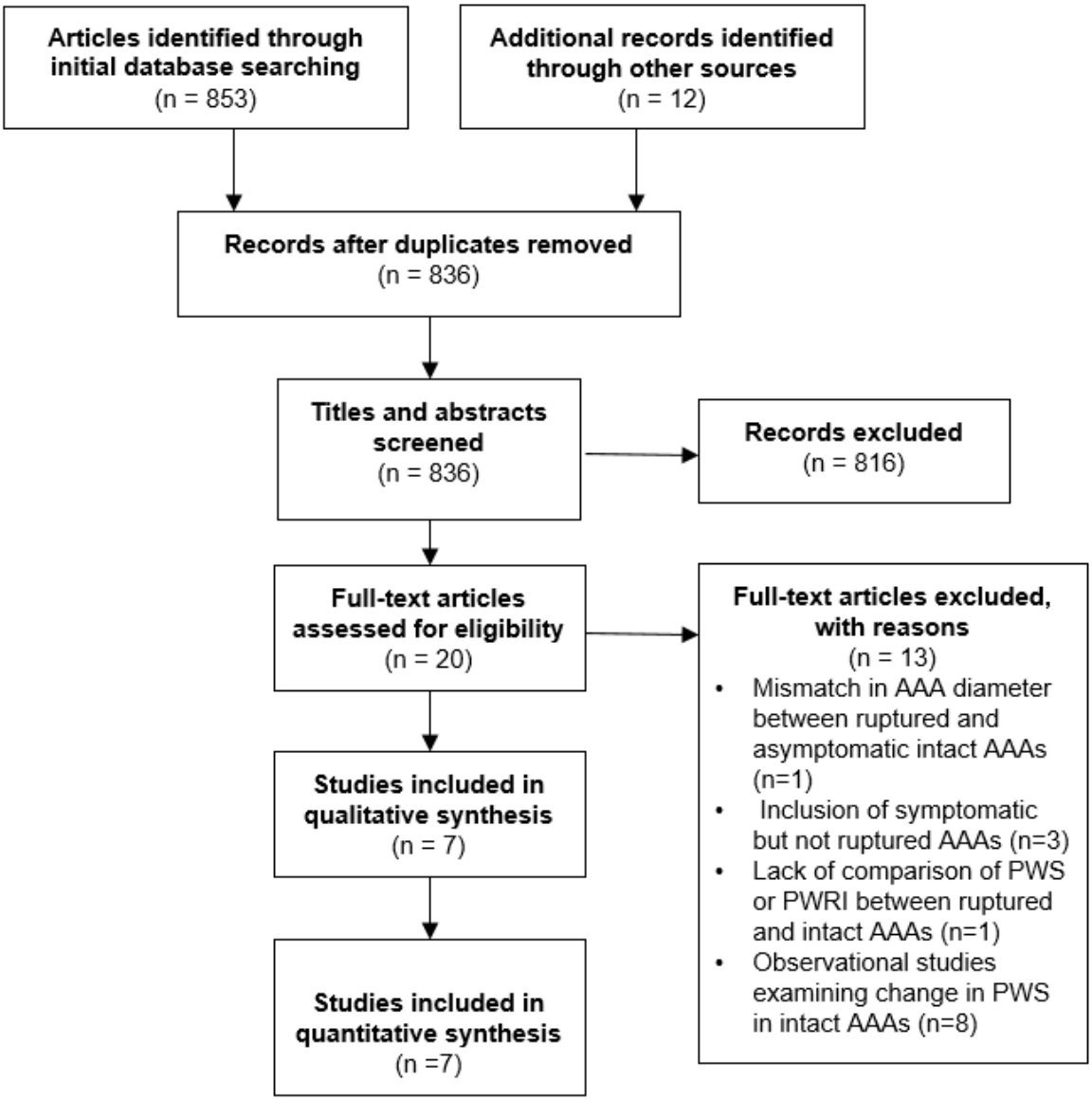
standardized BP of 140/80mmHg for the main analysis and sensitivity analyses were performed using a lower (120/70mmHg) and higher (160/90mmHg) BP.[7] For that study results from the main analysis were used in the meta-analysis. If studies did not use a standardised blood pressure, PWS and PWRI values computed with patient specific blood pressures were used.[28, 62, 72] In one study the standard deviation of PWS was not reported and this was derived from the standard error using Review Manager version 5.4 (The Cochrane Collaboration) as previously described.[24, 70] To identify sources of heterogeneity a leave-one-out-sensitivity analysis was performed by excluding individual studies one at a time and recalculating the pooled estimates for the remaining studies. Publication bias was assessed by funnel plots comparing the summary estimate of each study to its precision (1/standard error) for outcomes that were reported in ≥5 studies.[73] Analyses were conducted using Stata version 16.1 (StataCorp LP, College Station, Texas, USA). All statistical tests were two-sided and a p-value of <0.05 was considered significant.

4.5 Results

4.5.1 Study identification

The initial database searches identified eight hundred and thirty six studies after removal of duplicates. After title and abstract screening, the full texts of 20 studies were assessed against the inclusion criteria. Thirteen articles were excluded after full text review. Common reasons for exclusion included mismatch in AAA diameter between ruptured and intact AAAs[58], inclusion of symptomatic but not ruptured AAAs[58, 74, 75] and lack of comparison of PWS or PWRI between ruptured and intact AAAs[76]. Ultimately seven studies were included (Figure 4.2).

Figure 4.2. PRISMA diagram describing the literature search.



4.5.2 Study characteristics

A total of 309 participants with ruptured (n=139) and asymptomatic intact (n=170) AAAs of similar aortic diameter were investigated in the seven included studies.[27-29, 36, 62, 72, 77] All studies were of case-control design and samples sizes ranged between 14 and 75 (see Table 4.1). [27-29, 36, 62, 72, 77] Three studies were performed in Sweden[27, 29, 62] and the remaining studies were conducted in Australia[77], Spain[28], Czechia[72] and The Netherlands.[36] Six studies used the A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria) platform[27-29, 62, 72, 77] while one study used

ABAQUS v.6.5 (Hibbit, Karlsson and Sorensen, Inc, Pawtucket, R) for FEA.[36] One study used a combination of the A4 Clinics 5.0 and the ANSYS (Ansys Inc.) platforms.[72] The inclusion criteria varied between studies. In four studies AAA cases were only included if the available CT scan satisfied specific imaging criteria[28, 29, 62, 77], whereas other studies did not report this as a requirement for inclusion.[27, 36, 72] The imaging criteria used to select CT scans differed between studies. One study specifically reported excluding patients with juxtarenal or thoracoabdominal aneurysms and patients with ruptured AAAs that had massive contrast extravasation.[77] Another study only included participants with CT scans in which the aorta was visible from the renal arteries to the iliac bifurcation and the lumen was distinguishable from intra-luminal thrombus.[28] One study required CT scans to have a sufficiently high out-of-plane image resolution with good visibility of the exterior aneurysm surface[29]. In another study, only participants with good quality CT scans were included however the criteria used to determine this was not reported.[62] All studies either matched cases and controls for aortic diameter or included cases and controls with similar mean aortic diameter (within 3mm difference; see Table 4.1 and 4.2). Three studies used a standardised blood pressure to compute PWS or PWRI in all participants[77], or matched cases and controls for blood pressures[29], or omitted blood pressure from calculations.[27] The remaining studies used patient specific blood pressures although the relationship between their measurement and the timing of CT scan varied across studies (Table 4.1). For ruptured AAA cases, blood pressure readings prior to rupture were frequently used[28, 29, 36]. For participants with asymptomatic intact AAAs, measurements were either taken from the same hospital visit[29] in which the CT scan was performed or from a prior visit.[28, 36] The timing of blood pressure measurements in relation to CT scans were not reported in two studies.[62, 72] Three studies reported the reproducibility of their FEA estimates (Table 4.1).[62, 72, 77]

Table 4.1 Characteristics of case control studies comparing PWS and PWRI between ruptured and asymptomatic intact AAAs of similar aortic diameter.

Study	**Total sample size**	**Sample size (asymptomatic intact: ruptured)***	**Biomechanical measurements**	**Software used**	**Variables that were balanced between asymptomatic iAAA and rAAAs**	**Blood pressure used in PWS or PWRI analysis**	**Reproducibility of biomechanical measurements**
Singh et al. (2020)	75	75 (50:25)	PWS, PWRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria).	Diameter and blood pressure	Standardised blood pressure (140/80mmHg) used and sensitivity analysis with lower and higher blood pressures (120/70mmHg and	Intra-observer reproducibility; CV 2.7% and 4.7% for PWS in iAAA and rAAAs respectively

						160/90mmHg) for all participants.	
Siika et al. (2019)	283	60 (40:20)	PWS, PWRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria).	Diameter, sex, age and blood pressure	Blood pressure omitted from analyses.	NR
Siika et al. (2018)	90	43 (15:28)	PWS, PWRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria).	Diameter	Patient specific blood pressure; timing of blood pressure measurement in relation to CT scan not reported.	Intra-observer reproducibility; Mean % difference of 6.86 ± 6.46 and 7.70 ± 6.26 for PWS and PWRI respectively. Inter-observer reproducibility; Mean % difference 7.09 ±

							6.16 and 9.47 ± 8.18**
Leemans et al. (2018)	175	62 (31:31)	PWS, PWRI, rupture risk equivalent diameter	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria).	Diameter	Patient specific blood pressure obtained from the last measurement in a non-critical setting within one year prior to presentation	NR
Polzer et al. (2015)	14	14 (7:7)	PWRI and PRRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria) and ANSYS (Ansys Inc.)	Diameter	Patient specific blood pressure; timing of blood pressure measurement not reported.	Intra-observer reproducibility; CV <5.5% for PWS and PWRI in participants with iAAAs. Inter-observer reproducibility; ICC

							0.98 (range 0.97–0.99) for PWS and PWRI **
Gasser et al. (2010)	50	35 (17:18)	PWS, PWRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria).	Diameter and blood pressure	Participants were matched for blood pressure between groups. Blood pressure measurements obtained in the same admission in which CT scan was performed or earlier hospital or health care centre visit (for ruptured cases).	NR

Truijers et al. (2007)	30	20 (10:10)	PWS	ABAQUS v.6.5 (Hibbit, Karlsson and Sorensen, Inc, Pawtucket, R)	Diameter and blood pressure	Patient specific blood pressure obtained from a year prior to CT scan; Sensitivity analysis also performed in which a standardised blood pressure (120mmHg systolic) was used.	NR

AAA, abdominal aortic aneurysm; iAAA, asymptomatic intact AAA; rAAA, ruptured AAA; ILT, intra-luminal thrombus; PWS, peak wall stress; PWRI, peak wall rupture index; PRRI, probabilistic rupture risk index; CV, coefficient of variation; ICC, intraclass correlation coefficient; NR, not reported. * Sample sizes reported are reflective of the cases and control that were similar in AAA diameter and excluded symptomatic AAA cases. ** reported in an external publication.

Table 4.2 Clinical characteristics of participants with ruptured and asymptomatic intact AAAs of similar aortic diameter.

Study	Group	Number	Age	Male	Diabetes	IHD	Stroke	COPD	Smoking	Systolic blood pressure (mmHg)
Singh et al. (2020)	iAAA	50	72 ± 7	94	18	52	10	24	94	140*
	rAAA	25	73 ± 7	72	13	38	0	13	88	140*
Siika et al. (2019)	iAAA	40	78 ± 7	60	NR	NR	NR	NR	NR	NR†
	rAAA	20	79 ± 7	55	NR	NR	NR	NR	NR	NR†
Siika et al. (2018)	iAAA	15	75 ± 8	87	NR	NR	NR	NR	NR	NR
	rAAA	28	76 ± 10	75	NR	NR	NR	NR	NR	NR
Leemans et al. (2018)	iAAA	31	NR	NR	NR	NR	NR	NR	NR	NR
	rAAA	31	NR	NR	NR	NR	NR	NR	NR	NR
Polzer et al. (2015)	iAAA	7	NR	NR	NR	NR	NR	NR	NR	132 ± 8
	rAAA	7	NR	NR	NR	NR	NR	NR	NR	152 ± 26

Gasser et al. (2010)	iAAA	17	75 ± 8	78	NR	NR	NR	NR	NR	NR**
	rAAA	18	76±11	78	NR	NR	NR	NR	NR	NR**
Truijers et al. (2007)	iAAA	10	72 ± 2	90	10	70	20	30	40	120*
	rAAA	10	70 ± 2	70	10	30	20	20	40	120*

Values are expressed as mean ± standard deviation, median [interquartile range] or n (%). AAA, abdominal aortic aneurysm; iAAA, asymptomatic intact AAA; rAAA=ruptured AAA; IHD; ischaemic heart disease; COPD; chronic obstructive pulmonary disease; NR, not reported. *a standardised blood pressure was used for biomechanical analyses; ** iAAAs and rAAAs were matched for blood pressure; † blood pressure was omitted from patient-specific parameters.

4.5.3 Participant characteristics

The participant characteristics are summarised in Table 4.2. The average age of participants ranged between 70 and 79 years.[27-29, 36, 62, 72, 77] There were no significant differences in the average age of participants between asymptomatic intact and ruptured AAA groups in the three studies that statistically assessed this.[27, 62, 77] The proportion of males in the asymptomatic intact and ruptured groups were 60 to 94% and 55 to 78% respectively. One study included a significantly larger proportion of females in the ruptured AAA group[77], while two studies reported no significant differences in sex between groups.[27, 62] The remaining studies either did not report sex[28, 72] or statistically compare this.[29, 36] Details regarding diabetes, IHD, stroke, COPD, smoking and blood pressure were only reported in two studies (Table 4.2).

4.5.4 Risk of bias assessment

The methodological quality assessment and overall risk of bias of the included studies are reported in Table 4.3. Six studies were assessed to have a high risk of bias[27-29, 36, 62, 72], while one study was assessed to have a medium risk of bias.[77] Six studies were of retrospective design, the design of one study was unclear.[72] Only one study used an objective definition of AAA rupture which was defined as the presence of blood in the retroperitoneum or peritoneum identified on CT by a consultant vascular specialist.[77] The method of estimating PWS and PWRI was well described in three out of the seven studies which included the reporting of the reproducibility of the method[77] within the same or a previous publication (see Table 4.3).[62, 72] Only two of these studies assessed intra- and inter-observer reproducibility (see Table 4.1).[62, 72] One study assessed the reproducibility of methods in both asymptomatic and ruptured AAAs (coefficients of variation 2.7% and 4.7% for PWS in asymptomatic intact AAA and ruptured AAAs respectively[77] while in the other two studies reproducibility was

assessed in asymptomatic intact AAAs only. Six studies matched ruptured and asymptomatic intact AAA cases by AAA diameter[27-29, 62, 72, 77] whereas in one study participants were not matched however the mean diameter between intact and ruptured cases was similar (51 ± 2 vs 53 ± 2mm respectively).[36] Three studies used a standardised blood pressure to calculate PWS and PWRI while the other three studies[28, 62, 72] used patient specific blood pressures. One study matched participants for age and sex[27] in addition to AAA diameter. An *a priori* sample size calculation was performed in only one study.[77]

Table 4.3 Strengths and weaknesses of studies included in this systematic review.

Study	Clearly defined objective	Prospective study design	Selection criteria described	Objective definition of AAA rupture	Method of estimating PWS and PWRI well described	Standardised blood pressure	Sample size calculation	Sample size	Inclusion of CT scan before rupture and after rupture	Participant characteristics described	Matching for AAA diameter	Matching for other confounding variables	Overall risk of bias
Singh et al. (2020)													Medium
Siika et al. (2019)				*		‡‡						**	High
Siika et al. (2018)					†								High
Leemans et al. (2018)													High
Polzer et al. (2015)					#†								High
Gasser et al. (2010)												††	High
Truijers et al. (2007)											‡		High

The yellow and red coloured cells represent criteria, which were and not met in each study respectively. For the sample size criterion, red coloured cells represent studies that had a sample size <100 while yellow coloured cells represent studies that had sample sizes >100. The green coloured cells represent criteria that were partially met in each study. A blue coloured cell was used if it was unclear whether a criterion was met by a study. AAA, abdominal aortic aneurysm; CT, computed tomography; PWS, peak wall stress; PWRI, peak wall rupture index. *AAA rupture cases were identified using International Classification; ** cases and controls matched for age and sex; † reproducibility reported in an external publication; †† cases and controls matched for blood pressure; ‡ cases and controls were not matched by study design however AAA diameter was similar between groups; ‡‡ in this study blood pressure was omitted from biomechanical calculations; # PWS not assessed in this study.

4.5.5 Reported association of PWS and PWRI with AAA rupture

The mean aortic diameter of included patients ranged between 51 to 82mm and 53 to 82mm in included asymptomatic intact and ruptured AAAs respectively (see Table 4.4). No significant differences in PWS between groups were reported, although in one study PWS was not assessed[72] and another study did not statistically compare PWS between groups in the matched participants.[29] PWRI was significantly higher in ruptured AAAs than asymptomatic intact AAAs in two studies.[27, 62] PWRI was higher in the remaining studies that assessed this[77] however differences were not statistically significant (see Table 4.4).[28, 77]

Table 4.4 Comparison of PWS and PWRI of participants with ruptured and asymptomatic intact AAAs of similar aortic diameter.

Study	Group	Number	Diameter (mm)	p-value	PWS (kPa)	p-value	PWRI	p-value
Singh et al. (2020)	iAAA	50	82 ± 14	0.906	263.8 ± 69.4	0.192	1.09 ± 0.52	0.982
	rAAA	25	82 ± 13		279.8 ± 90.5		1.20 ± 0.76	
Siika et al. (2019)	iAAA	40	53 ± 5	0.319	197.0 ± 40.3	0.162	0.35 ± 0.08	0.016
	rAAA	20	55 ± 5		216.3 ± 45.3		0.43 ± 0.11	
Siika et al. (2018)	iAAA	15	73 ± 11	0.674	284 ± 53.4**	0.194	0.48 ± 0.11**	<0.001

	rAAA	28	74 ± 12		249 ± 53.9**		0.80 ± 0.54**	
Leemans et al. (2018)	iAAA	31	71 ± 15	0.81	261 ± 89*	0.99	0.69 ± 0.33	0.61
	rAAA	31	72 ± 18		262 ± 75*		0.70 ± 0.27	
Polzer et al. (2015)	iAAA	7	73 ± 11	NR	NR		0.48 ± 0.41†	NR
	rAAA	7	76 ± 14		NR		0.69 ± 0.41†	
Gasser et al. (2010)	iAAA	17	75 ± 12	NR	292.0 ± 108.7	NR	0.61 ± 0.26	NR
	rAAA	18	77 ± 15		330.8 ± 114.2		0.74 ± 0.29	
Truijers et al. (2007)	iAAA	10	51 ± 2	0.57	317 ± 73*	0.30	NR	
	rAAA	10	53 ± 2		367 ± 126*		NR	

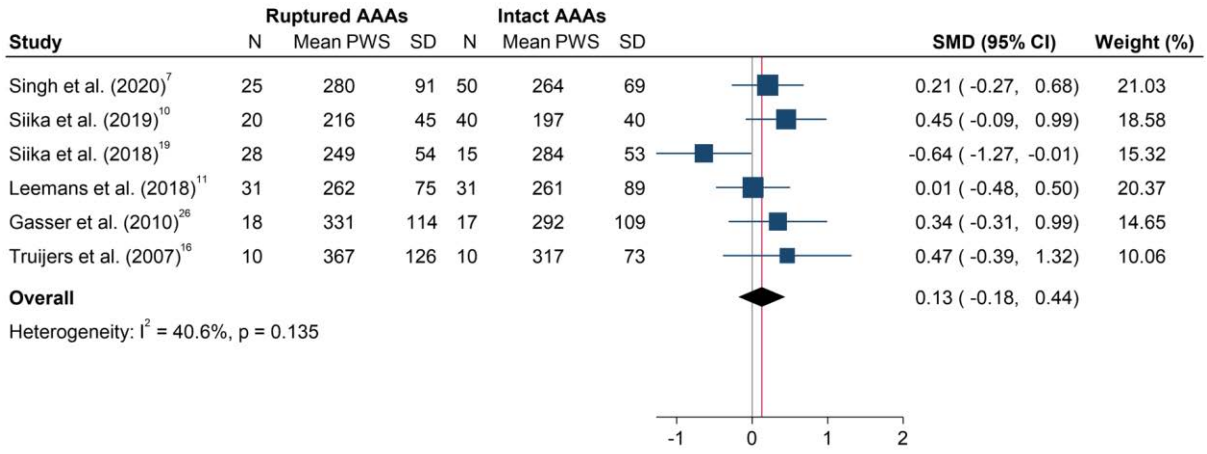
Values are expressed as mean ± standard deviation unless indicated otherwise. AAA, abdominal aortic aneurysm; iAAA, asymptomatic intact AAA; rAAA=ruptured AAA; ILT, intra-luminal thrombus; NR, not reported; PWS, peak wall stress; PWRI, peak wall rupture index. *PWS converted from N/cm^2 to kPa; **SD not available and were imputed from the diameter mismatched analysis reported in the same study. † derived PWRI values reported

which have been divided by the mean arterial pressure inflation factor use in the study to obtain comparable results.

4.5.6 Data synthesis

In the meta-analysis, PWS was not significantly different between ruptured and asymptomatic AAAs (SMD 0.13, 95% CI -0.18, 0.44, p=0.418; Figure 4.3). Moderate heterogeneity was observed (I^2=40.6%). In contrast, PWRI was significantly higher in participants with ruptured compared to asymptomatic intact AAA (SMD 0.42, 95% CI 0.14, 0.70, p=0.004; Figure 4.4). Inter-study heterogeneity was low (I^2=25.5%). Leave-one-out sensitivity analysis suggested that this result was not dependant on the inclusion of any single study (Appendix, figure 2). The funnel plot for PWRI appeared asymmetrical (Appendix, figure 3) suggesting potential publication bias.

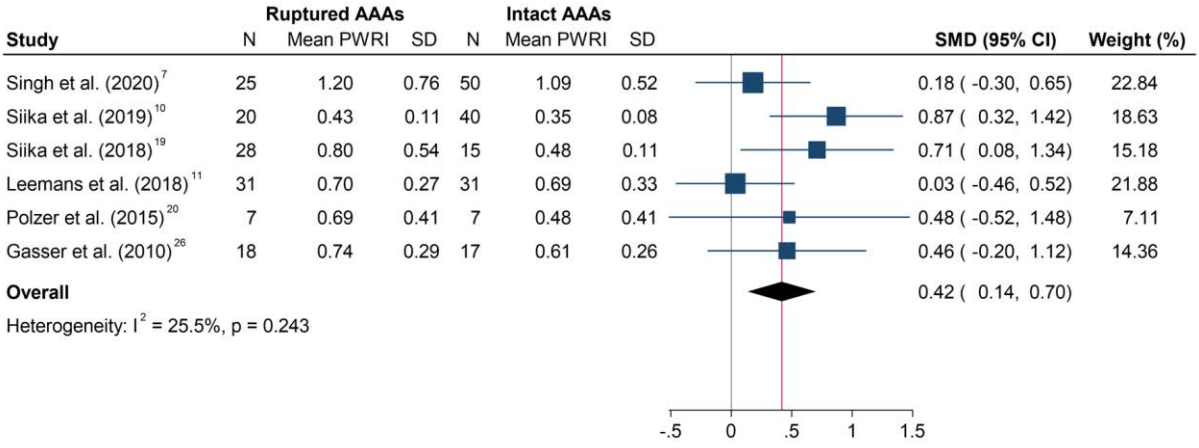
Figure 4.3. Differences in peak wall stress in ruptured and asymptomatic intact AAAs.



The SMD is the mean difference between both groups, standardised to one standard deviation difference in PWS (kPa) within that study. The summary SMD is estimated from inverse variance-weighted meta-analysis. Box areas are inversely proportional to the variance of the

SMD and horizontal lines illustrate 95% confidence intervals. AAA, abdominal aortic aneurysm; SMD, standardised mean difference; CI, confidence intervals.

Figure 4.4 Differences in peak wall rupture index in ruptured and asymptomatic intact AAAs.



The SMD is the mean difference between both groups, standardised to one standard deviation difference in PWRI within that study. The summary SMD is estimated from inverse variance-weighted meta-analysis. Box areas are inversely proportional to the variance of the SMD and horizontal lines illustrate 95% confidence intervals. SMD, standardised mean difference; CI, confidence intervals.

4.6 Discussion

This meta-analysis suggested that PWRI, but not PWS, is greater in ruptured than asymptomatic intact AAAs of similar diameter. This finding is in contrast with a previous meta-analysis which reported greater PWS in ruptured than intact AAAs.[24] A major limitation of the previous meta-analysis was the mismatch in aortic diameter between groups

and inclusion of symptomatic patients in the ruptured group. Participants with symptomatic intact AAAs were not included in the current study as their risk of rupture is uncertain.[41, 63] Maximum aortic diameter is currently the most established measure of AAA rupture risk.[1, 63, 78] There are however a number of limitations in using aortic diameter in clinical practice, particular the measurement error which may be greater than the annual change in diameter. [3, 79] Additional methods of estimating rupture risk and determining management may therefore be valuable. The findings of this study suggest that measurement of PWRI may add to aortic diameter in assessing the risk of AAA rupture. There are however many limitations of this technology which need to be addressed. There is currently no standardised approach to conducting FEA. There was substantial variation in the approach used to incorporate blood pressures in the calculation of PWS and PWRI in the included studies. Some studies used an arbitrary blood pressure for all participants, while others used patient specific blood pressures. It is currently unclear which approach is most appropriate. Additionally, wall thickness and strength has an important effect on the risk of aortic rupture and prior investigations have suggested that increased aortic wall thickness is associated with reduced aortic wall stress.[29, 54] Currently there is no accurate and feasible method to estimate wall thickness from imaging.[77] Six of the seven studies used FEA software to estimate PWRI using the same formula which was derived from prior tensile testing of human AAA wall specimens *ex vivo*, but this may not be representative of the situation in individual patients *in vivo*.[54] Aortic calcification has previously been suggested to have an important influence on biomechanical forces but there remains no standardised method of including this in estimations of wall stress.[80, 81]

While the current meta-analysis suggested that PWRI is likely to be higher in ruptured AAAs compared to asymptomatic intact AAAs of similar diameter, the confidence in this finding is lessened as the included studies were assessed to have either a medium or high risk of bias

due to a number of design limitations. Firstly, studies included participants with CT scans performed after rupture and it is likely that the biomechanical forces prior to rupture were different. Secondly, some studies used patient specific blood pressures to perform biomechanical analyses rather than a standardised blood pressure.[28, 62, 72] This may have contributed to heterogeneity and led to under or overestimation of PWS and PWRI. While patients with asymptomatic intact and ruptured AAAs had similar aortic diameter, other characteristics were generally poorly reported and confounding due to an unmeasured factor cannot be ruled out. Additionally, the CT scans of ruptured AAA cases were required to meet certain inclusion criteria in some studies and selection bias cannot be excluded.[28, 29, 62, 77] We were unsuccessful in contacting the corresponding author of two studies[27, 62] to clarify whether there was an overlap in participants included in these investigations. Nevertheless, the leave-one-sensitivity analysis suggested that the findings of the PWRI meta-analysis was not materially altered with individual omission of either of these studies.[27, 62] Lastly the relevance of the findings of this meta-analysis to small AAAs is limited as five studies only included patients with large AAAs[28, 29, 62, 72, 77] (mean ± SD aortic diameter [mm] ranged between 71 ± 15 and 82 ± 14 for the asymptomatic intact AAAs; 72 ± 18 and 82 ± 13 for the ruptured AAAs). Furthermore, this meta-analysis compared PWS and PWRI in individuals with asymptomatic intact and ruptured AAAs, but did not examine the predictive ability of these biomechanical measures for AAA rupture. Investigating this would require a large observational study; however due to the low rupture rate of small AAAs and the high repair rate of large AAAs, such a study maybe infeasible to perform.

In conclusion the results of this study suggest that PWRI is greater in ruptured than asymptomatic intact AAAs of similar diameter. The findings suggest the potential value of biomechanical measures in estimating AAA rupture risk accepting the medium to high risk of bias of the included studies.

Chapter 5. Association between aortic peak wall stress and peak wall rupture index with abdominal aortic aneurysm related events

5.1 Preface

In this chapter, the findings of an original research study is presented which has investigated the association between PWS/PWRI with the risk of future AAA events (rupture and AAA repair). To our knowledge, this is the first study that has prospectively investigated the predictive utility of PWS and PWRI for AAA events.

5.2 Abstract

Background: Prior studies suggest that PWS and PWRI are associated with AAA growth, however there has been no prior investigation of the association of these measures with AAA-related clinical events. The aim of this study was to assess whether aortic peak wall stress (PWS) and peak wall rupture index (PWRI) were associated with the risk of AAA rupture or repair (defined as AAA events) among participants with small abdominal aortic aneurysms (AAA).

Methods: PWS and PWRI were estimated from computed tomography angiography (CTA) scans of 210 participants with small AAAs (≥30 and ≤50 mm) recruited between 2002 and 2014. Participants were followed for a median of 2.0 (inter-quartile range 1.9, 2.8) years to record the incidence of AAA events. The associations between PWS and PWRI with AAA events were assessed using Cox proportional hazard analyses. The ability of PWS and PWRI to reclassify the risk of AAA events compared to initial AAA diameter was examined using net reclassification index (NRI) and classification and regression tree (CART) analysis.

Results: After adjusting for other risk factors, PWS (Hazard ratio, HR, 1.56, 95% Confidence intervals, CI 1.19, 2.06; p=0.001) and PWRI (HR 1.74, 95% CI 1.29, 2.34; p<0.001) were associated with a significantly higher risk of AAA events. According to CART analysis, PWRI was identified as the best single predictor of AAA events. PWRI, but not PWS, significantly improved the classification of risk of AAA events compared to initial AAA diameter alone.

Conclusions: PWS and PWRI were independently predictive of AAA events. PWRI, but not PWS, improved the risk stratification compared to initial AAA diameter alone.

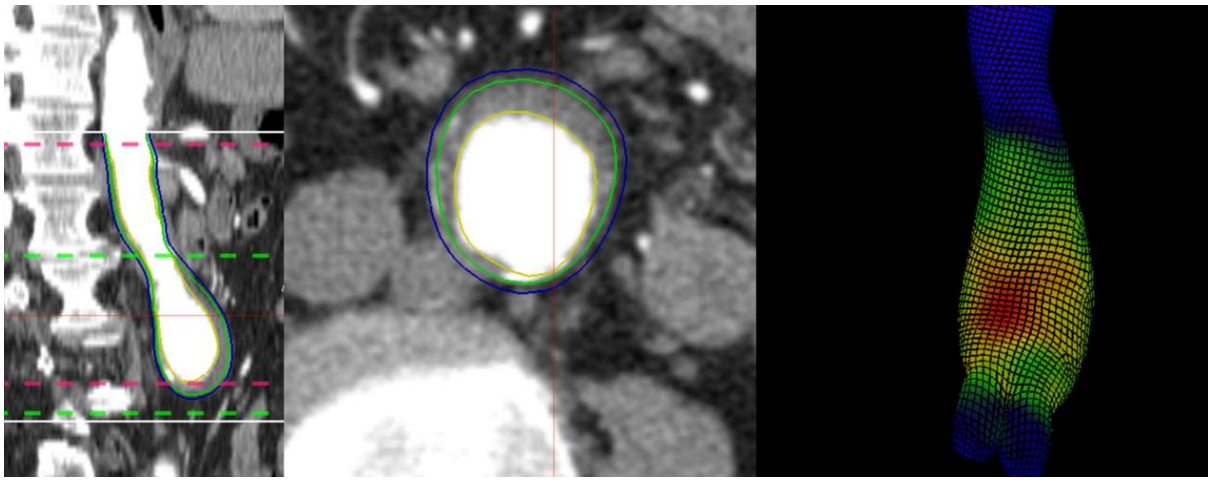
5.3 Introduction

Abdominal aortic aneurysm (AAA) rupture is responsible for approximately 200,000 deaths each year worldwide.[1, 2, 82] Maximum AAA diameter is the most established method of estimating AAA rupture risk and is used by clinicians to help select patients for elective AAA repair.[1] Current guidelines recommend that small (less than 55mm diameter in men and 50mm in women) asymptomatic AAAs are managed conservatively while larger AAAs are considered for surgical repair.[64] Some large AAAs do not rupture during a patient's life time[8], while 1-2% of small AAAs rupture per year,[40] suggesting that AAA diameter is not a perfect measure of rupture risk. More accurate methods to estimate AAA rupture risk could benefit patient management.

Finite element analysis (FEA) is an established engineering technique that can non-invasively estimate the peak tensile stress within the AAA wall (peak wall stress) from computed tomography images (Figure 5.1).[77] A recent prospective study of AAA patients reported for the first time that the dimensionless ratio of wall stress and wall strength (ABR) was a significant predictor of AAA rupture or repair (AAA events) independent of risk factors including initial AAA diameter.[81] Importantly, the ABR incorporated measurements of aortic

wall thickness allowing more accurate biomechanical simulations than previously reported methods.[62, 83] Aortic wall thickness measurement however required magnetic resonance imaging (MRI) which is not routinely performed in AAA management.[37, 81] Furthermore, the method employed in that study has not be widely studied,[37, 81] and required multiple software packages to perform the biomechanical analysis.[37] Notwithstanding these limitations, there is a need to evaluate the predictive ability of other biomechanical estimates to further evaluate their clinical value.

Figure 5.1 Example of a three-dimensional (3D) segmentation produced using finite element analysis on the computed tomography image of an AAA.



A prior meta-analysis reported that the ratio between the aortic wall stress and wall strength estimated assuming a constant wall-thickness[23, 84] (i.e. peak wall rupture index, PWRI), but not peak wall stress (PWS), was greater in ruptured than asymptomatic intact AAAs of similar diameter.[20] Both measurements can be estimated from a contrast-enhanced computed tomography angiogram (CTA) using one software package with good reported repeatability across a number of studies.[42, 77, 83, 85] The studies included in that systematic review[20] and prior reviews[24] however were cross-sectional, had important design limitations and ostensibly

included patients with large AAAs. There is a lack of observational studies investigating the association between PWS and PWRI with the future risk of AAA events among individuals with small AAAs (maximum orthogonal aortic diameter of ≥30 and ≤50 mm).[22, 81] Such data is required to assess whether PWS and PWRI can predict the risk of future AAA events amongst people with a low risk of AAA rupture.[22, 81] Furthermore, it is unclear whether PWS and PWRI can improve the classification of risk of AAA events in comparison to using AAA diameter alone. The primary objective of this prospective observational study was to assess whether baseline PWS and PWRI were independently associated with the risk of future AAA events among individuals with small AAAs. The secondary objective was to examine whether PWS and PWRI significantly improved stratification of risk of AAA events over using AAA diameter alone.

5.4 Methods

5.4.1 Study design and participants

Participants were recruited from sites across Australia, The US and Netherlands between 29/05/2002 and 12/05/2014 via two sources. Firstly participants were included from those taking part in an ongoing multi-centre prospective cohort study aimed to identify risk factors for the outcomes of people with peripheral vascular disease.[47, 48] Secondly, participants were included from an international multi-centre trial which showed that telmisartan did not slow AAA growth, as previously reported.[64] Participants were eligible for the current study if they had a small (maximum orthogonal infra-renal aortic diameter of ≥30 and ≤50 mm) asymptomatic intact AAA which had been imaged by a CTA of adequate quality for FEA.[83] CTAs needed to have a slice thickness of 3mm or less and visualise the whole infra-renal aorta including the bifurcation into the common iliac arteries.[83] Patients with symptomatic or

ruptured AAAs were excluded. The study was approved by relevant ethics committees and written informed consent was obtained from all participants.[44, 48, 86]

5.4.2 Participant characteristics

Risk factors and medication prescription records were collected at the time of enrolment into the study.[44, 48, 86] Coronary heart disease (CHD) was defined by a history of myocardial infarction, angina or coronary revascularisation.[87, 88] Current smoking was defined by smoking within the last month based on participants' history. Hypertension, diabetes and chronic obstructive pulmonary disease (COPD) were defined by a prior diagnosis or treatment for these conditions.[44, 48, 86] Blood pressure was measured at recruitment using a digital monitor (Omron Intellisense, HEM-907) after participants had rested supine for a 20 minute period.[86, 89] Current prescriptions for aspirin, anticoagulants, statins, calcium channel blockers, beta-blockers and metformin were obtained from medical records.

5.4.3 CTA

CTAs were performed at recruitment sites using departmental scanners as previously reported.[45, 48, 83, 86] All CTAs were transferred to the core imaging reading site (Townsville, Australia), where they were analysed using the Philips MxView Visualisation Workstation using the Advance Vessel Analysis application (v7).[45, 48, 83, 86] This programme was used to estimate maximum orthogonal aortic diameter using a validated protocol as previously described.[50, 51, 83] A region of interest (ROI) was selected, which included the region marked by the slice inferior to the origin of the lowest renal artery (excluding accessory arteries) to the slice superior to the aortic bifurcation. Within this ROI, the aorta was scouted to identify the region of maximal diameter by performing many measurements.[50, 51, 83] Anterior–posterior outer-to-outer orthogonal diameters were estimated by tracing the lumen of the

infrarenal aorta and measuring perpendicular to this axis. The measurement was recorded to the nearest 0.1mm.[50, 51, 83] The reproducibility of this method has been previously assessed (coefficient of variation < 4 %).[51]

5.4.4 Biomechanical analysis

PWS and PWRI were estimated from FEA of CTAs using a commercially available software (A4 Research 5.0, VASCOPS GmbH, Graz, Austria) as previously described.[23, 77, 83] PWS estimated the maximum tensile stress subjected to the aortic wall based on AAA morphology and BP. PWRI estimated the maximum ratio between wall stress and the estimated local aortic wall strength.[20, 83] Three-dimensional (3D) reconstructions of the AAA were created from a ROI using the boundaries as defined earlier. The 3D model was processed into a hexahedral mesh to prevent volume locking of incompressible solids.[23, 83] AAA wall strength was estimated using a statistical model incorporating intra-luminal thrombus thickness, AAA diameter and sex as previously described.[23, 25, 83] Wall strength values related to the variables included in this model were estimated from tensile testing of human AAA wall specimens, as described previously.[34, 55] The AAA FEA model was pressurised by inputting blood pressure (BP), which in turn estimated the mechanical stress on the aortic wall.[23, 26, 77, 83] The main analysis used patient specific BP at recruitment to compute PWS and PWRI. A sensitivity analysis was performed using a standardized BP of 140/80mmHg consistent with the approach of prior studies.[77, 83] Biomechanical analyses were performed by a medical doctor who received training in FEA. The intra-observer reproducibility of PWS in asymptomatic intact AAAs has previously been assessed and reported (coefficient of variation 2.7%).[83]

5.4.5 Definition and assessment of outcome

The primary outcome was AAA events defined as AAA rupture or repair.[86] This was recorded through prospective follow-up and clinical reviews and confirmed using medical record reviews and linked data on inpatient admissions as previously described.[44, 48, 86] Decisions regarding requirement for surgical repair were at the discretion of the treating vascular surgeon but were consistent with current international guidelines.[1, 63] Participants were censored at the first outcome event, or at the date of last review or linked data request, if an outcome event did not occur.

5.4.6 Sample size

The sample size for the present study was based on the planned Cox regression analyses to assess the associations between PWS/ PWRI and the risk of AAA events. Based on previous studies of patients with small AAAs, the rate of AAA events was estimated to be 20% over 2 years.[81, 86] The Cox proportion hazard analyses were planned to include 3 covariates (AAA diameter, statin prescription, and age). It was estimated that at least 200 individuals would lead to a well powered analysis in order to attain at least 10 outcome events per degree of freedom according to Monte-Carlo simulations.[90]

5.4.7 Data analysis

Nominal data were compared between groups using Pearson χ^2 test. Most continuous variables were not normally distributed according to Q-Q plots and Kolmogorov-Smirnov testing and therefore non-parametric Mann-Whitney U tests were used to compare groups. Kaplan Meier curves with log rank test were used to compare the proportion of participants having AAA events. Cox proportional hazard analyses were undertaken to assess the association between PWS and PWRI with AAA events. To examine whether PWS and PWRI

were independently associated with AAA events Cox proportional hazard analyses were adjusted for age, male sex, statin prescription and AAA diameter. These variables were selected for adjustment as they were different ($p<0.100$) between participants who had an AAA event and those who did not. Results were presented as hazard ratios (HR) and 95% confidence intervals (CI). A correlation matrix of coefficients in the Cox models was used to assess if there was co-linearity between variables included in the regression analyses.[91, 92] A correlation coefficient ≥ 0.60 was considered to indicate a high likelihood of co-linearity and was not found with any of the variables included in the final models.[91-93] Whether PWS and PWRI with or without clinical risk factors significantly improved stratification of risk of AAA events over using AAA diameter alone was examined using the net reclassification index (NRI).[44] Clinical risk factors included were diabetes and current smoking as these are recognised risk factors for AAA growth.[18, 63] Classification and regression tree analysis (CART) was used to determine the optimal predictive cut-off of variables that were found to best stratify the risk of AAA events. The sample was segregated according to a decision tree consisting of progressive binary splits as previously described.[94] Every value of each predictive variable was considered as a potential split and the optimal split was based on the impurity criterion.[95] The maximum P value for a split was set at 0.050. A sensitivity analysis was performed in which a standardized BP of 140/80mmHg was used to calculate PWS and PWRI. Data were analysed using the Stata v16.1 (StataCorp LP, College Station, Texas, USA) software package. P values of <0.05 were accepted to be significant for all analyses.

5.5 Results

5.5.1 Participant characteristics

A total of 210 participants were included and followed-up for a median of 2.0 (inter-quartile range [IQR] 1.9, 2.8) years. During this time 45 (21%) participants had an AAA event including 43 who had an AAA repair and 2 that had AAA rupture. Repairs included 36 endovascular and 7 open surgical repairs. Baseline characteristics of participants in relation to whether they later had an AAA event are presented in Table 5.1. Participants who had an AAA event had a significantly larger initial maximum orthogonal aortic diameter (median [IQR], 44.4 [40.8, 47.0] vs 40.2 [36.5, 42.8] mm; p<0.001) and were significantly younger at the time of recruitment than those not having an event (p=0.038). No significant differences in sex, current smoking, diabetes, CHD, blood pressure and other risk factors between groups were identified (see Table 5.1).

Table 5.1 Baseline characteristics of participants with small AAAs who experienced an AAA event and those who did not.

	No AAA event (n=165)	**AAA event (n=45)**	**P-value**
Age	74 (68, 80)	71 (67, 77)	**0.038**
Male sex	150 (91)	37 (82)	0.098
Current smoking	39 (24)	13 (29)	0.469
Hypertension	86 (52)	24 (53)	0.885
Diabetes	33 (20)	7 (16)	0.501
CHD	67 (41)	18 (40)	0.941
COPD	46 (28)	10 (22)	0.447

Aspirin	93 (56)	29 (64)	0.330
Anticoagulation	17 (10)	3 (7)	0.461
Statin	104 (63)	34 (77)	0.084
Calcium channel blocker	28 (17)	5 (11)	0.338
Beta blocker	43 (26)	11 (24)	0.826
Metformin	21 (13)	5 (11)	0.770
Systolic blood pressure (mmHg)	137 (125, 150)	135 (125, 146)	0.423
Diastolic blood pressure (mmHg)	78 (71, 85)	76 (70, 83)	0.413
Maximum orthogonal diameter (mm)	40.2 (36.5, 42.8)	44.4 (40.8, 47.0)	**<0.001**
PWS (kPa)	157.4 (142.9, 180.1)	182.5 (153.6, 209.4)	**<0.001**
PWRI	0.352 (0.308, 0.404)	0.415 (0.363, 0.514)	**<0.001**

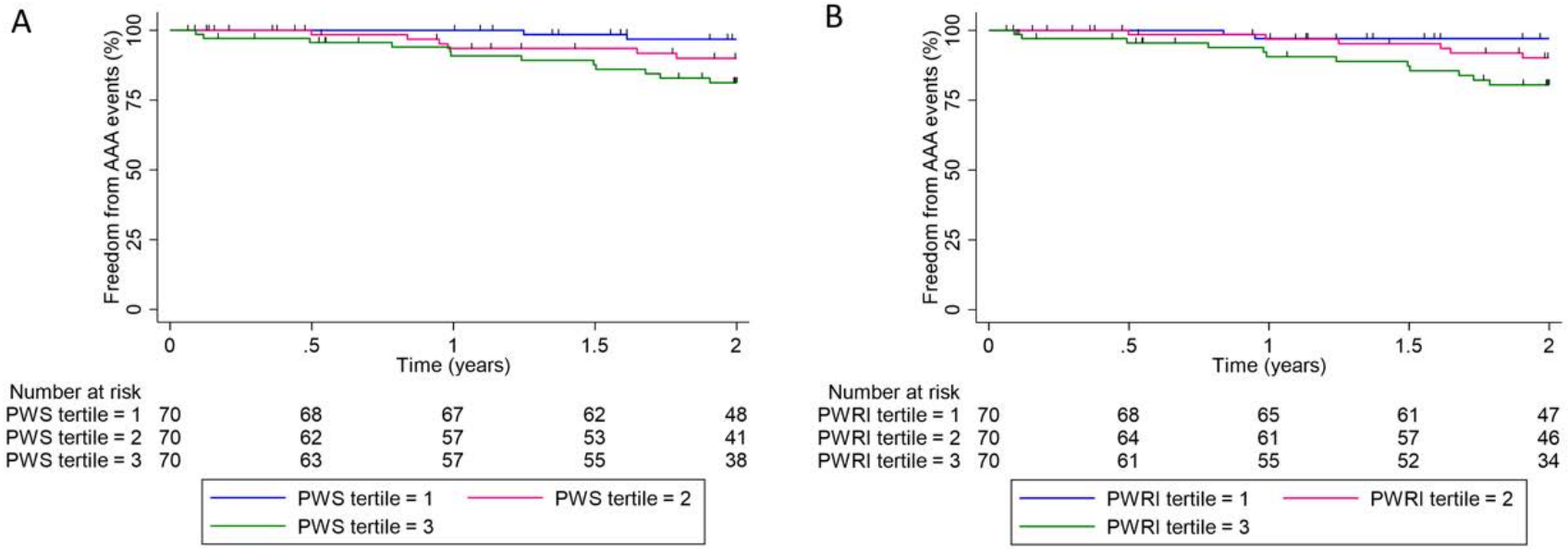
AAA, abdominal aortic aneurysm; PWS, peak wall stress; kPa, Kilopascal; PWRI, peak wall rupture index; CHD, coronary heart disease; COPD, Chronic obstructive pulmonary disease. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test. Nominal data are presented as number (%) and were compared using Pearson's $\chi 2$ test. P-values highlighted in bold indicate significant differences.

5.5.2 Association between PWS and PWRI at entry and AAA events

PWS and PWRI at entry were significantly greater in participants who later had an AAA event compared to those that did not ($p<0.001$ and $p<0.001$ respectively; see Table 5.1). Figure 5.2 illustrates the proportion of participants who had an AAA event in relation to the

tertiles of PWS and PWRI measured at entry. A greater proportion of participants grouped in tertile 3 of PWS and PWRI had an AAA event compared to individuals in tertile 1 (log-rank test $p<0.001$ and $p<0.001$ for PWS and PWRI respectively).

Figure 5.2 Kaplan Meier curves illustrating the freedom from AAA events according to tertiles of peak wall stress (PWS) and peak wall rupture index (PWRI).



A) PWS; B) PWRI. Differences between both groups compared using the log-rank test ($p=0.001$ and $p<0.001$ for PWS and PWRI respectively)

Findings from the Cox proportional hazard analysis are reported in Table 5.2. In the unadjusted analysis, both higher PWS and PWRI at entry were associated with a significant higher risk of an AAA event. In the adjusted analysis both higher PWS (HR 1.56, 95% CI 1.19, 2.06; p=0.001) and PWRI (HR 1.74, 95% CI 1.29, 2.34; p<0.001) were associated with a significantly increased risk of AAA events.

Table 5.2 Association between PWS and PWRI with AAA events in individuals with small AAA.

	AAA events (AAA rupture or repair)		
	Hazard ratio (HR) †	**95% CI**	**p-value**
	Unadjusted analysis		
PWS (kPa)	1.89	1.52, 2.33	**<0.001**
PWRI	1.92	1.58, 2.34	**<0.001**
	Adjusted analysis*		
PWS (kPa)	1.56	1.19, 2.06	**0.001**
PWRI	1.74	1.29, 2.34	**<0.001**

AAA, abdominal aortic aneurysm; PWS, peak wall stress; kPa, Kilopascal; PWRI, peak wall rupture index. *Adjusted for variables that were found to be different (p<0.100) between participants who had events and those who did not have events (i.e AAA diameter, statin prescription, age and male sex); † Hazard ratios expressed per 1 standard deviation increase in PWS or PWRI.

5.5.3 Ability of PWS and PWRI to improve stratification of risk of AAA events

PWRI (NRI 0.42 95% CI 0.09, 0.75; p=0.013), but not PWS (NRI 0.26 95% CI -0.07, 0.59; p=0.124), significantly improved the classification of risk of AAA events compared to AAA diameter alone. Models incorporating clinical risk factors, AAA diameter and PWRI (but not PWS) significantly improved classification of risk of AAA events compared to AAA diameter alone (Table 5.3).

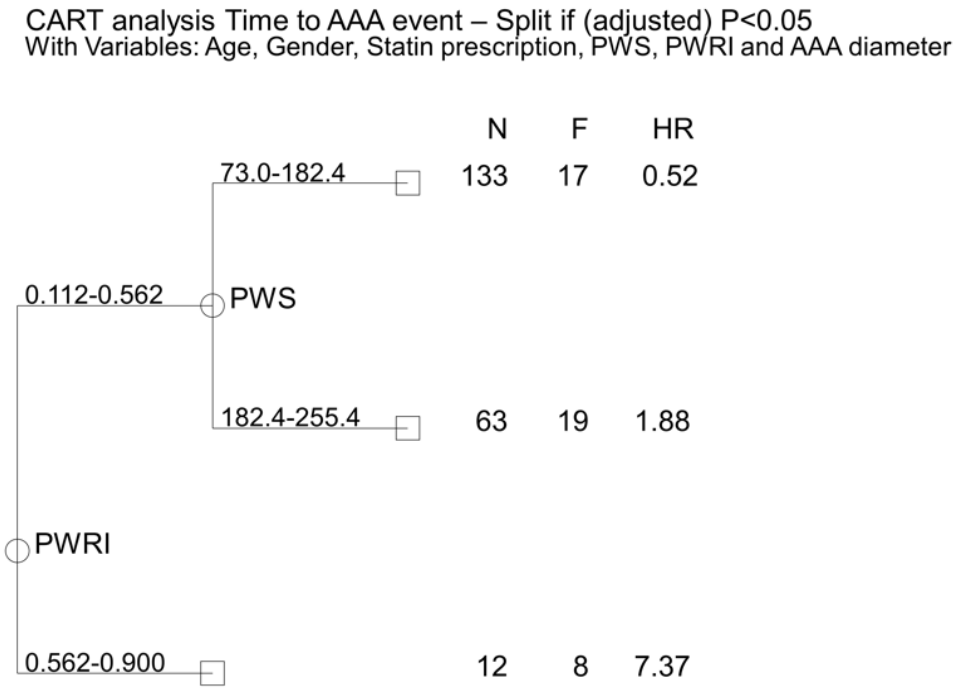
Table 5.3. Discrimination and reclassification using PWS and PWRI for AAA events.

Models	**NRI (95% CI)**	**P-value**
AAA diameter (reference)	-	-
AAA diameter + PWS	0.26 (-0.07, 0.59)	0.124
AAA diameter + PWRI	0.42 (0.09, 0.75)	**0.013**
AAA diameter + clinical risk factors + PWS	0.23 (-0.10, 0.56)	0.164
AAA diameter + clinical risk factors + PWRI	0.43 (0.10, 0.76)	**0.011**

NRI, net reclassification index; CI, confidence intervals; PWS, peak wall stress; PWRI, peak wall rupture index. Clinical risk factors included diabetes and current smoking.

All baseline variables that were different between participants that did and did not have an AAA event (p<0.100) were entered into the CART analyses. PWS and PWRI contributed to the stratification of risk of AAA events, estimated between HR 0.52 and 7.37. PWRI was identified as the best single risk stratification measure for AAA events, using a cut-off value of 0.562 (Figure 5.3).

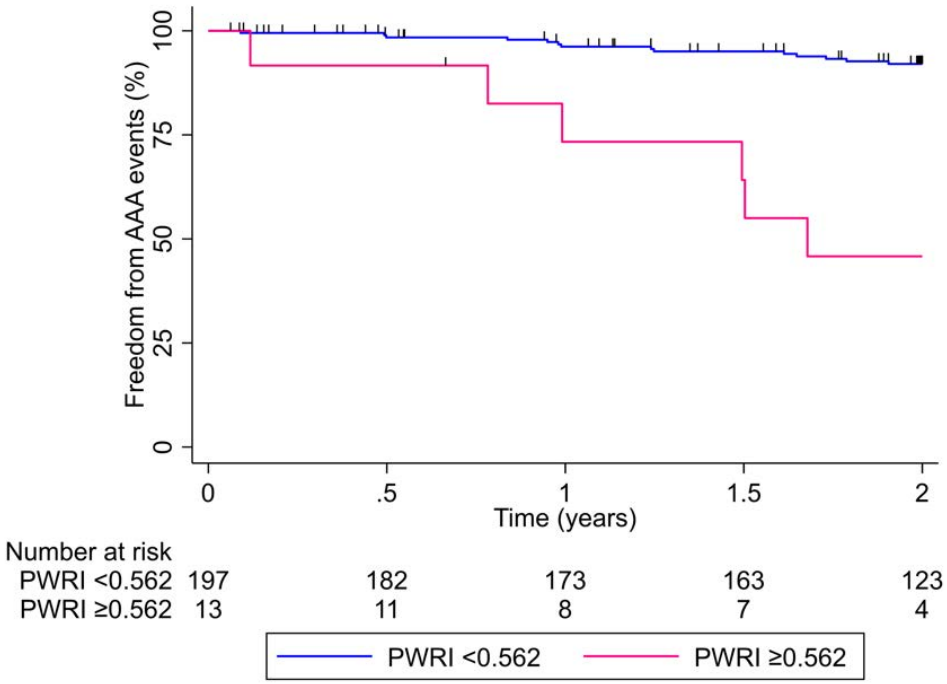
Figure 5.3. Classification and regression tree analysis (CART) for AAA events.



Variables different (p<0.100) between participants who had events and those who did not have events (age, statin prescription, peak wall stress [PWS], peak wall rupture index [PWRI] and AAA diameter) were entered into the analysis. The maximum p-value for a split was set at 0.050. N, numbers of individuals in subgroup; F, events; HR, hazard ratio.

Participants with PWRI ≥0.562 were significantly more likely to experience an AAA event than those with PWRI <0.562 (Cox proportional HR for AAA events: 5.55; 95% CI 2.67, 11.57, p<0.001; Figure 5.4).

Figure 5.4. Freedom from AAA events stratified by initial peak wall rupture index (PWRI).



The optimal PWRI cut-off was determined by classification and regression tree analysis. Difference between both groups compared using log-rank test ($p<0.001$).

5.5.4 Sensitivity analysis in which PWS and PWRI were estimated using a standardized BP

Using PWS and PWRI estimated using a standardized blood pressure of 140/80mmHg did not substantially change findings from the main analysis (Appendix C; Tables 1 to 3).

5.6 Discussion

The main finding of this investigation was that both higher PWS and PWRI were associated with a higher risk of AAA events after adjustment for other risk factors. PWRI was identified as the best risk stratification measure of AAA events in the CART analysis. When compared to AAA diameter alone, PWRI, but not PWS significantly improved the classification of risk for AAA events. Similarly, models including clinical risk factors, AAA diameter and PWRI

also improved the classification of the risk of AAA events compared to diameter alone. The findings are commensurate with a recent meta-analysis of case-control studies that reported that PWRI, but not PWS, was greater in ruptured than asymptomatic intact AAAs of similar diameter.[20] Overall, the findings suggest that PWRI can independently predict AAA events and may add to AAA diameter in stratifying the risk for events in patients with small AAAs. PWRI could potentially assist clinicians in identifying small AAA patients who may benefit from more frequent follow-up or better medical management, however larger studies are required to investigate this.

Maximum aortic diameter is currently the preferred surrogate marker for AAA progression in clinical practise however this measurement has a number of limitations including substantial intra and inter observer variability in measurement.[1, 3] Biomechanical measurements have been proposed to be useful in predicting AAA progression however there is currently limited evidence to support their use in clinical practise.[20, 24] PWS and PWRI are among the most widely studied biomechanical measures[20, 22, 24] however all prior investigations assessing the value of PWS and PWRI in estimating AAA events have been of retrospective and case-control design, had small sample sizes and focused on large AAAs.[20, 24] The current investigation had a number of strengths in comparison to prior studies including its prospective design and focus on individuals with small AAAs. While the main analysis used patient specific blood pressure to compute PWS and PWRI, a sensitivity analysis using standardised blood pressure was also performed. It remains unclear which method is most appropriate[20] however the findings were similar in both analyses.

Biomechanical analyses such as FEA are time and resource intensive (~40 minutes per CTA scan[37, 85]) in comparison to other simpler measures of rupture risk such as AAA diameter.[20, 23] It is therefore important that biomechanical measures have a demonstrated benefit in predicting events to support their use in clinical practice. The current study suggested that

PWRI was independently predictive of AAA events and may improve the classification of the risk of events compared to using AAA diameter alone. Further larger observational studies with longer follow-up are required to confirm or refute the findings of this study.

This investigation has a number limitations including its small sample size and relatively short follow-up time which was comparable to a recent observational study.[81] The decision to perform surgical repair was at the clinical discretion of the treating vascular surgeon and a standardised protocol was not followed for this study.[63] Importantly there are a number of limitations of FEA, which need to be addressed.[20, 22, 24] Firstly, there remains no standardised approach by which FEA is performed and significant heterogeneity in methods have been reported in prior reviews.[20, 24] Furthermore, there is currently no accurate method by which wall thickness and strength can be estimated from CTA.[20, 55]In the current study, aortic wall strength was estimated from previously reported tensile testing of human wall specimens[23, 26, 83] and assumed a constant wall thickness as this could not be accurately assessed from CTA. Indeed recent studies have demonstrated that wall thickness can be estimated from MRI,[37, 81] however this may not be feasible in clinical practise. Lastly, participants were recruited from a limited number of vascular centres and further investigation is needed to examine whether the findings are repeatable in other populations.

In conclusion, this study suggested that PWS and PWRI can independently predict the risk of AAA events in individuals with small AAAs. PWRI, but not PWS, may add in stratifying the risk for events compared to AAA diameter alone.

Chapter 6. Effect of telmisartan on the peak wall stress and peak wall rupture index of small abdominal aortic aneurysms: An exploratory analysis of the TEDY trial

6.1 Preface

In this chapter, the findings of an original research study is presented which investigated the effect of telmisartan, a commonly prescribed blood pressure lowering agent, on the aortic PWS and PWRI of small AAAs. To our knowledge, this is the first randomized controlled trial that has assessed the ability of a drug treatment to limit the increase in aortic PWS and PWRI of patients with small AAAs.

6.2 Abstract

Background: This study was an unplanned exploratory analysis of a subset of participants from the Telmisartan in the Management of Abdominal Aortic Aneurysm (TEDY) trial, and aimed to assess the efficacy of the angiotensin 1 receptor blocker telmisartan in reducing abdominal aortic aneurysm (AAA) peak wall stress (PWS) and peak wall rupture index (PWRI) among individuals with small AAAs.

Methods: Participants with AAAs measuring 35 to 49mm in maximum diameter were randomised to receive telmisartan 40mg or identical placebo in the TEDY trial. Participants who had computed tomography angiography performed at entry and at least one other time point during the trial (12 or 24 months) were included in the current study. Orthogonal AAA diameter, PWS and PWRI were measured using previously validated methods. The annual change in PWS and PWRI from baseline was compared between participants' allocated telmisartan and placebo using linear mixed effects models. Additional analyses were adjusted

for risk factors differently distributed between both groups at entry (p<0.100) or systolic blood pressure (SBP) at 1 year.

Results: One hundred and twenty four of the 207 participants recruited to TEDY were eligible for inclusion. The present study included 65 and 59 participants from the telmisartan and placebo group respectively. No significant differences in PWS and PWRI were observed between both groups at baseline. Participants allocated telmisartan had a slower annual increase in PWS (-4.19 (95% Confidence intervals, CI -8.24, -0.14 kPa/year, p=0.043) and PWRI (-0.014 (95% CI -0.026, -0.001, p=0.032) compared to those allocated placebo after adjusting for risk factors. After adjustment for SBP at 1 year, telmisartan did not significantly reduce annual increase in PWS or PWRI.

Conclusions: The findings of this study suggested that telmisartan limits the rate of increase in PWS and PWRI of small AAAs by reducing blood pressure.

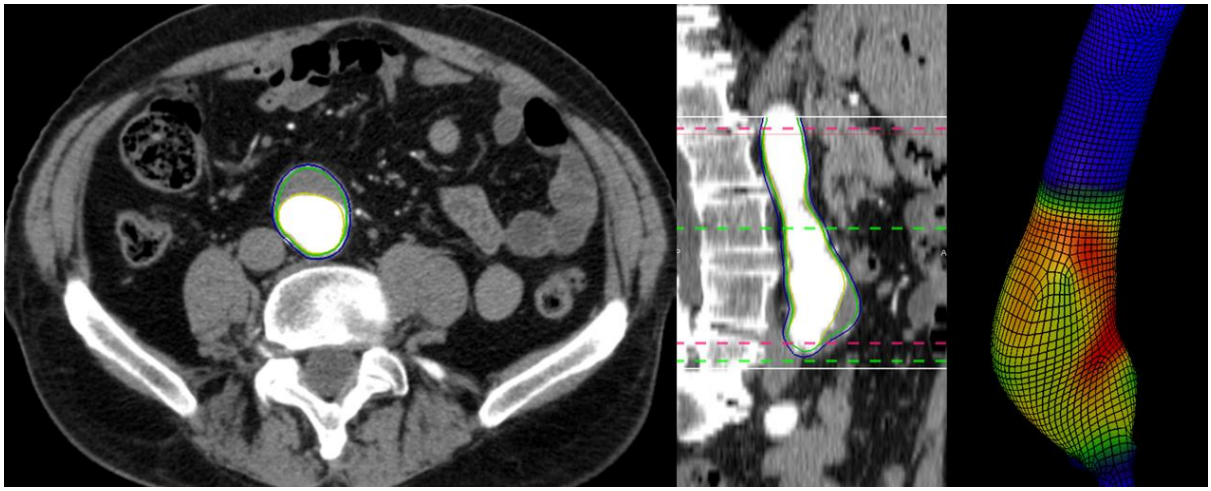
6.3 Introduction

Abdominal aortic aneurysm (AAA) rupture is responsible for approximately 200,000 deaths per year worldwide.[82] Elective endovascular or open surgical repair is the only established treatment to reduce the risk of AAA rupture, however surgical repair has been shown not to benefit people with small asymptomatic AAAs measuring <55mm in maximum diameter.[1] There has been great interest in identifying medical treatments that can effectively reduce the risk of small AAA rupture, however prior clinical trials have reported no benefit of previously investigated drug treatments.[1, 16, 64] A recent meta-analysis which pooled data from ten previous randomised controlled trials demonstrated that previously tested blood-pressure lowering medications and antibiotics did not significantly reduce progression or clinically relevant events (AAA rupture or repair) in participants with small AAAs.[16] All previous trials have tested the effects of medications through examining their efficacy in limiting the increase in maximum AAA diameter (referred to as AAA growth).[64] Estimation of AAA

diameter is subject to significant measurement error, which is estimated to be similar to the annual change in AAA size.[3] Maximum AAA diameter is also an imperfect measure of AAA rupture risk, since some large AAAs remaining intact throughout a patient's lifetime,[8] while some small AAAs rupture.[40] In view of these limitations of using AAA diameter, use of alternative surrogate measures of AAA rupture risk may enable better assessment of the efficacy of potential AAA drugs.[64]

Recent studies have suggested that the maximum tensile stress within the AAA wall (peak wall stress, PWS) and the ratio between estimated wall stress and wall strength (peak wall rupture index, PWRI) is higher in ruptured than intact AAAs.[16, 75, 96] These measurements have been proposed to predict the rupture risk of asymptomatic intact AAAs.[20, 75, 96] PWS and PWRI can be measured non-invasively from finite element analysis (FEA) of routinely conducted computed tomography (CT) scans using semi-automated methods that have excellent intra- and inter-observer reproducibility[20, 23] and can be easily performed by clinicians without engineering experience in a timely manner (Figure 6.1).[20, 23]

Figure 6.1. Example of three-dimensional segmentation of an AAA using finite element analysis.



PWS and PWRI are dependent on systemic blood pressure[16], with reductions in blood pressure expected to reduce PWS and possibly also rupture risk.[18] To our knowledge, no previous randomised controlled trial has examined the effects of a drug treatment on aortic PWS and PWRI. Telmisartan is a potent, long-acting angiotensin 1 (AT1) blocker commonly used to control blood pressure.[86] Previous studies have suggested that telmisartan reduces aortic wall inflammation and extracellular matrix degradation.[86, 97] High blood pressure is a risk factor for rupture of small AAAs and would be expected to increase PWS.[18, 23] Thus telmisartan might limit PWS, AAA growth and rupture risk. The Telmisartan in the Management of Abdominal Aortic Aneurysm (TEDY) trial found that telmisartan did not significantly slow AAA growth.[86] The effect of telmisartan on AAA growth and rupture risk may not be the same. This exploratory analysis aimed to assess the efficacy of telmisartan in limiting increase in AAA PWS and PWRI over a two year period, among a subset of the TEDY participants.[86]

6.4 Materials and methods

6.4.1 Study design and patient recruitment

This study was an unplanned exploratory analysis of a subset of patients who participated in the TElmisartan in the management of abdominal aortic aneurysm (TEDY) trial. The main outcome of TEDY, that telmisartan did not significantly slow growth of 35-49mm AAAs has been previously reported.[86] The trial was registered prior to commencing (Australian New Zealand Clinical Trials Registry: ACTRN12611000931976 listed 30/8/2011 for all sites; Clinicaltrials.gov: NCT01683084; listed 11/9/2012 for North American site). This was a parallel, randomized, multicenter, double-blind, placebo-controlled clinical trial and participants were randomised to receive identical capsules containing either telmisartan, 40 mg, or placebo once daily for 2 years in a 1:1 ratio. Participants were recruited from vascular

centers in Australia, The Netherlands and United States of America.[86] TEDY entry criteria have been reported previously.[86] Individuals with small asymptomatic AAAs (maximum orthogonal infra-renal aortic diameter of 35-49mm), with no current indication for AAA repair, not currently taking an AT1 blocker or angiotensin-converting enzyme inhibitor, with no contraindications to telmisartan were included. Patients with a diagnosis of hypertension were not excluded. Medical management of all participants during the study period was under the discretion of the treating primary physician or vascular surgeon. This was an exploratory analysis using CT imaging data that was collected as a part of the TEDY trial.[98] For inclusion in the current study, participants had to have undergone at least two CT scans; one scan performed at entry and at least one scan performed at another time point during the trial study period (12 or 24 months) that met the following quality requirements for FEA : 1) contrast-enhanced CT scan (CTA); 2) images at 3mm intervals or less under a set protocol as described previously[45]; 3) inclusion of the region between the infra-renal aorta and the iliac bifurcation.[77] The quality of each CT scan as assessed by a medical doctor trained in FEA. If the suitability of a CT scan was uncertain, an expert at FEA was consulted. All participants provided written informed consent and ethics approval was obtained at all study sites for the current study. The research was conducted in accordance with the Declaration of Helsinki. Further details regarding the trial protocol and primary findings has been previously published.[86, 98]

6.4.2 Participant characteristics

All participants underwent an interview and physical examination at entry to collect medical risk factors, medication prescriptions and brachial blood pressure.[86, 98] Adherence to allocated treatment was assessed by pill counts performed at 3, 6, 12, 18, and 24 months. Blood pressure was measured at recruitment and every 6 months at the participating site using a

digital monitor (Omron Intellisense, HEM-907) after participants had rested supine for a 20 minute period.[86, 98] Blood pressure measurements were recorded three times and averaged. Smoking was defined as current (smoking within the last month) or ex-smoking based on participants' history. Hypertension was defined by a prior diagnosis or medical prescription for hypertension. Cardiovascular disease was defined to include participants with a documented history of coronary heart disease, stroke or peripheral artery disease (PAD).

6.4.3 CT acquisition

CTAs were performed at baseline, 1 year, and/or 2 years using scanners at each participating centre, as previously described.[86, 98] CTAs were approved to occur at baseline, one and two years at Australian sites whereas the ethics approval at the Netherlands and USA sites only permitted CTAs to be performed at entry and two years. All CTAs were transferred to the core imaging reading site (Townsville, Australia), where they were analysed using the Philips MxView Visualisation Workstation using the Advance Vessel Analysis application (version seven).[86, 98] This programme was used to estimate maximum aortic diameter by following a validated protocol as previously described.[50, 77, 86, 98] A region of interest (ROI) was selected, which included the region marked by the slice inferior to the origin of the lowest renal artery (excluding accessory arteries) to the slice superior to the aortic bifurcation. Areas of maximal diameter were identified from this ROI, and multiple measurements were taken using electronic callipers. Anterior–posterior outer-to-outer orthogonal diameters were estimated by tracing the lumen of the infrarenal aorta and measuring perpendicular to this axis. The measurement was recorded to the nearest 0·1mm.[50, 51] The reproducibility of this method has been previously assessed (coefficient of variation < 4 %).[51, 77]

6.4.4 Biomechanical analysis

Aortic PWS and PWRI was estimated from FEA of CTAs using a commercially available software (A4 Research 5.0, VASCOPS GmbH, Graz, Austria) as previously described.[23, 86] 3-dimensional reconstructions of the AAA were created from the ROI defined above. The models were transformed into hexahedral meshes as previously described.[23, 26] AAA wall strength distribution was estimated using a statistical model incorporating intra-luminal thrombus thickness, AAA diameter and sex as previously described.[23, 34] PWS estimated the maximum tensile stress applied to the aortic wall based on AAA morphology and blood pressure.[23, 77] PWRI estimated the maximum ratio between wall stress and the estimated local aortic wall strength.[23, 77] The blood pressure values used to pressurise the AAA FEA model were patient specific and obtained at the same visit during which the CTA was performed.[86, 98] The coefficient of variations for the intra-observer reproducibility of PWS in asymptomatic intact AAAs has previously been assessed (coefficient of variation 2.7%).[77]

6.4.5 Sample size

Sample size and power calculations employed for the TEDY trial have been reported previously and were based on a clinically relevant reduction of 30% in annual AAA growth estimated by maximum aortic diameter.[86, 98] The current study included a subset of TEDY participants who underwent at least two CTAs. A sample size estimation was performed retrospectively and based on a planned regression analysis assessing the effect of telmisartan on increase in PWS over 24 months. The model was planned to include 3 covariates (dyslipidaemia, aspirin and statin prescription). We estimated that 120 participants would lead to an adequately powered analysis in order to attain at least 10 outcome events per degree of freedom according to Monte- Carlo simulations.[90]

6.4.6 Data analysis

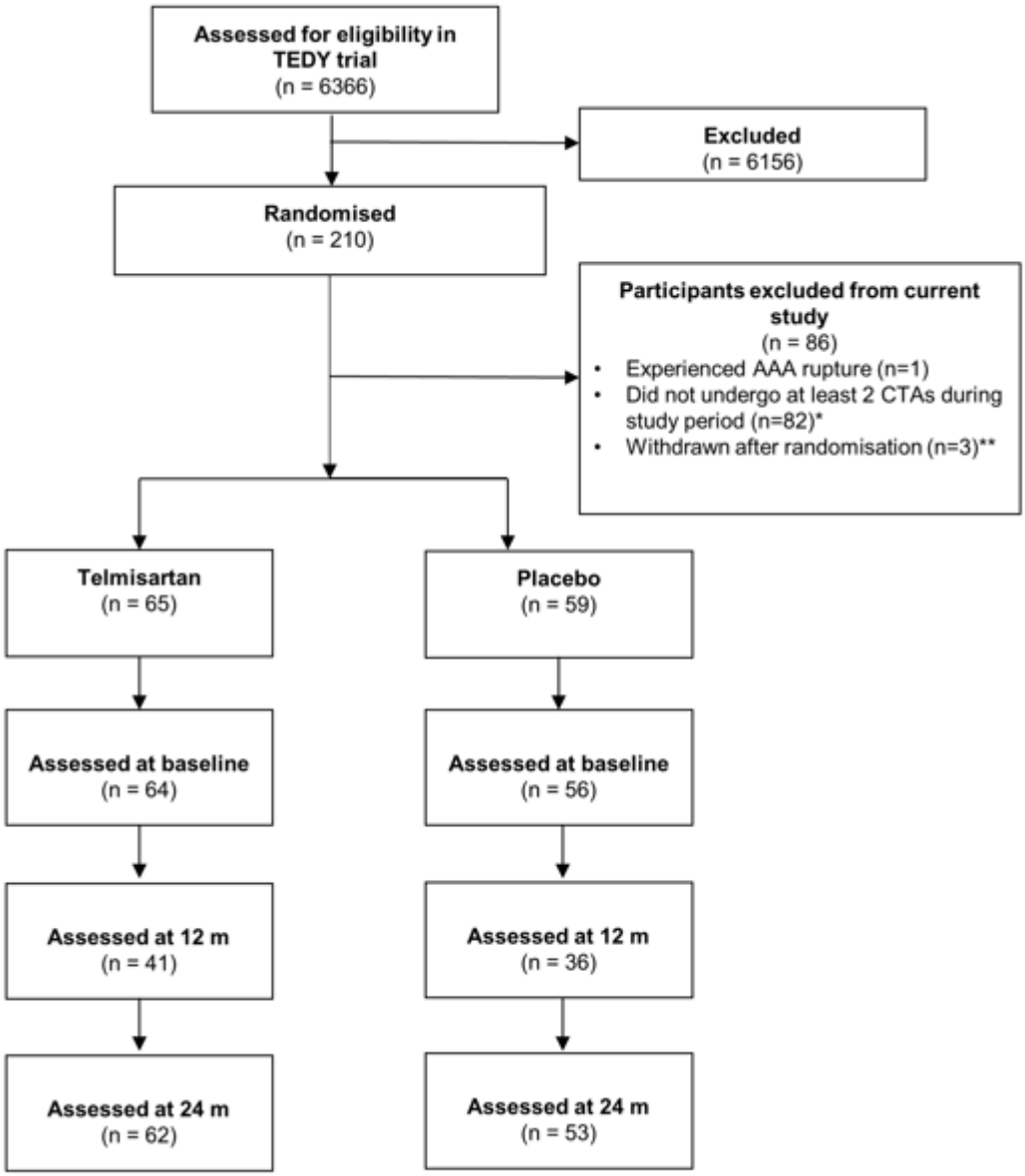
Patient characteristics were compared between groups using Pearson χ^2 for nominal data. Most continuous variables were not normally distributed according to Q-Q plots and Kolmogorov-Smirnov testing and therefore non-parametric Mann-Whitney U tests were used to compare between groups. The effect of telmisartan on change in PWS and PWRI over 24 months was estimated using linear mixed effects modelling. The interaction of time and allocated treatment was modelled with a random coefficient and random slope of time to enable participants to differ in the rate of change in PWS and PWRI. Multivariable linear mixed effects models were planned to include risk factors or medications that were different between participants allocated telmisartan and placebo at entry ($p<0.100$). This included dyslipidaemia, aspirin and statin prescription. A further linear mixed effects model was created to examine if any effect of telmisartan on increase in PWS and PWRI were explained by reductions in systolic blood pressure measured at 1 year. Variance inflation factor (VIF) was calculated to assess if there was co-linearity between variables included in the linear mixed regression. A VIF≥5 was considered to indicate a high likelihood of co-linearity and was not found with any of the reported models.[99] The effect of telmisartan on the blood pressure was assessed by linear mixed effects models as previously reported.[86, 98] Mean differences in systolic and diastolic blood pressure were reported at 1 year (trial mid-point) similar to previous blood pressure lowering trials.[16, 86] The relationship between baseline systolic blood pressure and annual changes in PWS and PWRI were also assessed by linear mixed effects analyses. The distribution of residuals was examined via QQ-normal plots and scatter plots of fitted values vs standardised residuals and did not indicate problems with residual distributions and residuals were normally distributed. All analyses were performed using Stata®version 16.1 (StataCorp, College Station, Texas, USA). All statistical tests were 2-sided and a P value <0.05 was considered significant.

6.5 Results

6.5.1 Participant characteristics

A total of 124 of the 210 TEDY participants who underwent at least two CTAs during the study period were included. Participants were mainly excluded as they did not have at least two CTAs from which PWS and PWRI could be estimated (n=82). One participant experienced an AAA rupture as previously reported[86] and was excluded from the current analysis as PWS and PWRI could not be accurately estimated from the second CTA due to a retroperitoneal haematoma. Three participants were withdrawn after randomisation owing to ineligibility, complete withdrawal, and duplicate randomization as previously described (Figure 6.2).[86]

Figure 6.2. Flowchart illustrating participant selection into the current study.



* Seven participants had two CTs however only one of the two CTs were contrast-enhanced and therefore these patients were excluded. ** Three patients were withdrawn after randomisation owing to ineligibility, complete withdrawal, and duplicate randomisation.

The median, interquartile range (IQR) aortic diameter was similar at baseline between both intervention and placebo groups (39.7mm [37.2-43.6] vs 40.8mm [36.6-43.0], p=0.962). Similarly, median (IQR) systolic (139mmHg [125-147] vs 134 [125-150], p=0.584) and

diastolic (78mmHg [72-85] vs 78mmHg [70-85], p=0.715) blood pressures were not significantly different between groups. Telmisartan and placebo groups were balanced for other risk factors (Table 6.1). The clinical characteristics of participants included in the current study were similar to those of the total TEDY participant population (Appendix D, Table 1).[86] Adherence to telmisartan or placebo capsules was similar over the 2 years of follow-up (Appendix D, Table 2). Four participants (3 and 1 participants in the placebo and telmisartan group respectively) were prescribed an additional blood pressure lowering agent within the study period.

Table 6.1. Characteristics of participants at baseline.

	Telmisartan (n=65)	**Placebo (n=59)**	**P-value**
Maximum orthogonal diameter (mm)	39.7 [37.2-43.6]	40.8 [36.6-43.0]	0.962
Age	73.7 [68.7-79.4]	75.3 [71.5-80.4]	0.155
Sex	56 (86)	53 (90)	0.531
Ever smoking	59 (91)	55 (93)	0.617
Hypertension	31 (48)	21 (36)	0.173
Dyslipidaemia	51 (78)	38 (64)	0.082
Diabetes	9 (14)	7 (12)	0.742
CVD*	40 (62)	28 (47)	0.116
COPD	19 (29)	14 (24)	0.489
Aspirin	42 (65)	28 (47)	0.054
Other anti-platelet agent	8 (12)	5 (8)	0.487
Warfarin	2 (3)	4 (7)	0.337
NOAC	2 (3)	3 (5)	0.570

Statin	46 (71)	33 (56)	0.086
Calcium channel blocker	11 (17)	10 (17)	0.997
Beta blocker	14 (22)	10 (17)	0.518
Metformin	6 (9)	4 (7)	0.617
Systolic blood pressure (mmHg)	139 [125-147]	134 [125-150]	0.584
Diastolic blood pressure (mmHg)	78 [72-85]	78 [70-85]	0.715
Systolic blood pressure >140mmHg	29 (45)	22 (37)	0.408

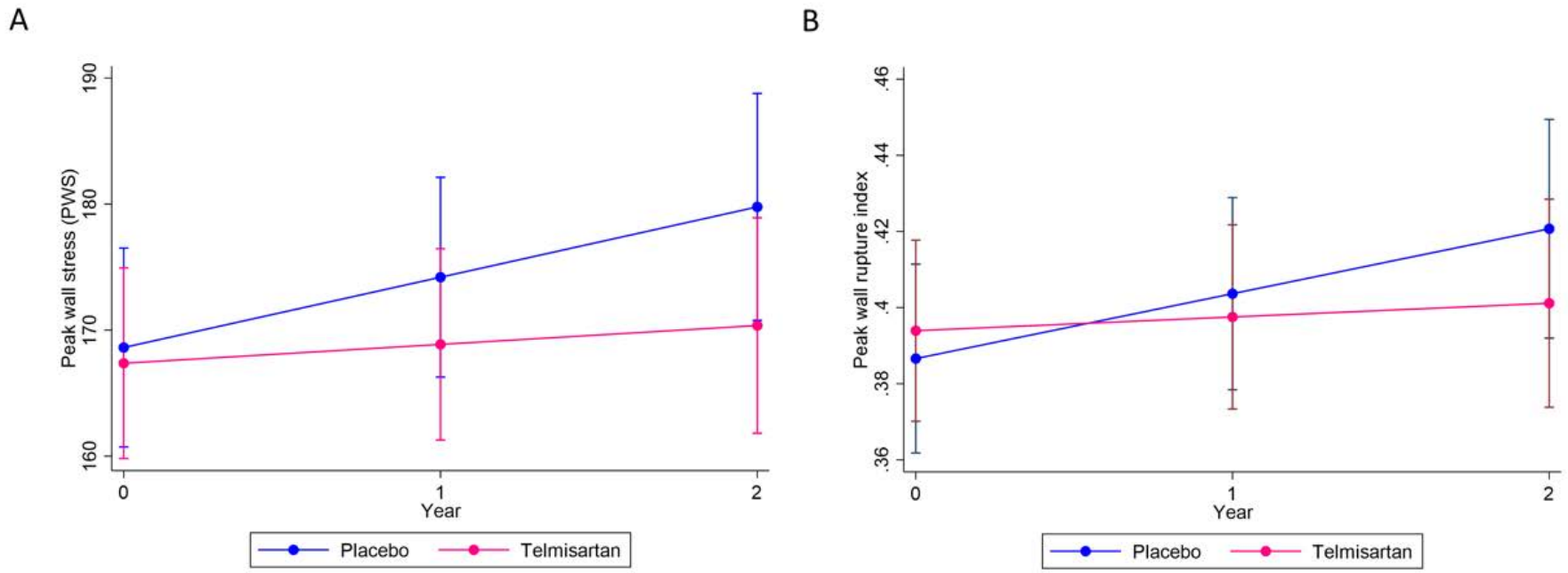
* CVD, Cardiovascular disease was defined by a documented history of coronary heart disease, stroke or peripheral artery disease. COPD, Chronic obstructive pulmonary disease; NOAC, Non-Vitamin K antagonist oral anticoagulants.

Ever smoking defined as current or former smoking. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test. Nominal data are presented as number (%) and were compared using Pearson's $\chi 2$ test. P-values highlighted in bold indicate significant differences.

6.5.2 Effect of telmisartan on aortic PWS and PWRI

At baseline the median (IQR) PWS and PWRI for participants allocated telmisartan and placebo were similar (164.5 kPa [148.9-184.4] vs 163.6 kPa [146.6-186.6], p=0.769 and 0.376 [0.318-0.441] vs 0.362 [0.330-0.425], p=0.729 for PWS and PWRI respectively). Estimated mean annual change in PWS were 1.50 (95% CI -1.25, 4.25 kPa/year) in participants randomised to receive telmisartan and 5.58 (95% CI 2.60, 8.56 kPa/year) for participants who were allocated placebo (Figure 6.3a). Estimated mean annual change in PWRI were 0.004 (95% CI -0.005, 0.012) and 0.017 (95% CI 0.008, 0.026) for participants randomized to receive telmisartan and placebo respectively (Figure 6.3b).

Figure 6.3. Effect of telmisartan on AAA PWS and PWRI measured from computed tomography imaging.



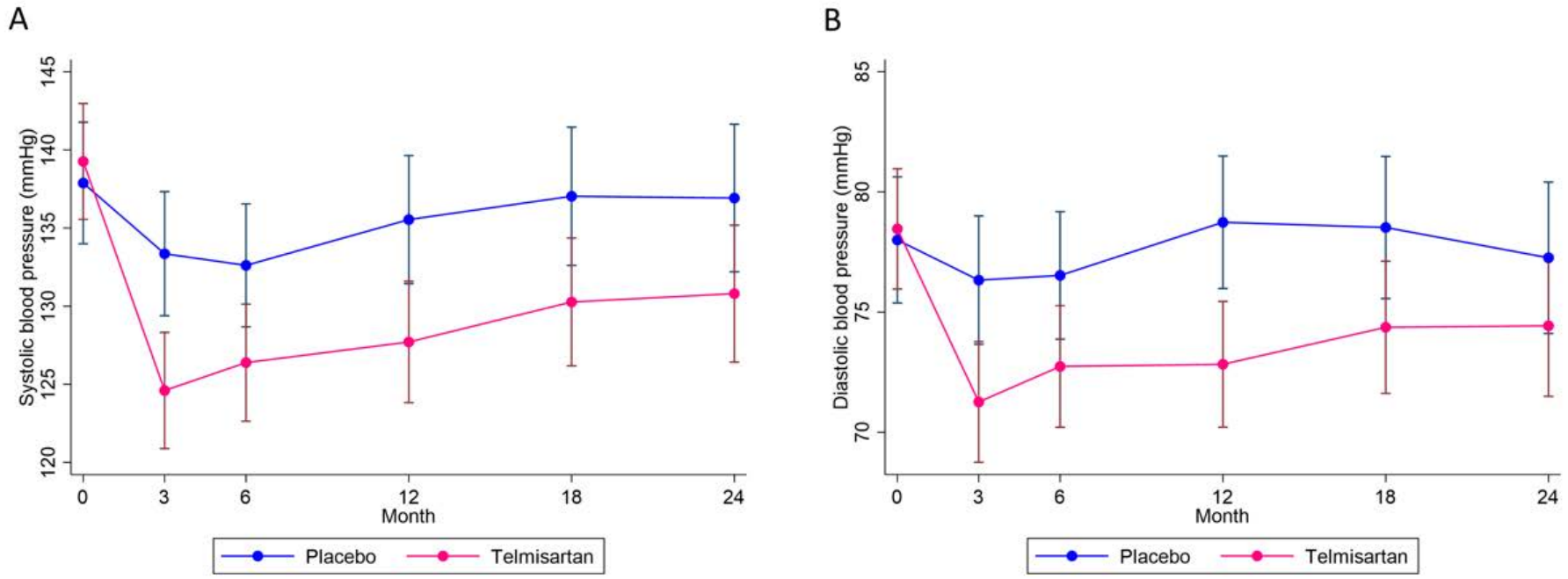
Estimated mean annual increases in PWS were 1.50 (95% CI -1.25, 4.25 kPa/year) and 5.58 (95% CI 2.60, 8.56 kPa/year) for participants randomized to receive telmisartan and placebo respectively. Estimated mean annual increases in PWRI were 0.004 (95% CI -0.005, 0.012) and 0.017 (95% CI 0.008, 0.026) for participants randomized to receive telmisartan and placebo respectively. Mean differences between groups were -4.08 (95% CI -8.13, -0.03 kPa/year) p=**0.048** and -0.013 (95% CI -0.026, -0.001) p=**0.033** for PWS and PWRI respectively. P values were generated from linear mixed effects modelling.

The mean difference in annual change in PWS and PWRI between groups was -4.08 (95% CI -8.13, -0.03 kPa/year; p=0.048) and -0.013 (95% CI -0.026, -0.001; p=0.033) which suggested a significantly slower annual increase in PWS and PWRI for participants randomised to telmisartan compared to placebo. Findings were similar in the analysis adjusted for risk factors that were different between telmisartan and placebo groups (mean difference in annual change between groups -4.19 [-8.24, -0.14] kPa/year; p=0.043 and -0.014 [-0.026, -0.001]; p=0.032 for PWS and PWRI respectively).

6.5.3 Effect of telmisartan on blood pressure

Estimated mean changes in systolic and diastolic blood pressure are shown in Figure 6.4a and 6.4b. At 1 year, the mean difference in systolic and diastolic blood pressure between telmisartan and placebo groups were -9.21 mmHg (95% CI -15.06, -3.37; p=0.002) and -6.37 mmHg (95% CI -9.78, -2.95; p<0.001) for systolic and diastolic blood pressure respectively.

Figure 6.4. Effect of telmisartan compared with placebo on blood pressure.



Estimated mean difference in systolic (A) and diastolic (B) blood pressure in participants randomized to telmisartan and placebo. The mean differences in systolic and diastolic blood pressure between both groups at trial midpoint were -9.21 (95% CI -15.06, -3.37 mmHg; p=**0.002**) and -6.37 (95% CI -9.78, -2.95 mmHg; p<**0.001**). P values were generated from linear mixed effects modelling.

After adjusting for systolic blood pressure at 1 year, the mean difference in annual change in PWS and PWRI was not significantly different between telmisartan and placebo groups (-3.61 [95% CI -7.76, 0.53) kPa/year], p=0.087 and -0.012 [95% CI -0.025, 0.000], p=0.053 for PWS and PWRI respectively; see Table 6.2).

Table 6.2. Multivariable linear mixed effects models investigating the effect of telmisartan on peak wall stress.

	Mean annual difference in PWS (kPa), (95% CIs)	**p-value**	**Mean annual difference in PWRI (95% CIs)**	**p-value**
Unadjusted	-4.08 (-8.13, -0.03)	**0.048**	-0.013 (-0.026, -0.001)	**0.033**
Adjusted for risk factors*	-4.19 (-8.24, -0.14)	**0.043**	-0.014 (-0.026, -0.001)	**0.032**
Adjusted for systolic blood pressure at 1 year	-3.61 (-7.76, 0.53)	0.087	-0.012 (-0.025, 0.000)	0.053

AAA, abdominal aortic aneurysm; kPa, kilopascals; PWS, peak wall stress; CI, confidence intervals. * risk factors included variables different (<0.100) between groups at entry (dyslipidaemia, aspirin and statin prescription).

6.5.4 Association between baseline blood pressure and annual change in peak wall stress and peak wall rupture index

Annual changes in PWS (0.20 kPa [95% CI -0.13, 0.52]; p=0.241) or PWRI (0.001 [95% CI -0.000, 0.002]; p=0.057) were not significantly associated with baseline systolic blood pressure.

6.6 Discussion

To our knowledge, this is the first study that has investigated the effects of a potential medication treatment on aortic PWS and PWRI in a randomised clinical trial. The main findings from the current study suggest that telmisartan significantly reduced the rate of increase in aortic PWS and PWRI in individuals with small AAAs. Telmisartan was also found to have a significant blood pressure lowering effect which is consistent with prior reporting.[86] When adjusted for systolic blood pressure at 1 year, the reduction in increase of PWS and PWRI in the telmisartan group compared to the placebo group was not significant. Overall the findings suggest the telmisartan limited increase in AAA PWS and PWRI is at least in part due to reductions in blood pressure. The findings are consistent with other investigations that have reported that reductions in blood pressure can lead to reductions in aortic wall stress among patients with thoracic aortic aneurysms.[100] Other mechanisms by which Telmisartan may reduce PWS and PWRI include improved arterial elasticity and reduction in arterial stiffness.[97, 101] A sub-group analysis from a previously published meta-analysis of clinical trials reported that telmisartan significantly reduced arterial stiffness in comparison to control participants who were mainly allocated calcium channel blockers or angiotensin-converting enzyme inhbitors.[101] This suggests that telmisartan may potentially be more effective at reducing arterial stiffness and aortic wall stress than other blood pressure

lowering agents however further research is needed to investigate this. The FEA method used in the current study estimated aortic wall properties based on previous tensile testing of human AAA wall specimens.[23, 26, 77] AAA morphology has been shown to be the most important factor in PWS computation.[102] While the FEA method employed in this study cannot incorporate patient specific mechanical characteristics of AAA tissue, previous studies have demonstrated that the AAA wall exhibits minimal anisotropy[34] and patient specific variation in mechanical characteristics of AAA tissue were not expected to substantially affect the PWS and PWRI values computed in this investigation.

The main objective of any AAA drug treatment is to prevent AAA rupture; however, since the likelihood of rupture in individuals with small AAAs is low[40] this is not a feasible end-point for trials testing new treatments.[3] This is particularly important, as prior trials have been underpowered to detect a potential treatment effect of the investigated drugs.[16, 64] All prior AAA medication trials have mainly focused on measurement of AAA diameter or volume as surrogate markers of rupture risk and requirement for surgical intervention.[3, 16, 64] PWS may be a more reliable means to estimate rupture risk.[20, 24, 103] The current study suggests blood pressure lowering with telmisartan limits increases in PWS and PWRI amongst patients with small AAAs. This was despite previous findings that telmisartan does not slow AAA growth as estimated by maximum diameter or aortic volume.[86] Interestingly, the reduction in the increase of PWS among participants allocated telmisartan was not significantly different from those given placebo when adjusted for systolic blood pressure at 1 year. Collectively this suggests that lowering blood pressure does not limit increase in AAA diameter but may reduce rupture risk. The findings are commensurate with those of a large observational study which reported that high blood pressure or a prior diagnosis of hypertension were not associated with increased AAA growth rates but were associated with increased AAA rupture risk.[18] Overall these data highlight the need for additional surrogate markers of AAA rupture

and emphasise the value of good blood pressure control in people with small AAAs.[18, 89] Further research is needed to assess which measures of blood pressure are more relevant to AAA rupture risk. Current international guidelines[63] recommend the use of blood pressure lowering agents to reduce the risk of future cardiovascular events among AAA patients, however they do not endorse blood pressure lowering treatments as effective strategies to reduce the rate of AAA growth or rupture.[63, 89, 104] Approximately 40% of the participants included in the current study had a systolic blood pressure greater than 140mmHg at entry highlighting the poor control of blood pressure in the participants as described in other cohorts.[89, 105]

This study has a number of limitations. The sample size included was relatively small and we were unable to include all participants from the TEDY trial as a limited number of participants had CTs that met the inclusion criteria, therefore, selection bias cannot be excluded. The confidence in the findings are lessened given the TEDY trial was underpowered to test a potential treatment effect of telmisartan. This study was an exploratory analysis of the TEDY trial[86], which reported no significant reduction in AAA growth in participants allocated to telmisartan compared to placebo. Given the negative primary result from this trial, the findings from the current study should be interpreted cautiously. Importantly, PWS and PWRI are calculated using blood pressure and it is likely that any blood pressure lowering agent will reduce PWS and PWRI. Also, it remains controversial how accurately PWS can estimate rupture risk. A number of previous studies have suggested that PWS is greater in ruptured or symptomatic and asymptomatic intact AAAs[24], however most have been of case-control design[24] and observational studies of AAAs under surveillance are limited and of small sample size.[81, 103] Further validation of PWS and PWRI as clinically valuable measures of AAA rupture risk is required. It is currently unclear what level of reduction in PWS or PWRI is clinically important. The lack of

an accepted approach to measuring FEA is another limitation of biomechanical indices such as PWS and PWRI.[20] Lastly, the participants included in the current study needed to meet the entry criteria for TEDY and all had small AAAs. It is unclear whether blood pressure lowering has favourable effects on PWS and PWRI in individuals not meeting the entry criteria for TEDY, such as people with large AAAs. Investigating this would be difficult as most large AAAs undergo repair.[63] Furthermore, this study included participants from centres in Australia, Netherlands and USA and the findings may not be generalizable to other populations.

In conclusion, this study suggests that telmisartan may reduce the rate of increase in aortic PWS and PWRI in participants with small AAAs. The findings support previous reports that high blood pressure is associated with an increased risk of AAA rupture in individuals with small AAAs. PWS and PWRI may be more appropriate measures of AAA rupture risk than AAA diameter however further research is required to determine their accuracy in estimating rupture risk. Larger studies with longer follow up are required to assess whether reductions in PWS and PWRI secondary to blood pressure lowering can reduce the risk of AAA rupture or requirement for AAA repair.

Chapter 7. Discussion and recommendations

This concluding chapter will summarize the findings from the previous six chapters, list the limitations and strengths of the investigations, and outline recommendations for prospective research.

Briefly, the research presented in this thesis has contributed original knowledge by; 1) Evaluating the reproducibility of PWS and comparing PWS and PWRI among individuals with ruptured and asymptomatic intact AAAs of similar aortic diameter; 2) synthesizing the existing evidence comparing PWS, PWRI between individuals with ruptured and asymptomatic intact AAAs; 3) Assessing the association between baseline PWS and PWRI with the risk of future clinically important AAA events among individuals with small AAAs in a prospective observational study; 4) Evaluating the ability of a commonly prescribed blood pressure lowering agent in reducing the PWS and PWRI of patients with small AAAs.

7.1 Summary findings from the research

The key findings from the research presented in this thesis have been summarized in table 7.1

Table 7.1. Summary of key findings from the research presented in this thesis.

Chapter number	**Title**	**Key findings**	**Conclusion**
3	Comparison of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms	Patients with high PWS were approximately five times more likely to have a ruptured AAA than those with lower PWS after adjusting for confounding factors.	High aortic PWS was associated with greater odds of aneurysm rupture in patients with a large AAA.
4	Systematic review and meta-analysis of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms	PWRI, but not PWS, is greater in ruptured than asymptomatic intact AAAs of similar maximum aortic diameter. There are a number of limitations of prior studies investigating the utility of PWS and PWRI. There is a lack of prospective evidence investigating the association between	PWRI is greater in ruptured than asymptomatic intact AAAs of similar maximum aortic diameter.

		baseline PWS and PWRI with future clinically important AAA events.	
5	Association between aortic peak wall stress and peak wall rupture index with abdominal aortic aneurysm related events	Both higher PWS and PWRI were associated with a higher risk of future AAA events (rupture or AAA repair) after adjustment for risk factors. PWRI, but not PWS significantly improved the classification of risk for AAA events.	PWRI can independently predict AAA events and may add to AAA diameter in stratifying the risk for events in patients with small AAAs.
6	Effect of telmisartan on the peak wall stress and peak wall rupture index of small abdominal aortic aneurysms: An exploratory analysis of the TEDY trial	Telmisartan significantly reduced the rate of increase in aortic PWS and PWRI in individuals with small AAAs. When adjusted for systolic blood pressure at 1 year, the reduction in increase of PWS and PWRI in the telmisartan group compared to the placebo group was not significant.	Telmisartan may reduce the rate of increase in aortic PWS and PWRI in participants with small AAAs, in part due to its blood pressure lowering effects.

7.2 Discussion of the key findings from the research reported in this thesis

This section will discuss the key findings of the research presented in this thesis with relation to the original research questions outlined in Chapter 1.

Question 1: Is PWS a reproducible measurement and is PWS and PWRI greater among patients with ruptured than asymptomatic intact AAAs ?

7.2.1 PWS can be measured reproducibly. High PWS has an inconsistent association with greater odds of aneurysm rupture in patients with large AAAs.

Findings from this original study reported in Chapter 2 demonstrate that PWS can be estimated with high intra-observer reproducibility. Findings from Chapter 3 suggest that patients with high PWS have a higher odds of having a ruptured AAA compared to individuals with low PWS. This association was not robust when using continuous values of PWS. Collectively the findings highlight an inconsistent association between high PWS and AAA rupture.

Question 2: What are the findings of other investigations that have compared PWS and PWRI among patients with AAAs of similar diameter? What does a pooled analysis of all prior studies comparing PWS and PWRI between ruptured and asymptomatic AAAs suggest?

7.2.3 After pooling all prior case control evidence, including the research presented in Chapter 3, PWRI was found to be greater in ruptured than asymptomatic intact AAAs of similar maximum diameter. PWS was not found to be significantly different between groups.

The findings of the systematic review and meta-analysis presented in Chapter 4 suggest that PWRI, but not PWS, is greater in ruptured than asymptomatic intact AAAs of similar maximum AAA diameter. The finding of the meta-analysis was robust in leave-one-out sensitivity analysis.

The finding that PWS was not significantly different between ruptured and asymptomatic intact AAA groups is in contrast with the results of Chapter 3. There could be many reasons for this discrepancy. Firstly, the sample size of both studies should be considered. The systematic review and meta-analysis presented in Chapter 4 included 309 participants while the case-control study presented in Chapter 3 only included 75 participants. Furthermore, there was substantial inter-study heterogeneity of the meta-analysis presented in Chapter 4 and is another important consideration when interpreting the results of that study. For example, three studies included in the meta-analysis used patient specific blood pressure[28, 62, 72] rather than a standardised blood pressure, which may have overestimated or underestimated the PWS values reported. In addition, the variables that were matched between ruptured and asymptomatic intact AAA groups were different between studies. Furthermore, only three studies[62, 72, 83] out of the seven studies reported the reproducibility of their FEA methods, limiting the confidence in the PWS and PWRI estimates.

Question 4: Is baseline PWS and PWRI associated with an increased risk of future AAA events (rupture or repair) among individuals with small AAAs ?

7.2.4 Both PWS and PWRI at baseline were found to be associated with an increased risk of future AAA events. PWRI was the single best risk stratification measure.

The findings of Chapter 5 indicate that both PWS and PWRI are associated with an increased risk of future AAA events after adjusting for maximum AAA diameter and other confounding risk factors. To our knowledge, this was the first prospective observational study that has assessed the utility of these measurements in predicting AAA events. Novel to this study is the finding that PWRI was the single best risk stratification measure for AAA events and significantly improved the risk stratification for events compared to diameter alone. Overall, the findings suggest that PWRI may add to AAA diameter in stratifying the risk for events in patients with small AAAs.

Question 5: Can a commonly used blood pressure lowering medication reduce the PWS and PWRI of individuals with small AAAs ?

7.2.5 Telmisartan limited the rate of increase in PWS and PWRI of small AAAs by reducing blood pressure.

The findings of this research (presented in Chapter 6) suggested that telmisartan limited the rate of increase in PWS and PWRI of small AAAs by reducing blood pressure. To our knowledge, this was the first study that has investigated the effects of a medication treatment on aortic PWS and PWRI in a clinical trial.

The primary finding of the TElmisartan in the management of abDominal aortic aneurYsm (TEDY) was that telmisartan prescription did not slow AAA growth as estimated by maximum diameter.[86] The finding of the research presented in Chapter 6 suggest that while telmisartan may not limit AAA growth, it might limit the rupture risk of an AAA by reducing PWS and PWRI. This is a practical hypothesis as prior studies have suggested that telmisartan reduces aortic wall inflammation and arterial wall stiffness.[97, 101] Furthermore, telmisartan has a known blood pressure lowering effect which is expected to reduce PWS and PWRI.[23, 83] Given the low rate of rupture of small AAAs, rupture is not a feasible end-point for AAA drug trials[3, 64] and an accurate surrogate measure for AAA rupture would greatly help future clinical trials assess the efficacy of novel drug treatments aimed at reducing the risk of rupture. This study and research presented in prior chapters supports the utility of PWS/PWRI as surrogate markers of AAA rupture risk that could be included as outcome measures of future AAA drug trials.

7.3 Limitations of the research

There are a number of limitations of the research presented within this thesis. The main limitation of the systematic review and meta-analysis in Chapter 4 is the inter-study

heterogeneity with the risk of bias estimated to be medium-high across all individual studies. This substantially lessens the confidence in the findings of the study. We attempted to address this by using a random-effects model for the meta-analysis. More specific limitations concerning this study have been reported in Chapter 4 and Chapter 7 (7.2.3).

The main limitations of the case-control study reported in Chapter 3 include its retrospective design and small sample size. Although patients were matched for AAA diameter, it was not possible to match for other important risk factors such as sex due to the difficulties in identifying the required number of women with asymptomatic intact AAAs that matched in diameter with ruptured AAAs among women. We attempted to address this by adjusting for sex in the regression analysis. Furthermore, the generalisability of the study was limited to patients recruited from centres within Queensland and individuals with large AAAs. The prospective observational cohort study presented in Chapter 5 was limited by its small sample size and relatively short follow-up period of a median of 2.0 (inter-quartile range 1.9, 2.8) years. Importantly, AAA repair was performed at the clinical discretion of the treating vascular surgeon and discrepancies in timing of surgical repair between centres cannot be ruled out. The research presented in Chapter 6 is an unplanned exploratory analysis of the previously published TEDY trial[64], which reported no significant reduction in AAA growth in participant's allocated telmisartan compared to placebo. The findings of Chapter 6 must therefore be interpreted with caution. Not all participants from the TEDY trial were included in Chapter 6 due to the inclusion criteria of the investigation and therefore selection bias cannot be excluded. Finally, an underlying limitation of Chapters 3, 4, 5 and 6 are the lack of an accepted approach to FEA. For example it remains unclear whether patient-specific blood pressure or a standardised blood pressure should be used to compute PWS/PWRI. Furthermore, there remains a lack of validation of PWS and PWRI as clinically useful

measures. It is also currently unclear what constitutes as a clinically important reduction in PWS and PWRI.

7.4 Strengths of the research

There are a number of strengths of this research. Firstly, we conducted the first systematic review and meta-analysis comparing PWS and PWRI among patients with asymptomatic intact AAAs and ruptured AAAs of 'similar diameter'. The diameter differences between groups in a prior systematic review was a major limitation of that investigation.[24] Strengths of the case-control study presented in Chapter 3 include the inclusion of a sample size estimation, assessment of reproducibility of PWS and clear selection criteria. No prior case-control study had addressed all these important study design considerations in the same investigation. The research presented in Chapter 5 has a number of strengths including its novelty of being the first prospective observational cohort study assessing the utility of PWS/PWRI in predicting AAA events. To our knowledge, there has been one other study[81] which has prospectively assessed the predictive utility of another biomechanical measurement (The ABR) for AAA events.[81] The ABR may be a more superior measure to PWS/PWRI as it incorporates aortic wall thickness[37] enabling more accurate biomechanical simulations. However, a major limitation of this measurement is the requirement of multiple software packages to perform the biomechanical analysis (see Chapter 2, Table 2.3).[37, 81] Furthermore, the ABR requires magnetic resonance imaging (MRI) to estimate aortic wall thickness.[81] MRI is expensive to perform and is not routinely used in AAA surveillance and therefore the uptake of this measurement is likely to be limited. A major strength of the A4 Research 5.0 software is the ability to perform FEA and PWS/PWRI measurements using one single software in a semi-automated manner rather than using multiple packages.[23] The research presented in Chapter 6 is also novel as it is the first AAA clinical trial that has

assessed the efficacy of a drug treatment to limit the increase of PWS and PWRI. The findings of that study suggests that while lowering blood pressure does not limit increases in AAA diameter it may reduce rupture risk of an AAA. The findings echo the results of a previous meta-analysis which reported that high blood pressure was not associated with increased AAA growth but was associated with increased AAA rupture risk.[18] Collectively this research highlights that the risk factors for AAA rupture and growth are different and more accurate surrogate measures for AAA rupture are required.

7.5 Recommendations for future research

Considering the above discussion regarding the research presented within this thesis, the following recommendations for future research are suggested:

- Further validation of the utility of PWS/PWRI in other populations is required. Ideally, a large cohort of small AAAs under surveillance followed-up for a long duration is required to better assess the utility of PWS/PWRI. Furthermore, it would be useful to look at changes in PWS/PWRI during follow-up and investigate what factors are associated with a higher rate of increase in PWS/PWRI. Such an analysis could help identify potential targets for novel treatments to limit the increase in PWS/PWRI and potentially the rupture risk of an AAA.
- Further work is required to determine the best approach to FEA. Currently significant heterogeneity in FEA methods exists as identified in Chapter 4. A standardised approach towards FEA is required to ensure that future studies employ homogenous methods allowing for useful interpretation of results.
- Further research is required to understand what are clinically useful cut-offs of PWS and PWRI. In Chapter 5, we used the Classification and regression tree analysis (CART) to determine the optimal predictive cut-off of PWRI for AAA events

(0.562). The utility of this proposed cut-off could be assessed in a larger prospective study of individuals with small AAAs.

- The findings of Chapter 6 suggest that telmisartan reduces the PWS and PWRI of small AAAs. Further research is warranted to validate the findings before this treatment could be considered in AAA management.

7.6 Conclusions

AAA rupture is an important cause of mortality. There remains no medical treatment to prevent AAA rupture and surgery is the only treatment available. AAA diameter is currently the most established measure to predict the risk of AAA rupture although there are many limitations of this measurement. Biomechanical measures may be able to more accurately predict the rupture risk of an AAA. The research presented within this thesis demonstrate that FEA can be performed in a semi-automated method with high reproducibility. PWS and PWRI may predict the risk of future AAA events (AAA rupture or repair) independent of AAA diameter and other risk factors. While prior evidence suggests telmisartan does not limit AAA growth (as measured by diameter), the research presented in this thesis suggests that telmisartan may be able to limit the increase in PWS and PWRI of individuals with small AAAs. There are some limitations of FEA that need to be addressed in future research.

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Appendices

Appendix A: Supporting files, figures and tables for Chapter 3

Appendix B: Supporting files, figures and tables for Chapter 4

Appendix C: Supporting files, figures and tables for Chapter 5

Appendix D: Supporting files, figures and tables for Chapter 6

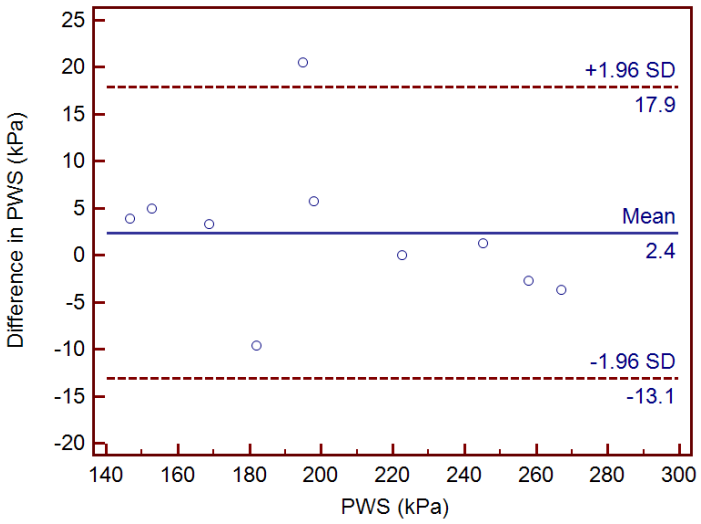
Appendix E: Published papers as a result of this PhD

Appendix A: Supporting files, figures and tables for Chapter 3

Table 1. Intra-observer reproducibility.

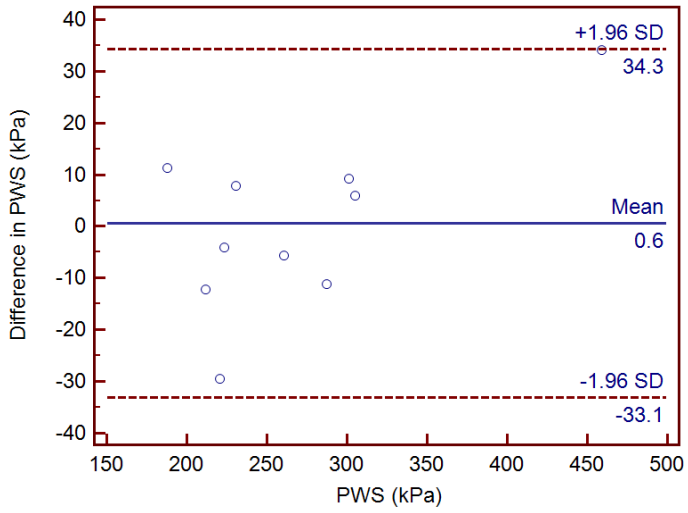
Group	Mean Difference	Concordance correlation coefficient (95% CI)	Coefficient of variation (COV)
Intact AAAs (n=10)			
Maximum axial diameter (mm)	0.4	0.997 (0.988, 0.999)	1.8%
Peak Wall Stress (kPa)	2.4	0.982 (0.933, 0.995)	2.7%
Ruptured AAAs (n=10)			
Maximum axial diameter (mm)	0.1	0.966 (0.892, 0.989)	3.2%
Peak wall Stress (kPa)	0.6	0.976 (0.933, 0.991)	4.3%

Intact AAAs



Bland-Altman plot of difference in peak wall stress (PWS) against the mean AAA PWS of two independent measurements from one observer.

Ruptured AAAs



Bland-Altman plot of difference in peak wall stress (PWS) against the mean AAA PWS of two independent measurements from one observer.

Table 2. Estimated PWS in asymptomatic intact and ruptured AAAs when computed at low (120/70mmHg) and high (160/90mmHg) blood pressures.

	Intact AAA (n=50)	Ruptured AAA (n=25)	P-value
Low BP			
PWS (kPa)	242.5 [204.5-296.8]	280.4 [204.0-310.5]	0.206
PWRI	0.92 [0.65-1.38]	0.89 [0.51-1.83]	0.736
High BP			
PWS (kPa)	249.0 [221.8-305.8]	291.2 [227.3-328.6]	0.323
PWRI	1.03 [0.78-1.51]	1.03 [0.63-1.95]	0.822

AAA, abdominal aortic aneurysm; PWS, peak wall stress; PWRI, peak wall rupture index. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test.

Table 3. Logistic regression analysis examining the association of high PWS with AAA rupture at low and high blood pressures.

	Odds Ratio*	95% CI	P-value
Low BP			
PWS ≤ 260 kPa	(reference)		
PWS > 260 kPa	4.67	1.05-20.62	**0.042**
High BP			
PWS ≤ 280 kPa	(reference)		

PWS > 280 kPa	4.99	1.11-22.47	**0.036**

*Adjusted for age, sex, smoking, orthogonal diameter, Ischaemic heart disease, hypertension, diabetes and Angiotensin II receptor blocker prescription. High PWS cut off values based on approximate median of PWS when computed at low (120/70mmHg) and high (160/90mmHg) blood pressures.

Table 4. Patient characteristics of asymptomatic intact and ruptured AAAs in male patients (n=65).

	Intact AAA (n=47)	Ruptured AAA (n=18)	p-value
Age	73 [66-77]	75 [67-80]	0.300
Smoking	45 (96%)	16 (89%)	0.303
Diabetes	8 (17%)	3 (17%)	0.973
IHD	24 (51%)	7 (39%)	0.379
Hypertension	31 (66%)	13 (72%)	0.629
Stroke	3 (6%)	0 (0%)	0.272
COPD	12 (26%)	3 (18%)	0.485
Aspirin	24 (51%)	10 (56%)	0.746
Other anti-platelet	11 (23%)	2 (11%)	0.268
ACEi	21 (45%)	3 (17%)	**0.036**
ARB	2 (4%)	7 (39%)	**<0.001**
Statin	29 (62%)	9 (50%)	0.392
Metformin	1 (2%)	1 (6%)	0.474

AAA, abdominal aortic aneurysm; IHD, ischemic heart disease; COPD, Chronic obstructive pulmonary disease; ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker. Smoking as defined as patients that were current or ex-smokers. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test. Nominal data are presented as number (%) and were compared using Pearson's $\chi 2$ test. P-values highlighted in bold indicate significant differences.

Table 5. Biomechanical markers in asymptomatic intact and ruptured AAAs in male patients (n=65).

	Intact AAA (n=47)	Ruptured AAA (n=18)	P-value
Maximum axial diameter (mm)	82.2 [73.2-93.1]	84.3 [71.3-94.0]	0.942
Total vessel volume (cm^3)	353.4 [209.2-535.2]	301.8 [205.9-548.2]	0.747
ILT volume (cm^3)	144.8 [94.3-238.2]	183.2 [87.5-242.8]	0.573
PWS (kPa)	251.8 [218.0-304.6]	278.0 [217.2-329.6]	0.528
PWRI	0.99 [0.68-1.46]	0.74 [0.49-1.14]	0.147

AAA, abdominal aortic aneurysm; PWS, peak wall stress; PWRI, peak wall rupture index; ILT, intra-luminal thrombus. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test.

Appendix B: Supporting files, figures and tables for Chapter 4

Supplementary File 1. Protocol for systematic review and meta-analysis

Protocol for a systematic review and meta-analysis of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms.

Tejas P. Singh MBBS MPH, Joseph V. Moxon PhD, T. Christian Gasser PhD, Jonathan Golledge MChir FRACS

Background: Aortic peak wall stress (PWS) and peak wall rupture index (PWRI) are established surrogate measures of abdominal aortic aneurysm (AAA) rupture risk. Prior studies have suggested that PWS and PWRI is greater in ruptured than asymptomatic intact AAAs, although it remains unclear whether these measures confer any benefit in predicting AAA rupture compared to AAA diameter. The aim of this planned systematic review and meta-analysis is to compare PWS and PWRI in participants with ruptured and asymptomatic intact AAAs of similar diameter.

Methods: A systematic review and meta-analysis will be conducted. An electronic database search will be performed using predefined search terms to identify relevant studies. Eligible studies will be required to compare PWS and PWRI in ruptured and asymptomatic intact AAAs of similar diameter. Random-effects meta-analysis will be performed and leave-one-out sensitivity analyses will be conducted to assess the robustness of the findings. Risk of bias will be assessed using a modification of the Newcastle-Ottawa scale and standard quality assessment criteria for evaluating primary research papers.

Discussion: This meta-analysis will be the first to compare PWS and PWRI in asymptomatic intact and ruptured AAAs of similar diameter.

Introduction

Abdominal aortic aneurysm (AAA) rupture is an important cause of mortality.[1] In current clinical practice, AAA aortic diameter is the main measure used by clinicians to estimate the risk of AAA rupture.[1, 5] Evidence from prior randomized controlled trials suggest that some large AAAs remain stable throughout a patient's lifetime, while some small AAAs can rupture.[2] This suggests that diameter is not a perfect measure of estimating the rupture risk of AAAs.[1, 5] There has been considerable interest in utilizing biomechanical measures to estimate and predict AAA rupture risk.[3, 7] Aortic peak wall stress (PWS) and peak wall rupture index (PWRI) are examples of two widely reported biomechanical indices.[7, 26] Prior meta-analyses have suggested that PWS is greater in asymptomatic intact and ruptured AAAs although the diameter in both groups were different in that analysis.[3] A meta-analysis comparing PWRI in asymptomatic intact and ruptured AAAs in individuals with similar aortic diameter has not been performed. In light of the limitations of prior studies and the paucity of pooled evidence in this area an updated systematic review and meta-analysis is required.

Systematic review question

Is PWS and PWRI greater in asymptomatic intact and ruptured AAAs of similar aortic diameter ?

Data sources search terms and search strategy

This literature review will be performed using the Web of Science (via ISI Web of Knowledge; 1965), Scopus (1966), Medline (via OvidSP, 1966) and The Cochrane Library. A combination of the following search terms will be used: "peak wall stress" OR "peak wall rupture index" OR "rupture potential index" AND "abdominal aortic aneurysm". Specific search criteria database are reported below:

Medline (via OvidSP, 1966): ((peak wall stress) OR (peak wall rupture index)) AND (abdominal aortic aneurysm) [Across all fields]

Web of Science (via ISI Web of Knowledge; 1965): (((peak wall stress) OR (peak wall rupture index)) AND (abdominal aortic aneurysm)) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

Scopus (1966): TITLE-ABS-KEY (((peak AND wall AND stress) OR (peak AND wall AND rupture AND index)) AND (abdominal AND aortic AND aneurysm))

The Cochrane Library: peak wall stress in All Text OR peak wall rupture index in Title Abstract Keyword AND abdominal aortic aneurysm in Title Abstract Keyword - (Word variations have been searched)

Inclusion and exclusion criteria

Case-control studies investigating PWS in patients with ruptured and diameter matched asymptomatic intact AAAs. Eligible studies should be of case-control design. The AAA diameter between asymptomatic intact and ruptured groups should be similar (within 3mm mean difference). Studies that include symptomatic AAA patients in the ruptured group will be excluded. To avoid double-counting of data, the study population in a given publication should not have been used in a previous study of those included in the review.

Data extraction (selection and coding)

Data will be extracted by three authors independently (TS, JM and JG). The following data will be collected: Sample sizes for the ruptured and asymptomatic intact AAA group, study design, software used to perform finite element analysis (FEA), PWS and PWRI estimates, AAA diameter, risk factors (including age, sex, smoking history, hypertension, diabetes, ischaemic heart disease [IHD], stroke, chronic obstructive pulmonary disease [COPD]) and systolic blood pressure. If relevant data is not reported in the publication, the corresponding will be contacted via email.

Assessment of methodological quality (risk of bias)

A quality assessment tool has been created to assess the risk of bias of the included studies. This tool was created by the authors and incorporates components of two widely reported quality assessment tools (Newcastle-Ottawa scale and Standard quality assessment criteria for evaluating primary research papers).[13, 14] A number of additional criteria relevant to this systematic review will also be included. This includes: criteria used to define AAA rupture; reporting of the method used to estimate PWS and PWRI and reproducibility; use of a standardised blood pressure in PWS and PWRI calculations (i.e. use of a single blood pressure measurement for all participants or omission of blood pressure in calculations); inclusion of CT scan prior to or after rupture (for ruptured cases); matching for AAA diameter between asymptomatic intact and ruptured cases; matching for other confounding variables. The overall risk of bias assessed within each study will be assessed as low, medium or high based on predefined criteria. Please see Supplementary Table 1 for further details regarding the quality assessment tool.

Approach to meta-analysis

Meta-analyses will be performed using inverse variance-weighted methods.[15] Standardised mean differences (SMD) with 95% confidence intervals (CI) will be calculated for both PWS and PWRI pooled estimates. Previous meta-analyses have identified there is no standardised method of computing PWS and PWRI and therefore SMDs will be calculated using random-effects weighting to account for likely inter-study methodological heterogeneity.[17] PWS outcome data will be converted from Newton Per Square Centimeter (N/cm^2) to kilopascal (kPa) where required to ensure that units are consistent for the meta-analysis.[16] Inter-study heterogeneity will be assessed using the I^2 index and values <25%, between 25-75% and >75% will be considered to represent low, moderate and high heterogeneity, respectively.[17] If PWS and PWRI are computed at a standardised blood pressure (i.e single blood pressure for all participants) this value will be used in the meta-analysis. If a standardised blood pressure

is not used, PWS and PWRI calculated at patient specific blood pressures will be used. To identify sources of heterogeneity a leave-one-out-sensitivity analysis will be planned. This will involve excluding individual studies one at a time and recalculating the pooled estimates for the remaining studies. Publication bias will be assessed by funnel plots comparing the summary estimate of each study to its precision (1/standard error) for outcomes that are reported in ≥5 studies.[21] Analyses will be conducted using Stata version 16.1 (StataCorp LP, College Station, Texas, USA). All statistical tests will be two-sided and a p-value of <0.05 will be considered significant.

Ethics and dissemination

Ethical approval is not required for this systematic review and meta-analysis as data already available in scientific databases will be analysed. The results of this review will be submitted for peer-reviewed publication and findings will be presented at conferences.

Table 1. Criteria used to perform the assessment of methodological quality.

Quality assessment				
Category	**Criteria**	**Response**		
		Yes	Partial	No
Clearly defined objective?	Clear hypothesis stated and tested. Objective easily identified in introductory section (or first paragraph of methods section). • Specifies all the following: purpose, subjects/target population, and the specific association(s)/descriptive parameter(s) under the investigation.	**X**		
	Vaguely/incompletely reported (e.g. "describe the effect of" or "examine the role of") OR substantial information must be collected from parts of the paper other than introduction/background/objective section.		**X**	

	Question or objective is not reported or is incomprehensible.			X
Prospective study design?	Hypothesis designed prior to selection of participants.	X		
	• Hypothesis and selection criteria designed after the occurrence of respective endpoints (e.g. AAA rupture). • Data collection conducted retrospectively after participants experienced outcomes of interest (e.g AAA rupture)			X
Selection criteria well described?	Selection strategy designed to obtain an unbiased sample of the relevant target population. • Methods for selection/recruitment/sampling reported in the study. • Definition of AAA adequately described (appropriate investigations used including ultrasound, angiography, or clinical assessment by a vascular specialist, or scheduled surgical repair of AAA etc.) • At least 3 of the specified exclusion criteria described [listed below]	X		
	Selection methods (and inclusion/exclusion criteria) are not completely described OR selection methods described elsewhere. • Included patients who have either an intact OR ruptured AAA AND no previous endovascular or open surgical repair • Available CT scan of non-ruptured AAA OR • Available CT scan of ruptured AAA at the time of rupture prior to any surgical intervention. • Excluded patients where there was no CT scan of the AAA available for analysis. • Excluded patients where poor quality of CT scans or technical factors (e.g. extreme vessel wall		X	

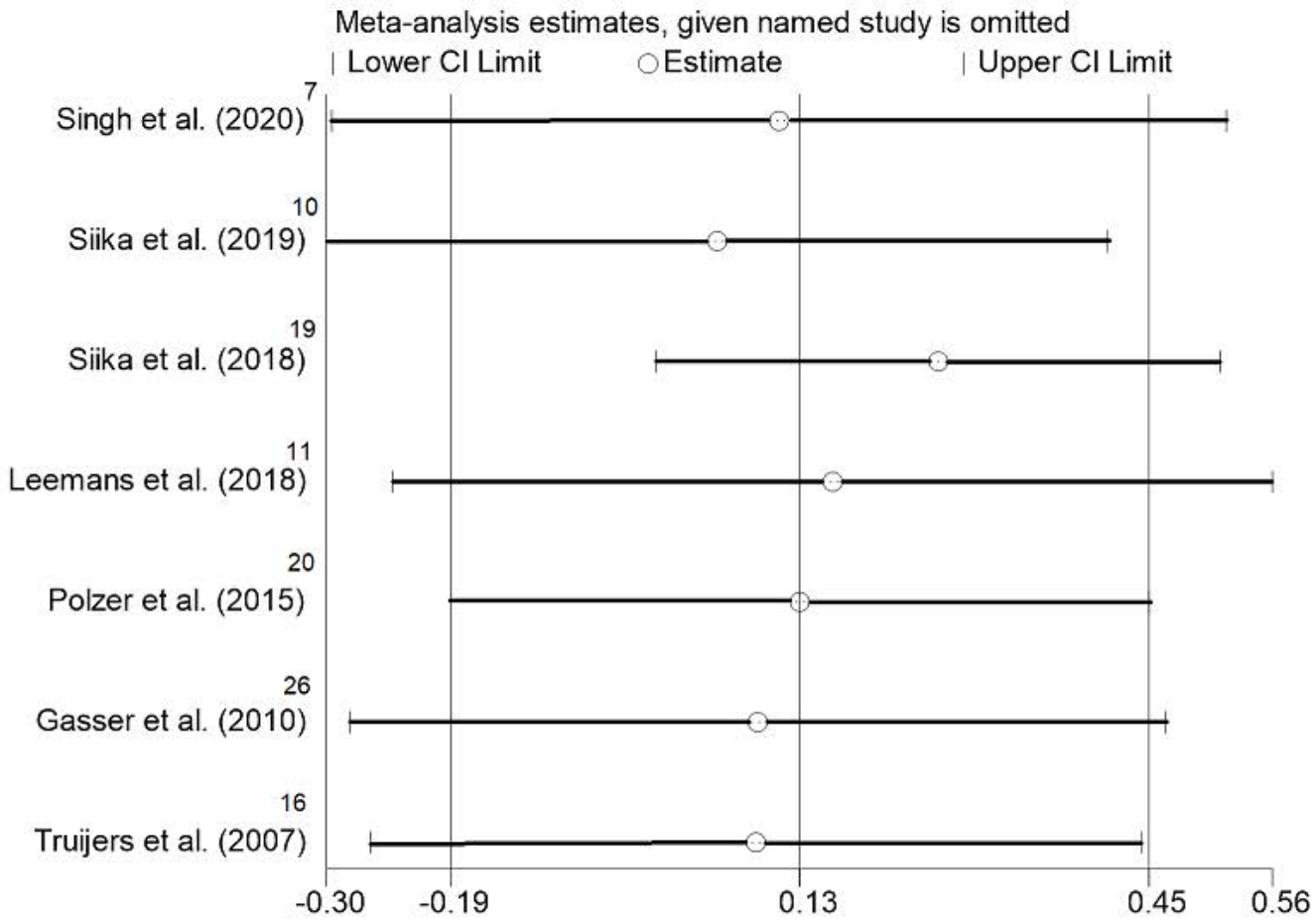
	angulation; contrast extravasation) precluded PWS/PWRI estimation.			
	No information provided; OR obviously inappropriate selection procedures.			X
Was an objective definition of AAA rupture utilised?	Appropriate definition of AAA rupture used including both of the following criteria: • Diagnosis of a ruptured AAA by a consultant vascular physician/surgeon • AAA associated with objective evidence of blood within the peritoneum identified on a CT scan or alternate imaging modality	X		
	Limited definition of ruptured AAA described: • Definition restricted to diagnosis by consultant vascular physician/surgeon OR • Definition restricted to diagnosis on imaging, but no description of radiological findings to support diagnosis of ruptured AAA • AAA rupture diagnosis based on electronic coding		X	
	No definition of ruptured AAA described			X
Assessment of outcome – Method of estimating PWS and PWRI well described	Method of estimating PWS and PWRI well described and: • Reproducibility evaluated and reported within paper AND • Reproducibility determined to be moderate-high	X		
	Method of estimating ILT well described: • no assessment of reproducibility reported OR • Reproducibility determined to be low		X	

	Method of estimating ILT not described OR limited description provided AND no assessment of reproducibility made			X
Standardised blood pressure used for PWS/PWRI measurements?	A standard blood pressure (e.g 140/80 mmHg) was used to compute PWS and PWRI measurements for all patients	X		
	Patient specific blood pressure (at the time of CT scan) was used to perform PWS/PWRI measurements			X
Sample size calculation/estimation reported in methodology.	Details of sample size calculation/estimation reported in methodology	X		
	Required sample size reported, but no details on how this was calculated/estimated		X	
	No sample size calculation/estimation conducted			X
What was the sample size?	<50 OR 50-100 OR >100	N/A	N/A	N/A
	Not reported	N/A	N/A	N/A
Did participants with AAA rupture undergo a CT scan prior rupture and after rupture	For all patients, CT data were present both before and during the rupture event.	X		
				X
Were participant characteristics adequately described?	Sufficient relevant baseline information clearly characterising the participants are provided (or reference to previously published baseline data is provided). Includes at least 5 of the following: • Age, Gender, AAA diameter (mm), smoking, HTN, diabetes, coronary artery disease, statin prescription, aspirin prescription.	X		
	Poorly defined criteria or incomplete relevant baseline / demographic information (e.g. Information on likely confounders not reported). • Includes less than 5 of the characteristics reported above.		X	
	No baseline / demographic information provided.			X

Were participants in the ruptured and intact AAA groups matched for diameter?	To provide an objective comparison of ruptured and intact AAAs, both groups were matched for maximum diameter.	X		
				X
Was participants matched for other confounding factors for AAA rupture?	Matching undertaken or adjustments are made for at least 2 of the following variables: • Age, sex, HTN, smoking and diabetes	X		
	Did not meet the criteria above OR did not specify which variables were adjusted or matched for		X	
	No adjustment or matching undertaken for confounding factors other than maximum diameter			X

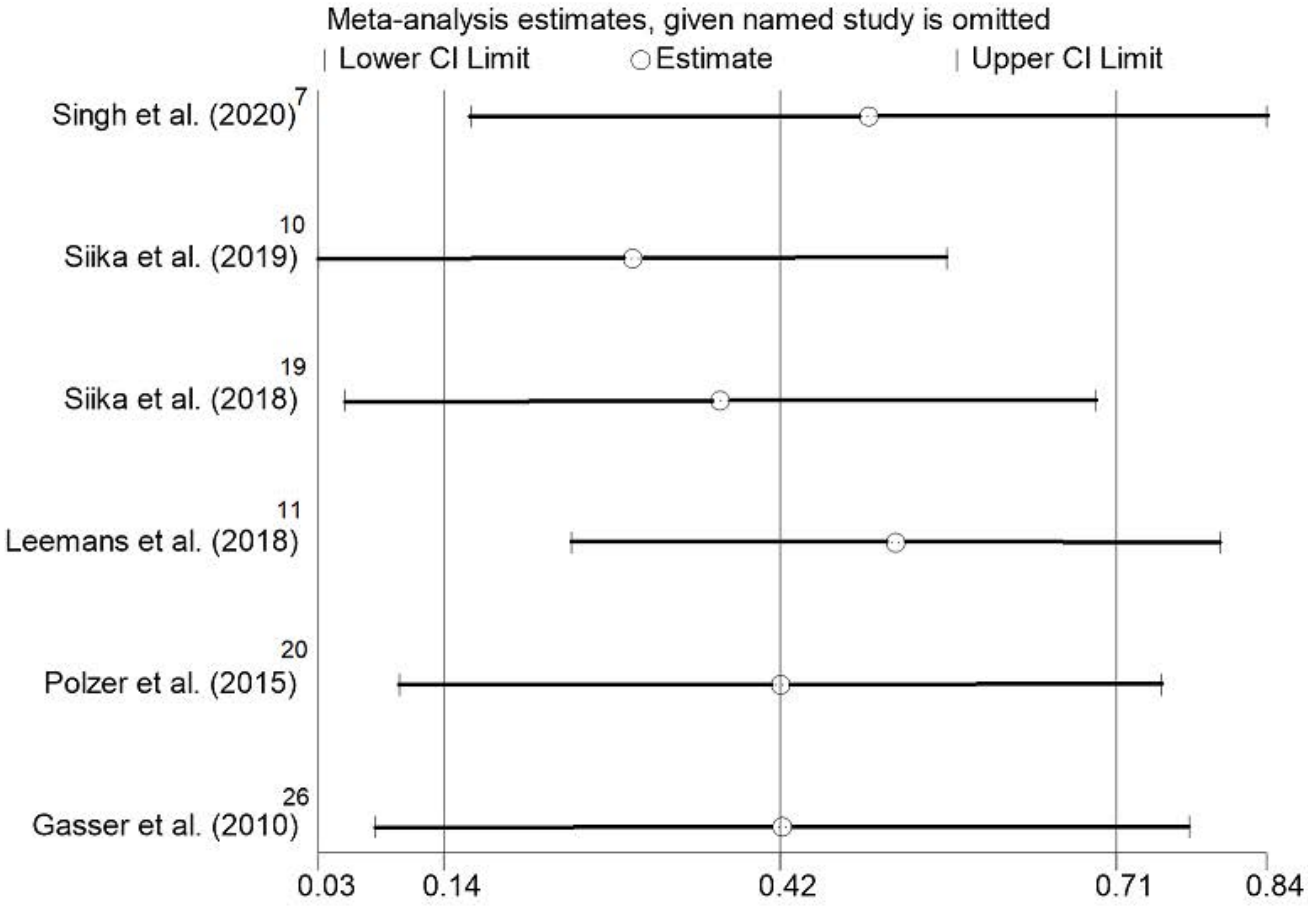
Overall risk of bias within study	**Criteria**
Low	>10 criteria with 'Yes' response and sample size > 100
Medium	>5 and ≤10 criteria with 'Yes' response and sample size between 50-100
High	≤5 criteria 'Yes' response and sample size between <50 or between 50-100.

Figure 1. Leave-one-out sensitivity analysis for meta-analysis of PWS in asymptomatic intact and ruptured AAAs.



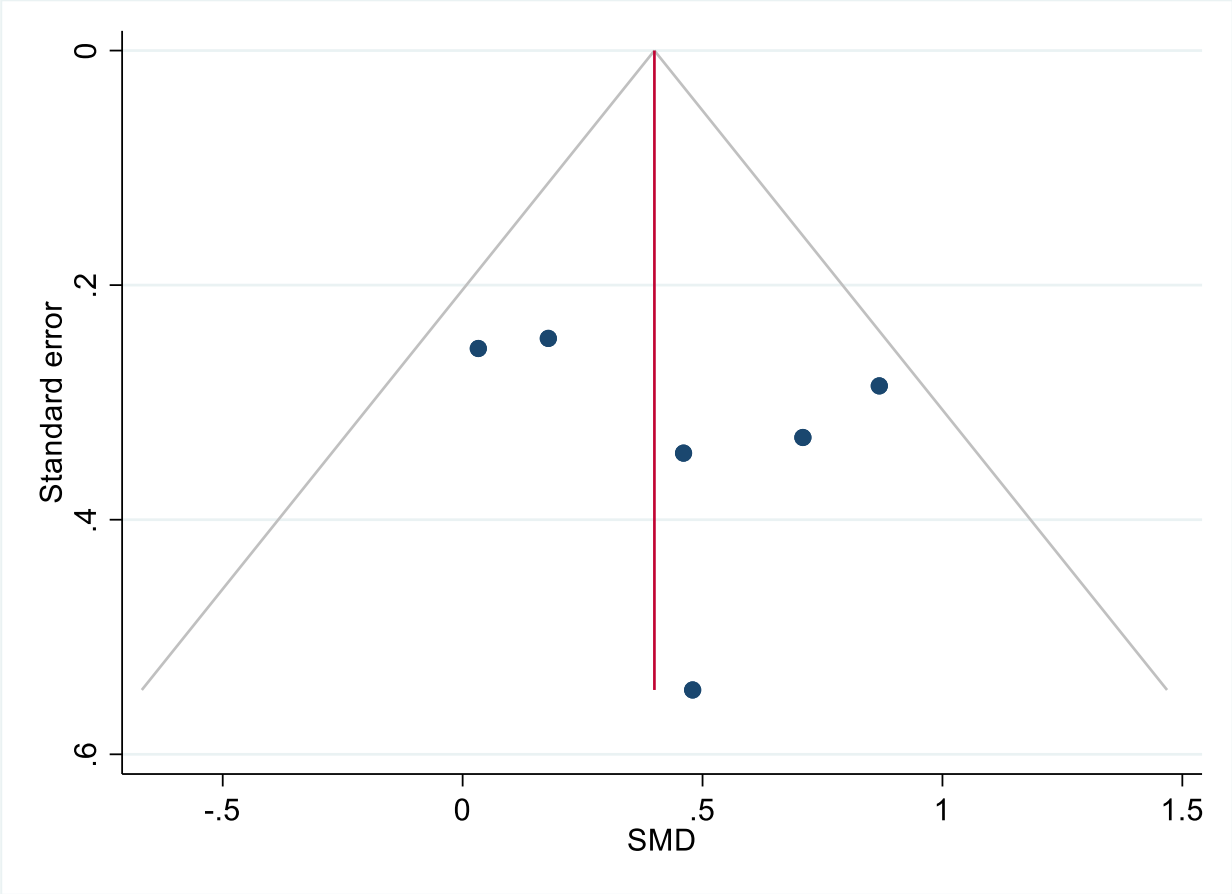
SMD, standardised mean difference; CI, confidence intervals. Indicates the pooled results with the corresponding study excluded from the analysis.

Figure 2. Leave-one-out sensitivity analysis for meta-analysis of PWRI in asymptomatic intact and ruptured AAAs.



SMD, standardised mean difference; CI, confidence intervals. Indicates the pooled results with the corresponding study excluded from the analysis.

Figure 3. Funnel plot with pseudo 95% CIs of the difference in PWRI between ruptured and asymptomatic intact AAAs.



SMD, standardised mean difference; PWRI, peak wall rupture index; CI, confidence intervals.

Appendix C: Supporting files, figures and tables for Chapter 5

Table 1. PWS and PWRI of participants with small AAAs who experienced an AAA event and those who did not, using a standardized blood pressure of 140/80mmHg.

	No AAA event (n=165)	**AAA event (n=45)**	**P-value**
PWS (kPa)	158.9 (143.6, 180.5)	179.4 (153.3, 202.2)	**<0.001**
PWRI	0.373 (0.311, 0.439)	0.450 (0.360, 0.566)	**<0.001**

PWS, peak wall stress; PWRI, peak wall rupture index. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test. P-values highlighted in bold indicate significant differences.

Table 2. Association between PWS and PWRI with AAA events in individuals with small AAA, using a standardized blood pressure of 140/80mmHg.

	AAA events (AAA rupture or repair)		
	Hazard ratio (HR) †	**95% CI**	**p-value**
	Unadjusted analysis		
PWS (kPa)	1.79	1.45, 2.22	**<0.001**
PWRI	1.95	1.55, 2.46	**<0.001**

	Adjusted analysis		
PWS (kPa)	1.46	1.11, 1.92	**0.007**
PWRI	1.71	1.27, 2.29	**<0.001**

*Adjusted for variables that were found to be different (p<0.100) between participants who had events and those who did not have events (i.e AAA diameter, statin prescription, and age); † Hazard ratios expressed per 1 standard deviation increase in PWS or PWRI.

Table 3. Discrimination and reclassification using PWS and PWRI for AAA events, using a standardized blood pressure of 140/80mmHg.

Models	**NRI (95% CI)**	**P-value**
AAA diameter (reference)	-	-
AAA diameter + PWS	0.18 (-0.15, 0.51)	0.291
AAA diameter + PWRI	0.44 (0.11, 0.77)	**0.008**
AAA diameter + clinical risk factors + PWS	0.21 (-0.12, 0.54)	0.212
AAA diameter + clinical risk factors + PWRI	0.50 (0.17, 0.83)	**0.003**

NRI, net reclassification index; CI, confidence intervals. Clinical risk factors included diabetes and current smoking.

Acknowledgements. Full list of names of TEDY principal investigators and trial coordinators.

Australia

Gosford Vascular Services, New South Wales

Principal Investigator Dr Bernie Bourke

Trial Coordinator Dr Michael Bourke

Queen Elizabeth Hospital, Adelaide, South Australia

Principal Investigator Professor Robert Fitridge

Trial Coordinators Ms Ruth Battersby and Dr. Prue Cowled

Royal Brisbane and Women's Hospital, Queensland

Principal Investigator Professor Jason Jenkins

Trial Coordinator Dr Sophie Rowbotham and Dr Brad Stefanovic

The Townsville University Hospital and the Mater Hospital Pilmico, Queensland

Principal Investigators Professor Jonathan Golledge and Dr Frank Quigley

Trial Coordinators Ms Jenna Pinchbeck and Ms Barbara Bradshaw

The Netherlands

Trial Coordinator Ms Stephanie Tomee

Leiden University Medical Centre, Leiden

Principal Investigators Associate Professor Jan Lindeman and Prof. Jaap F. Hamming

Jeroen Bosch Hospital, Hertogenbosch

Principal Investigator Dr. Jan Willem Hinnen

Deventer ziekenhuis

Principal Investigator Dr Robert B van Tongeren

Haga Ziekenhuis, Den Haag

Principal Investigator Dr. Jan J Wever

Haaglanden Medisch Centrum, Den Haag

Principal Investigator Dr. Daniël Eefting

Sint Franciscus Gasthuis en Vlietland, Rotterdam

Principal Investigator Dr. Jerome P van Brussel,

Antonius Ziekenhuis Nieuwegein

Principal Investigator Dr. Jean-Paul de Vries (current address: University Medical Center Groningen)

Elisabeth Tweesteden Ziekenhuis, Tilburg

Principal Investigator Dr. Patrick W. Vriens

The United States of America

Veterans Administration Hospital and Stanford University, Palo Alto, California

Principal Investigators Professor Ron Dalman and Dr. Oliver A. Aalami

Trial Coordinator Ms Lori McDonnell

Appendix D: Supporting files, figures and tables for Chapter 6

Table 1. Comparison of clinical characteristics between patients from the TEDY trial and patients included in the current study.

	Current study (n=124)	TEDY trial (n=207)	P-value
Maximum orthogonal diameter (mm)	40.2 [36.8-43.2]	40.8 [37.2-43.8]	0.241
Age	74.8 [69.3-80.0]	73.7 [67.7-79.4]	0.152
Sex	109 (88)	183 (88)	0.891
Ever smoking	114 (92)	192 (93)	0.785
Hypertension	52 (42)	88 (43)	0.918
Dyslipidaemia	89 (72)	158 (76)	0.357
Diabetes	16 (13)	23 (11)	0.624
CVD*	68 (55)	107 (52)	0.579
COPD	33 (27)	51 (25)	0.689
Aspirin	70 (56)	114 (55)	0.807
Other anti-platelet agent	13 (10)	13 (6)	0.169
Warfarin	6 (5)	9 (4)	0.835
NOAC	5 (4)	7 (3)	0.759
Statin	79 (64)	135 (65)	0.781
Calcium channel blocker	21 (17)	26 (13)	0.270
Beta blocker	24 (19)	45 (22)	0.605
Metformin	10 (8)	15 (7)	0.785
Systolic blood pressure (mmHg)	137 [125-150]	137 [125-148]	0.553
Diastolic blood pressure (mmHg)	78 [71-85]	79 [72-85]	0.587

Systolic blood pressure >140mmHg	51 (41)	79 (38)	0.593

* CVD, Cardiovascular disease was defined by a documented history of coronary heart disease, stroke or peripheral artery disease. COPD, Chronic obstructive pulmonary disease; NOAC, Non-Vitamin K antagonist oral anticoagulants.

Ever smoking as defined as current or former smoking. Continuous data are presented as median [interquartile range] and were compared using Mann-Whitney U test. Nominal data are presented as number (%) and were compared using Pearson's $\chi 2$ test. P-values highlighted in bold indicate significant differences.

Table 2. Adherence to allocated medication.

	Telmisartan (n=65)		**Placebo (n=59)**	
Time since randomisation	**Number assessed (%)**	**Taking ≥80% tablets (%)**	**Number assessed (%)**	**Taking ≥80% tablets (%)**
3 months	53 (82)	50/53 (94)	48 (81)	45/48 (94)
6 months	53 (82)	48/53 (91)	48 (81)	46/48 (96)
12 months	54 (83)	50/54 (93)	48 (81)	45/48 (94)
18 months	50 (77)	47/50 (94)	40 (68)	36/40 (90)
24 months	60 (92)	55/60 (92)	48 (81)	43/48 (90)

Full list of names and affiliations of TEDY investigators

Independent trial randomisation

Chris Reid, Monash and Curtin University, Australia

Data and safety monitoring board

John Walsh, South Australia

Andrew Tonkin, Victoria

Cindy Sealey, Queensland

Trial executive committee

Jonathan Golledge, Queensland

Rene Jaeggi, Queensland

Paul Norman, Western Australia

Sophie Rowbotham, Queensland

Jenna Pinchbeck, Queensland

Data quality oversight and checking

Cindy Sealey, Queensland

Rene Jaeggi, Queensland

Tejas Singh, Queensland

Joseph Moxon, Queensland

Jonathan Golledge, Queensland

Data analysis

Dylan Morris, Queensland

Core Imaging Laboratory

Jenna Pinchbeck, Queensland

Georgina Anderson, Queensland

Recruitment sites

Australia

Gosford Vascular Services, New South Wales

Principal Investigator Dr Bernie Bourke

Trial Coordinator Dr Michael Bourke

Queen Elizabeth Hospital, Adelaide, South Australia

Principal Investigator Professor Robert Fitridge

Trial Coordinators Ms Ruth Battersby and Dr. Prue Cowled

Royal Brisbane and Women's Hospital, Queensland

Principal Investigator Professor Jason Jenkins

Trial Coordinator Dr Sophie Rowbotham and Dr Brad Stefanovic

The Townsville University Hospital and the Mater Hospital Pilmico, Queensland

Principal Investigators Professor Jonathan Golledge and Dr Frank Quigley

Trial Coordinators Ms Jenna Pinchbeck and Ms Barbara Bradshaw

The Netherlands

Trial Coordinator Ms Stephanie Tomee

Leiden University Medical Centre, Leiden

Principal Investigators Associate Professor Jan Lindeman and Prof. Jaap F. Hamming

Jeroen Bosch Hospital, Hertogenbosch

Principal Investigator Dr. Jan Willem Hinnen

Deventer ziekenhuis

Principal Investigator Dr Robert B van Tongeren

Haga Ziekenhuis, Den Haag

Principal Investigator Dr. Jan J Wever

Haaglanden Medisch Centrum, Den Haag

Principal Investigator Dr. Daniël Eefting

Sint Franciscus Gasthuis en Vlietland, Rotterdam

Principal Investigator Dr. Jerome P van Brussel,

Antonius Ziekenhuis Nieuwegein

Principal Investigator Dr. Jean-Paul de Vries (current address: University Medical Center Groningen)

Elisabeth Tweesteden Ziekenhuis, Tilburg

Principal Investigator Dr. Patrick W. Vriens

The United States of America

Veterans Administration Hospital and Stanford University, Palo Alto, California

Principal Investigators Professor Ron Dalman and Dr. Oliver A. Aalami

Trial Coordinator Ms Lori McDonnell

Appendix E: Published papers as a result of this PhD

Original article

Comparison of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms

T. P. Singh[1,3], J. V. Moxon[1,2], V. Iyer[1,3,4], T. C. Gasser[5], J. Jenkins[4] and J. Golledge[1,2,3]

[1]Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, and [2]Australian Institute of Tropical Health and Medicine, James Cook University, and [3]Department of Vascular and Endovascular Surgery, Townsville University Hospital, Townsville, and [4]Department of Vascular and Endovascular Surgery, Royal Brisbane and Women's Hospital Brisbane, Queensland, Australia, and [5]KTH Solid Mechanics, Department of Engineering Mechanics, KTH Royal Institute of Technology, Stockholm, Sweden

Correspondence to: Professor J. Golledge, Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Queensland 4811, Australia (e-mail: jonathan.golledge@jcu.edu.au)

Background: Previous studies have suggested that finite element analysis (FEA) can estimate the rupture risk of an abdominal aortic aneurysm (AAA); however, the value of biomechanical estimates over measurement of AAA diameter alone remains unclear. This study aimed to compare peak wall stress (PWS) and peak wall rupture index (PWRI) in participants with ruptured and asymptomatic intact AAAs.

Methods: The reproducibility of semiautomated methods for estimating aortic PWS and PWRI from CT images was assessed. PWS and PWRI were estimated in people with ruptured AAAs and those with asymptomatic intact AAAs matched by orthogonal diameter on a 1:2 basis. Spearman's correlation coefficient was used to assess the association between PWS or PWRI and AAA diameter. Independent associations between PWS or PWRI and AAA rupture were identified by means of logistic regression analyses.

Results: Twenty individuals were included in the analysis of reproducibility. The main analysis included 50 patients with an intact AAA and 25 with a ruptured AAA. Median orthogonal diameter was similar in ruptured and intact AAAs (82·3 (i.q.r. 73·5–92·0) *versus* 81·0 (73·2–92·4) mm respectively; $P = 0·906$). Median PWS values were 286·8 (220·2–329·6) and 245·8 (215·2–302·3) kPa respectively ($P = 0·192$). There was no significant difference in PWRI between the two groups ($P = 0·982$). PWS and PWRI correlated positively with orthogonal diameter (both $P < 0·001$). Participants with high PWS, but not PWRI, were more likely to have a ruptured AAA after adjusting for potential confounders (odds ratio 5·84, 95 per cent c.i. 1·22 to 27·95; $P = 0·027$). This association was not maintained in all sensitivity analyses.

Conclusion: High aortic PWS had an inconsistent association with greater odds of aneurysm rupture in patients with a large AAA.

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Correspondence

Response to 'peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms'

T. P. Singh [1,2], J. V. Moxon[1,3], T. C. Gasser[4] and J. Golledge [1,2,3,*]

[1]Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia
[2]The Department of Vascular and Endovascular Surgery, The Townsville Hospital, Townsville, Queensland, Australia
[3]The Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, Queensland, Australia
[4]KTH Solid Mechanics, Department of Engineering Mechanics, KTH Royal Institute of Technology, Stockholm, Sweden

*Correspondence to: Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia (e-mail: jonathan.golledge@jcu.edu.au)

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SYSTEMATIC REVIEW AND META-ANALYSIS

Systematic Review and Meta-Analysis of Peak Wall Stress and Peak Wall Rupture Index in Ruptured and Asymptomatic Intact Abdominal Aortic Aneurysms

Tejas P. Singh, MBBS, MPH; Joseph V. Moxon, PhD; T. Christian Gasser, PhD; Jonathan Golledge, MChir

BACKGROUND: Prior studies have suggested aortic peak wall stress (PWS) and peak wall rupture index (PWRI) can estimate the rupture risk of an abdominal aortic aneurysm (AAA), but whether these measurements have independent predictive ability over assessing AAA diameter alone is unclear. The aim of this systematic review was to compare PWS and PWRI in participants with ruptured and asymptomatic intact AAAs of similar diameter.

METHODS AND RESULTS: Web of Science, Scopus, Medline, and The Cochrane Library were systematically searched to identify studies assessing PWS and PWRI in ruptured and asymptomatic intact AAAs of similar diameter. Random-effects meta-analyses were performed using inverse variance-weighted methods. Leave-one-out sensitivity analyses were conducted to assess the robustness of findings. Risk of bias was assessed using a modification of the Newcastle-Ottawa scale and standard quality assessment criteria for evaluating primary research papers. Seven case-control studies involving 309 participants were included. Meta-analyses suggested that PWRI (standardized mean difference, 0.42; 95% CI, 0.14–0.70; P=0.004) but not PWS (standardized mean difference, 0.13; 95% CI, −0.18 to 0.44; P=0.418) was greater in ruptured than intact AAAs. Sensitivity analyses suggested that the findings were not dependent on the inclusion of any single study. The included studies were assessed to have a medium to high risk of bias.

CONCLUSIONS: Based on limited evidence, this study suggested that PWRI, but not PWS, is greater in ruptured than asymptomatic intact AAAs of similar maximum aortic diameter.

Key Words: abdominal aortic aneurysm ■ biomechanics ■ computed tomography ■ finite element analysis ■ imaging ■ meta-analysis ■ systematic review

Abdominal aortic aneurysm (AAA) rupture is estimated to be responsible for 200 000 deaths annually worldwide.[1,2] AAA rupture is thought to occur when the hemodynamic forces exceed the aortic wall strength.[1,3] In clinical practice, maximum AAA diameter is the main measure used to estimate rupture risk and select patients for elective repair.[1] Current guidelines recommend elective repair of asymptomatic large AAAs (maximum aortic diameter ≥50 mm in women and ≥55 mm in men).[1,4,5] Approximately 1% to 2% of small asymptomatic AAAs rupture each year[4] and some large AAAs remain stable during a patient's lifetime,[6] suggesting that diameter is an imperfect measure of rupture risk.

Biomechanical imaging may provide a more precise means to estimate AAA rupture risk and select patients for repair. Finite element analysis (FEA) can noninvasively estimate the maximum tensile stress

Correspondence to: Jonathan Golledge, MChir, FRACS, Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Queensland 4811, Australia. E-mail: jonathan.golledge@jcu.edu.au

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CLINICAL PERSPECTIVE

What Is New?

- Prior studies have suggested that aortic peak wall stress and peak wall rupture index can predict abdominal aortic aneurysm rupture. However, the value of measuring peak wall stress and peak wall rupture index over simply measuring maximum abdominal aortic aneurysm diameter is unclear.
- This systematic review and meta-analysis suggests that peak wall rupture index, but not peak wall stress, is greater in ruptured than asymptomatic intact abdominal aortic aneurysms of similar diameter.

What Are the Clinical Implications?

- The measurement of peak wall rupture index may add to that of maximum aortic diameter in assessing the risk of abdominal aortic aneurysm rupture.

Nonstandard Abbreviations and Acronyms

FEA	finite element analysis
PWRI	peak wall rupture index
PWS	peak wall stress
SMD	standardized mean differences

within the AAA wall (peak wall stress; PWS) and the maximum ratio between wall stress and the estimated local wall strength (peak wall rupture index; PWRI).[3] Semiautomated systems have been developed to enable clinicians without engineering backgrounds to perform FEA using computed tomography (CT) scans that are routinely performed to assess people with AAA (Figure 1).[3,7] Thus, it would be feasible to use PWS and/or PWRI in clinical practice if these measures were shown to be independent predictors of AAA rupture. Currently, however, the value of measuring PWS and PWRI over simply measuring maximum AAA diameter is unclear.

Previous meta-analyses[3,8] have suggested that PWS is greater in patients with ruptured than intact AAAs; however, the generalizability of this finding is unclear owing to a number of limitations. These included lack of adjustment or matching for aortic diameter,[3] inclusion of symptomatic AAAs mixed with ruptured AAAs,[8] and small sample sizes.[9] These limitations have been addressed in more recent studies that have been reported after the publication of the most recent meta-analysis,[7,8] suggesting that higher quality data are now available for an updated meta-analysis. Furthermore, PWRI has been suggested by one,[10] but not another study,[11] to be a superior measure of rupture risk than PWS. No meta-analysis comparing PWRI in ruptured and intact AAA has been reported.[3,8] The aim of this systematic review and meta-analysis was to provide an up-to-date pooled analysis of prior studies that compared PWS and PWRI in patients with ruptured and asymptomatic intact AAA of similar diameter.

METHODS

Literature Search and Inclusion Criteria

The data that support the findings of this study are available from the corresponding author upon reasonable request. This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12] A study protocol for this systematic review was designed (Data S1) and was not preregistered with any database. A literature search was performed using the following databases: Web of Science (via Institute for Scientific Information Web of Knowledge; 1965), Scopus (1966), Medline (via OvidSP, 1966), and The Cochrane Library to identify case-control studies investigating PWS in patients with ruptured and diameter matched asymptomatic intact AAAs. The following search terms were applied: "peak wall stress" OR "peak wall rupture index" OR "rupture potential index" AND "abdominal aortic aneurysm." The search was performed in October 2020 without language restrictions by one author (T.P.S.). Reference lists of primary articles and reviews were searched to increase the yield of relevant publications. Titles and abstracts were screened to identify relevant studies. If the suitability of an article was uncertain, the full text was reviewed. For inclusion in the meta-analysis studies needed to have compared PWS or PWRI in asymptomatic intact AAAs and ruptured AAAs of similar diameter (within 3 mm mean difference between groups). Studies in which it was not possible to separate symptomatic from ruptured AAAs were excluded.

Data Extraction and Risk of Bias of the Included Studies

Data were extracted from included studies independently by 3 authors (T.S., J.M., and J.G.). The following data were collected: sample sizes for the ruptured and intact AAA group; study design; software used to perform FEA, PWS, and PWRI estimates; AAA diameter; risk factors (including age, sex, smoking history, hypertension, diabetes mellitus, ischemic heart disease;

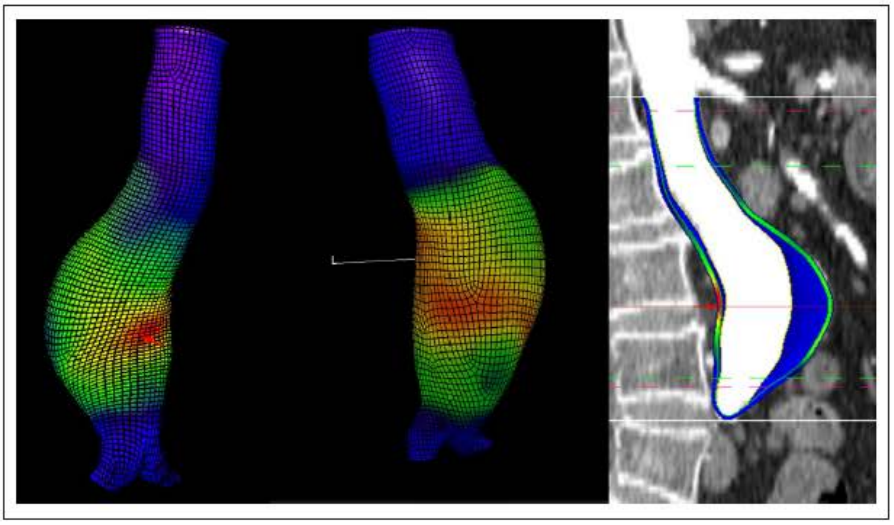

Figure 1. Examples of 3-dimensional segmentation produced using finite element analysis from computed tomography images of patients with AAA.
The red areas indicate areas of high aortic wall stress. AAA indicates abdominal aortic aneurysm.

stroke; chronic obstructive pulmonary disease); and systolic blood pressure. If relevant data were not reported in the publication, the corresponding author was contacted for this information. The risk of bias was assessed independently by 3 authors (T.S., J.M., and J.G.). A quality assessment tool was designed to assess the risk of bias of the included studies adapted from 2 previously reported tools (Newcastle-Ottawa scale and Standard Quality Assessment Criteria for Evaluating Primary Research Papers).[13,14] A number of additional aspects of the included studies relevant to this systematic review were also assessed including criteria used to define AAA rupture, method used to estimate PWS and PWRI and reproducibility reported, use of a standardized blood pressure in PWS and PWRI calculations (ie, use of a single blood pressure measurement for all participants or omission of blood pressure in calculations), inclusion of CT scan before or after rupture (for ruptured cases), matching for AAA diameter between asymptomatic intact and ruptured cases, and matching for other confounding variables. The overall risk of bias assessed within each study was assessed as low, medium, or high based on predefined criteria. Details regarding the quality assessment criteria can be found in Table S1.

Statistical Analysis

Meta-analysis was performed using inverse variance-weighted methods[15] in order to calculate standardized mean differences (SMD) with 95% (CI. PWS outcome data were converted from newton per square centimeter (N/cm^2) to kilopascal (kPa) where required.[16] Because of anticipated interstudy heterogeneity in methods and biomechanical analyses, SMDs were calculated using random-effects models.[17] Interstudy heterogeneity was assessed using the I^2 index and values <25%, between 25% to 75%, and >75% were considered to represent low, moderate, and high heterogeneity, respectively.[18] If PWS and PWRI were computed at a standardized blood pressure (ie, same blood pressure for all participants) this value was used in the meta-analysis. One study calculated PWS and PWRI using a standardized blood pressure of 140/80 mm Hg for the main analysis and sensitivity analyses were performed using a lower (120/70 mm Hg) and higher (160/90 mm Hg) blood pressure.[7] For that study, results from the main analysis were used in the meta-analysis. If studies did not use a standardized blood pressure, PWS and PWRI values computed with patient-specific blood pressures were used.[11,19,20] In one study the SD of PWS was not reported and this was derived from the SE using Review Manager version 5.4 (The Cochrane Collaboration) as previously described.[3,17] To identify sources of heterogeneity a leave-one-out-sensitivity analysis was performed by excluding individual studies one at a time and recalculating the pooled estimates for the remaining studies. Publication bias was assessed by funnel plots comparing the summary estimate of each study to its precision (1/SE) for outcomes that were reported in ≥5 studies.[21] Analyses were conducted using Stata version 16.1 (StataCorp LP, College Station, TX). All statistical tests were 2-sided and a P value of <0.05 was considered significant.

RESULTS

Study Identification

The initial database searches identified 836 studies after removal of duplicates. After title and abstract screening, the full texts of 20 studies were assessed against the inclusion criteria. Thirteen articles were excluded after full text review. Common reasons for exclusion included mismatch in AAA diameter between ruptured and intact AAAs,[22] inclusion of symptomatic but not ruptured AAAs[22–24] and lack of comparison of PWS or PWRI between ruptured and intact AAAs.[25] Ultimately 7 studies were included (Figure 2).

Study Characteristics

A total of 309 participants with ruptured (n=139) and asymptomatic intact (n=170) AAAs of similar aortic diameter were investigated in the 7 included studies.[7,10,11,16,19,20,26] All studies were of case-control design and sample sizes ranged between 14 and 75 (see Table 1).[7,10,11,16,19,20,26] Three studies were performed in Sweden[10,19,26] and the remaining studies were conducted in Australia,[7] Spain,[11] Czechia,[20] and The Netherlands.[16] Six studies used the A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria) platform[7,10,11,19,20,26] and 1 study used ABAQUS v.6.5 (Hibbit, Karlsson and Sorensen, Inc, Pawtucket, RI) for FEA.[16] One study used a combination of the A4 Clinics 5.0 and the ANSYS (Ansys Inc.) platforms.[20] The inclusion criteria varied between studies. In 4 studies AAA cases were included only if the available CT scan satisfied specific imaging criteria,[7,11,19,26] whereas other studies did not report this as a requirement for inclusion.[10,16,20] The imaging criteria used to select CT scans differed between studies. One study specifically reported excluding patients with juxtarenal or thoracoabdominal aneurysms and patients with ruptured AAAs that had massive contrast extravasation.[7] Another study included only participants

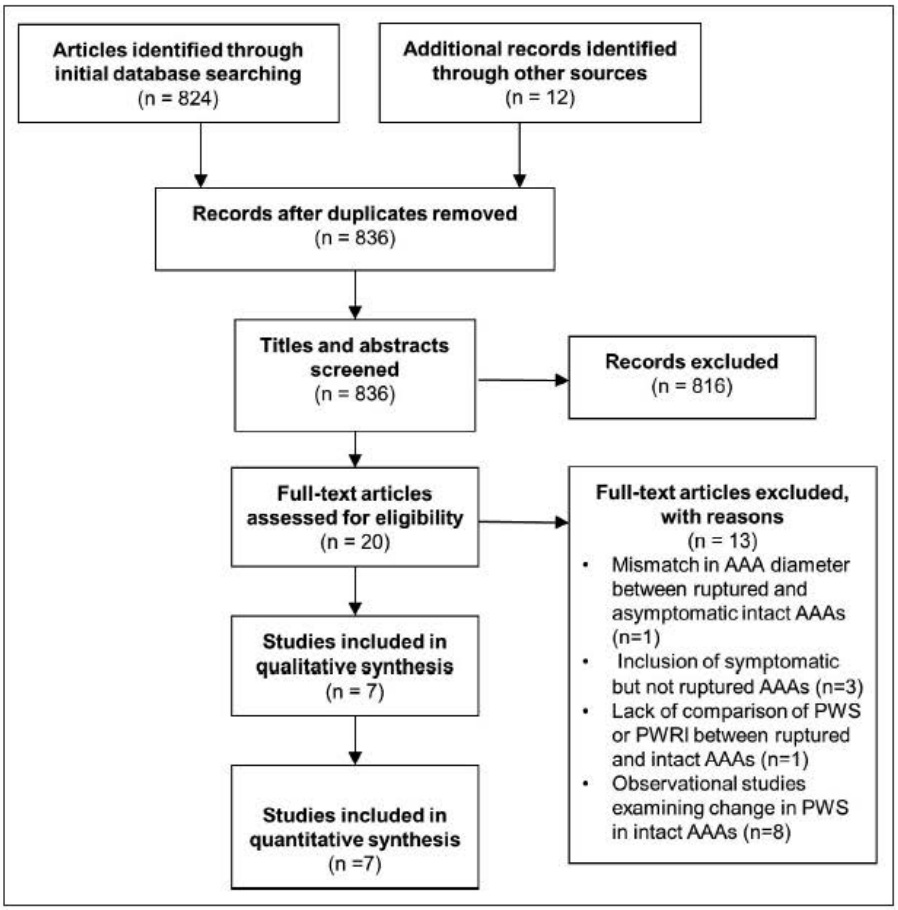

Figure 2. PRISMA diagram describing the literature search.
AAA indicates abdominal aortic aneurysm; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PWRI, peak wall rupture index; and PWS, peak wall stress.

Table 1. Characteristics of Case Control Studies Comparing PWS and PWRI Between Ruptured and Asymptomatic Intact AAAs of Similar Aortic Diameter

Study	Total Sample Size	Sample Size (Asymptomatic Intact: Ruptured)*	Biomechanical Measurements	Software Used	Variables That Were Balanced Between Asymptomatic iAAA and rAAAs	Blood Pressure Used in PWS or PWRI Analysis	Reproducibility of Biomechanical Measurements
Singh et al (2020)[7]	75	75 (50:25)	PWS, PWRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria).	Diameter and blood pressure	Standardized blood pressure (140/80 mm Hg) used and sensitivity analysis with lower and higher blood pressures (120/70 mm Hg and 160/90 mm Hg) for all participants	Intraobserver reproducibility; CV 2.7% and 4.7% for PWS in iAAA and rAAAs respectively
Silka et al (2019)[10]	283	60 (40:20)	PWS, PWRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria)	Diameter, sex, age and blood pressure	Blood pressure omitted from analyses	NR
Silka et al (2018)[19]	90	43 (15:28)	PWS, PWRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria)	Diameter	Patient-specific blood pressure; timing of blood pressure measurement in relation to CT scan not reported	Intraobserver reproducibility; Mean % difference of 6.86±6.46 and 7.70±6.26 for PWS and PWRI respectively. Interobserver reproducibility; mean % difference 7.09±6.16 and 9.47±8.18†
Leemans et al (2018)[11]	175	62 (31:31)	PWS, PWRI, rupture risk equivalent diameter	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria).	Diameter	Patient-specific blood pressure obtained from the last measurement in a noncritical setting within 1 year before presentation	NR
Polzer et al (2015)[20]	14	14 (7:7)	PWRI and probabilistic rupture risk index	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria) and ANSYS (Ansys Inc.)	Diameter	Patient-specific blood pressure; timing of blood pressure measurement not reported	Intraobserver reproducibility; CV <5.5% for PWS and PWRI in participants with iAAAs. Interobserver reproducibility; intraclass correlation coefficient 0.98 (range 0.97–0.99) for PWS and PWRI†
Gasser et al (2010)[28]	50	35 (17:18)	PWS, PWRI	A4 Clinics 5.0 (VASCOPS GmbH, Graz, Austria)	Diameter and blood pressure	Participants were matched for blood pressure between groups. Blood pressure measurements obtained in the same admission in which CT scan was performed or earlier hospital or healthcare center visit (for ruptured cases)	NR
Truijers et al (2007)[18]	30	20 (10:10)	PWS	ABAQUS v.6.5 (Hibbit, Karlsson and Sorensen, Inc, Pawtucket, RI)	Diameter and blood pressure	Patient-specific blood pressure obtained from a year before CT scan; Sensitivity analysis also performed in which a standardized blood pressure (120 mm Hg systolic) was used	NR

AAA indicates abdominal aortic aneurysm; CT, computed tomography; CV, coefficient of variation; iAAA, asymptomatic intact AAA; NR, not reported; PWRI, peak wall rupture index; PWS, peak wall stress; and rAAA, ruptured AAA.

*Sample sizes reported are reflective of the cases and control that were similar in AAA diameter and excluded symptomatic AAA cases.

†Reported in an external publication.

with CT scans in which the aorta was visible from the renal arteries to the iliac bifurcation and the lumen was distinguishable from intraluminal thrombus.[11] One study required CT scans to have a sufficiently high out-of-plane image resolution with good visibility of the exterior aneurysm surface.[26] In another study, only participants with good quality CT scans were included; however, the criteria used to determine this were not reported.[19] All studies either matched cases and controls for aortic diameter or included cases and controls with similar mean aortic diameter (within 3 mm difference; see Tables 1 and 2). Three studies used a standardized blood pressure to compute PWS or PWRI in all participants,[7] or matched cases and controls for blood pressures,[26] or omitted blood pressure from calculations.[10] The remaining studies used patient-specific blood pressures although the relationship between their measurement and the timing of CT scan varied across studies (Table 1). For ruptured AAA cases, blood pressure readings before rupture were frequently used.[11,16,26] For participants with asymptomatic intact AAAs, measurements were either taken from the same hospital visit[26] in which the CT scan was performed or from a prior visit.[11,16] The timing of blood pressure measurements in relation to CT scans were not reported in 2 studies.[19,20] Three studies reported the reproducibility of their FEA estimates (Table 1).[7,19,20]

Participant Characteristics

The participant characteristics are summarized in Table 2. The average age of participants ranged between 70 and 79 years.[7,10,16,19,26] There were no significant differences in the average age of participants between asymptomatic intact and ruptured AAA groups in the 3 studies that statistically assessed this.[7,10,19] The proportions of men in the asymptomatic intact and ruptured groups were 60% to 94% and 55% to 78% respectively. One study included a significantly larger proportion of women in the ruptured AAA group,[7] whereas 2 studies reported no significant differences in sex between groups.[10,19] The remaining studies either did not report sex[11,20] or did not statistically compare this.[16,26] Details regarding diabetes mellitus, ischemic heart disease, stroke, chronic obstructive pulmonary disease, smoking, and blood pressure were reported in only 2 studies (Table 2).

Risk of Bias Assessment

The methodological quality assessment and overall risk of bias of the included studies are reported in Figure 3. Six studies were assessed to have a high risk of bias,[10,11,16,19,20,26] and 1 study was assessed to have a medium risk of bias.[7] Six studies were of retrospective design, and the design of 1 study was unclear.[20] Only 1 study used an objective definition of AAA rupture, which was defined as the presence of blood in the retroperitoneum or peritoneum identified on CT by a consultant vascular specialist.[7] The method of estimating PWS and PWRI was well described in 3 out of the 7 studies that included the reporting of the reproducibility of the method[7] within the same or a previous publication (see Figure 3).[19,20] Only 2 of these studies assessed intra- and interobserver reproducibility (see Table 1).[19,20] One study assessed the reproducibility of methods in both asymptomatic and ruptured AAAs (coefficients of variation 2.7% and 4.7% for PWS in asymptomatic intact AAA and ruptured AAAs respectively[7]), whereas in the other 2 studies reproducibility was assessed in asymptomatic intact AAAs only. Six studies matched ruptured and asymptomatic intact AAA cases by AAA diameter,[7,10,11,19,20,26] whereas in one study participants were not matched; however, the mean diameter between intact and ruptured cases was similar (51±2 versus 53±2 mm respectively).[16] Three studies used a standardized blood pressure to calculate PWS and PWRI whereas the other 3 studies[11,19,20] used patient-specific blood pressures. One study matched participants for age and sex[10] in addition to AAA diameter. An a priori sample size calculation was performed in only 1 study.[7]

Reported Association of PWS and PWRI With AAA Rupture

The mean aortic diameter of included patients ranged between 51 to 82 mm and 53 to 82 mm in included asymptomatic intact and ruptured AAAs respectively (see Table 3). No significant differences in PWS between groups were reported, although in one study PWS was not assessed[20] and another study did not statistically compare PWS between groups in the matched participants.[26] PWRI was significantly higher in ruptured AAAs than asymptomatic intact AAAs in 2 studies.[10,19] PWRI was higher in the remaining studies that assessed this[7]; however, differences were not statistically significant (see Table 3).[7,11]

Data Synthesis

In the meta-analysis, PWS was not significantly different between ruptured and asymptomatic AAAs (SMD, 0.13; 95% CI, −0.18 to 0.44; P=0.418; Figure 4). Moderate heterogeneity was observed (I^2=40.6%). In contrast, PWRI was significantly higher in participants with ruptured compared with asymptomatic intact AAA (SMD, 0.42; 95% CI, 0.14–0.70, P=0.004; Figure 5). Interstudy heterogeneity was low (I^2=25.5%). Leave-one-out sensitivity analysis suggested that the results of the meta-analyses were not dependent on the inclusion of any single study (Figures S1 and S2). The funnel plot for PWRI appeared asymmetrical (Figure S3) suggesting potential publication bias.

Table 2. Clinical Characteristics of Participants With Ruptured and Asymptomatic Intact AAAs of Similar Aortic Diameter

Study	Group	Number	Age, y	Male	Diabetes Mellitus	Ischemic Heart Disease	Stroke	Chronic Obstructive Pulmonary Disease	Smoking	Systolic Blood Pressure (mm Hg)
Singh et al (2020)[7]	iAAA	50	72±7	94	18	52	10	24	94	140*
	rAAA	25	73±7	72	13	38	0	13	88	140*
Silka et al (2019)[10]	iAAA	40	78±7	60	NR	NR	NR	NR	NR	NR†
	rAAA	20	79±7	55	NR	NR	NR	NR	NR	NR†
Silka et al (2018)[19]	iAAA	15	75±8	87	NR	NR	NR	NR	NR	NR
	rAAA	28	76±10	75	NR	NR	NR	NR	NR	NR
Leemans et al (2018)[11]	iAAA	31	NR	NR	NR	NR	NR	NR	NR	NR
	rAAA	31	NR	NR	NR	NR	NR	NR	NR	NR
Polzer et al (2015)[20]	iAAA	7	NR	NR	NR	NR	NR	NR	NR	132±8
	rAAA	7	NR	NR	NR	NR	NR	NR	NR	152±26
Gasser et al (2010)[26]	iAAA	17	75±8	78	NR	NR	NR	NR	NR	NR‡
	rAAA	18	76±11	78	NR	NR	NR	NR	NR	NR‡
Truijers et al (2007)[18]	iAAA	10	72±2	90	10	70	20	30	40	120*
	rAAA	10	70±2	70	10	30	20	20	40	120*

Values are expressed as mean±SD, median [interquartile range] or n (%). AAA indicates abdominal aortic aneurysm; iAAA, asymptomatic intact AAA; NR, not reported; and rAAA, ruptured AAA.
*A standardized blood pressure was used for biomechanical analyses.
†Blood pressure was omitted from patient-specific parameters.
‡iAAAs and rAAAs were matched for blood pressure.

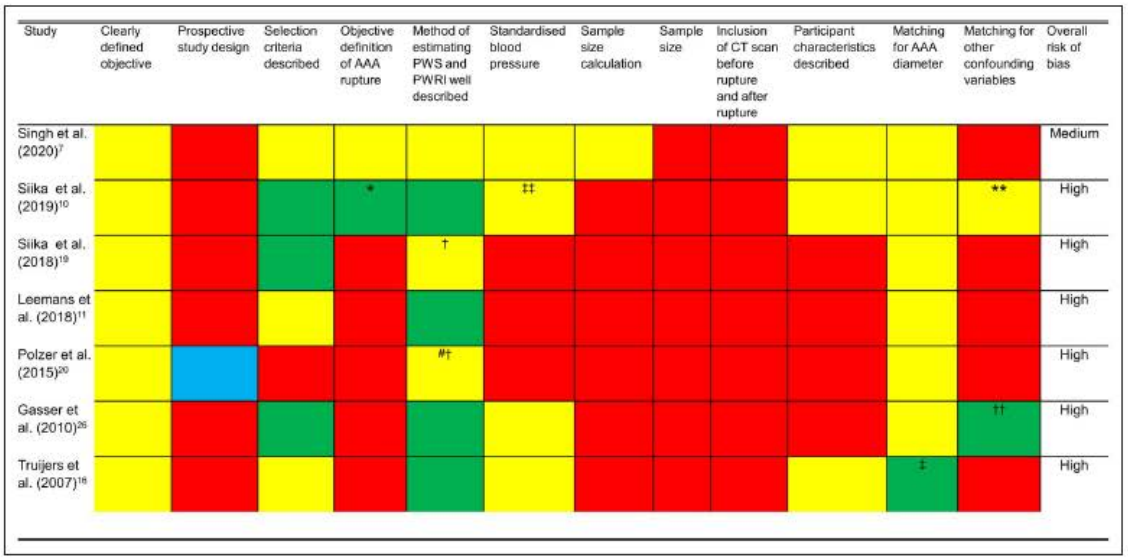

Figure 3. Strengths and weaknesses of studies included in this systematic review.
The yellow and red colored cells represent criteria, which were and not met in each study respectively. For the sample size criterion, red colored cells represent studies that had a sample size <100 and yellow-colored cells represent studies that had sample sizes >100. The green colored cells represent criteria that were partially met in each study. A blue colored cell was used if it was unclear whether a criterion was met by a study. AAA indicates abdominal aortic aneurysm; CT, computed tomography; PWRI, peak wall rupture index; and PWS, peak wall stress. *AAA rupture cases were identified using an International Classification; **cases and controls matched for age and sex; †reproducibility reported in an external publication; ††cases and controls matched for blood pressure; ‡cases and controls were not matched by study design although AAA diameter was similar between groups; ‡‡in this study blood pressure was omitted from biomechanical calculations; #PWS not assessed in this study.

DISCUSSION

This meta-analysis suggested that PWRI, but not PWS, is greater in ruptured than asymptomatic intact AAAs of similar diameter. This finding is in contrast with a previous meta-analysis that reported greater PWS in ruptured than intact AAAs.[3] A major limitation of the previous meta-analysis was the mismatch

Table 3. Comparison of PWS and PWRI of Participants With Ruptured and Asymptomatic Intact AAAs of Similar Aortic Diameter

Study	Group	Number	Diameter (mm)	*P* Value	PWS (kPa)	*P* Value	PWRI	*P* Value
Singh et al (2020)[7]	iAAA	50	82±14	0.906	263.8±69.4	0.192	1.09±0.52	0.982
	rAAA	25	82±13		279.8±90.5		1.20±0.76	
Siika et al (2019)[10]	iAAA	40	53±5	0.319	197.0±40.3	0.162	0.35±0.08	0.016
	rAAA	20	55±5		216.3±45.3		0.43±0.11	
Siika et al (2018)[19]	iAAA	15	73±11	0.674	284±53.4*	0.194	0.48±0.11*	<0.001
	rAAA	28	74±12		249±53.9*		0.80±0.54*	
Leemans et al (2018)[11]	iAAA	31	71±15	0.81	261±89†	0.99	0.69±0.33	0.61
	rAAA	31	72±18		262±75†		0.70±0.27	
Polzer et al (2015)[20]	iAAA	7	73±11	NR	NR		0.48±0.41‡	NR
	rAAA	7	76±14		NR		0.69±0.41‡	
Gasser et al (2010)[26]	iAAA	17	75±12	NR	292.0±108.7	NR	0.61±0.26	NR
	rAAA	18	77±15		330.8±114.2		0.74±0.29	
Truijers et al (2007)[16]	iAAA	10	51±2	0.57	317±73†	0.30	NR	
	rAAA	10	53±2		367±126†		NR	

Values are expressed as mean±SD unless indicated otherwise. AAA indicates abdominal aortic aneurysm; iAAA, asymptomatic intact AAA; kPa, kilopascal; NR, not reported; PWRI, peak wall rupture index; PWS, peak wall stress; and rAAA, ruptured AAA.
*SDs not available and were imputed from the diameter mismatched analysis reported in the same study.
†PWS converted from newton per square centimeter to kPa.
‡Derived PWRI values reported that have been divided by the mean arterial pressure inflation factor used in the study to obtain comparable results.

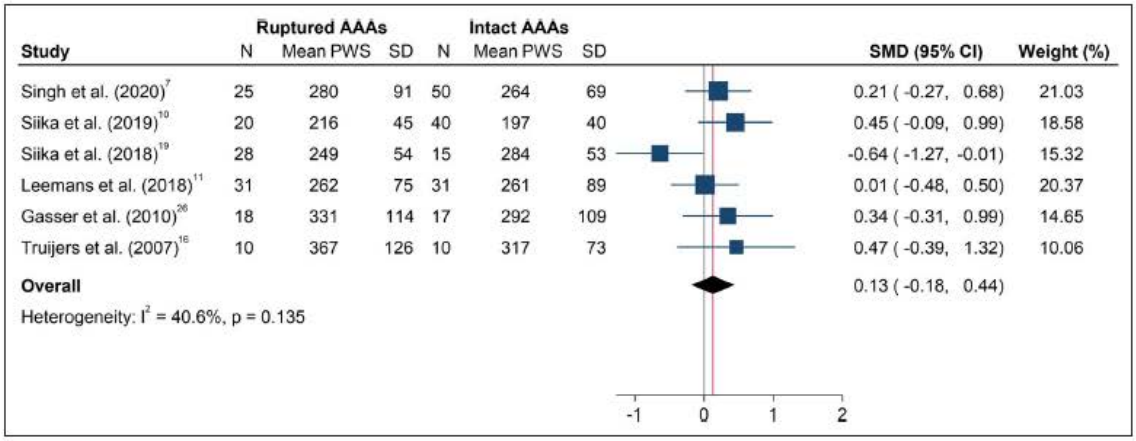

Figure 4. Differences in peak wall stress in ruptured and asymptomatic intact AAAs.
The SMD is the mean difference between both groups, standardized to 1 SD difference in PWS (kilopascal) within that study. The summary SMD is estimated from inverse variance-weighted meta-analysis. Box areas are inversely proportional to the variance of the SMD and horizontal lines illustrate 95%CIs. AAA indicates abdominal aortic aneurysm; PWS, peak wall stress; and SMD, standardized mean difference.

in aortic diameter between groups and inclusion of symptomatic patients in the ruptured group. Participants with symptomatic intact AAAs were not included in the current study as their risk of rupture is uncertain.[5,9]

Maximum aortic diameter is currently the most established measure of AAA rupture risk.[1,5,27] There are, however, a number of limitations in using aortic diameter in clinical practice, in particular the measurement error, which may be greater than the annual change in diameter.[28,29] Additional methods of estimating rupture risk and determining management may therefore be valuable. The findings of this study suggest that measurement of PWRI may add to aortic diameter in assessing the risk of AAA rupture. There are, however, many limitations of this technology that need to be addressed. There is currently no standardized approach to conducting FEA. There was substantial variation in the approach used to incorporate blood pressures in the calculation of PWS and PWRI in the included studies. Some studies used an arbitrary blood pressure for all participants, whereas others used patient-specific blood pressures. It is currently unclear which approach is most appropriate. Additionally, wall thickness and strength have an

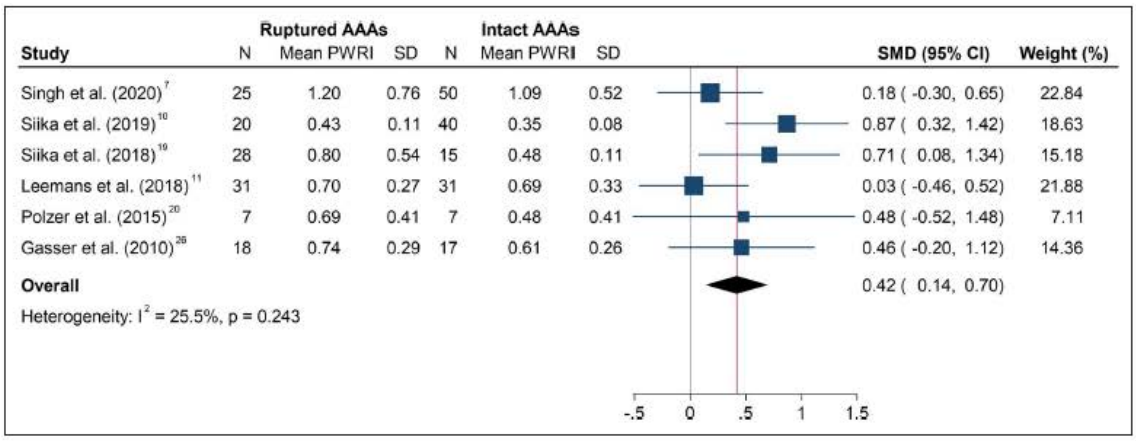

Figure 5. Differences in peak wall rupture index in ruptured and asymptomatic intact AAAs.
The SMD is the mean difference between both groups, standardized to 1 SD difference in PWRI within that study. The summary SMD is estimated from inverse variance-weighted meta-analysis. Box areas are inversely proportional to the variance of the SMD and horizontal lines illustrate 95% CIs. AAA indicates abdominal aortic aneurysm; CT, computed tomography; PWRI, peak wall rupture index; and SMD, standardized mean difference.

important effect on the risk of aortic rupture and prior investigations have suggested that increased aortic wall thickness is associated with reduced aortic wall stress.[26,30] Currently there is no accurate and feasible method to estimate wall thickness from imaging.[7] Six of the 7 studies used FEA software to estimate PWRI using the same formula that was derived from prior tensile testing of human AAA wall specimens ex vivo, but this may not be representative of the situation in individual patients in vivo.[30] Aortic calcification has previously been suggested to have an important influence on biomechanical forces but there remains no standardized method of including this in estimations of wall stress.[31,32]

Although the current meta-analysis suggested that PWRI is likely to be higher in ruptured AAAs compared with asymptomatic intact AAAs of similar diameter, the confidence in this finding is lessened as the included studies were assessed to have either a medium or high risk of bias because of a number of design limitations. First, studies included participants with CT scans performed after rupture and it is likely that the biomechanical forces before rupture were different. Second, some studies used patient-specific blood pressures to perform biomechanical analyses rather than a standardized blood pressure.[11,19,20] This may have contributed to heterogeneity and led to under- or overestimation of PWS and PWRI. Although patients with asymptomatic intact and ruptured AAAs had similar aortic diameter, other characteristics were generally poorly reported and confounding owing to an unmeasured factor cannot be ruled out. Additionally, the CT scans of ruptured AAA cases were required to meet certain inclusion criteria in some studies and selection bias cannot be excluded.[7,11,19,26] We were unsuccessful in contacting the corresponding author of 2 studies[10,19] to clarify whether there was an overlap in participants included in these investigations. Nevertheless, the leave-one-sensitivity analysis suggested that the findings of the PWRI meta-analysis was not materially altered with individual omission of either of these studies.[10,19] Lastly the relevance of the findings of this meta-analysis to small AAAs is limited as 5 studies included only patients with large AAAs[7,11,19,20,26] (mean±SD aortic diameter [mm] ranged between 71±15 and 82±14 for the asymptomatic intact AAAs; 72±18 and 82±13 for the ruptured AAAs). Furthermore, this meta-analysis compared PWS and PWRI in individuals with asymptomatic intact and ruptured AAAs but did not examine the predictive ability of these biomechanical measures for AAA rupture. Investigating this would require a large observational study; however, owing to the low rupture rate of small AAAs and the high repair rate of large AAAs, such a study maybe infeasible to perform.

CONCLUSIONS

In conclusion the results of this study suggest that PWRI is greater in ruptured than asymptomatic intact AAAs of similar diameter. The findings suggest the potential value of biomechanical measures in estimating AAA rupture risk accepting the medium to high risk of bias of the included studies.

ARTICLE INFORMATION

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Affiliations

From the Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia (T.P.S., J.V.M., J.G.); The Department of Vascular and Endovascular Surgery, The Townsville University Hospital, Townsville, Queensland, Australia (T.P.S., J.G.); The Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, Queensland, Australia (J.V.M., J.G.); and Department of Engineering Mechanics, KTH Solid Mechanics, KTH Royal Institute of Technology, Stockholm, Sweden (T.C.G.).

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Disclosures

T. Christian Gasser is a scientific advisor for VASCOPS GmbH. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Table S1
Figures S1–S3

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ORIGINAL RESEARCH

Effect of blood pressure lowering drugs and antibiotics on abdominal aortic aneurysm growth: a systematic review and meta-analysis

Jonathan Golledge [1,2] Tejas P Singh[1]

ABSTRACT

Objective There is currently no medical treatment proven to limit abdominal aortic aneurysm (AAA) progression. The aim of this systematic review and meta-analysis was to pool data from previous randomised controlled trials assessing the efficacy of blood pressure-lowering and antibiotic medications in limiting AAA growth and AAA-related events, that is, rupture or repair.

Methods A systematic literature search was performed to identify randomised controlled trials that examined the efficacy of blood pressure-lowering medications or antibiotics in reducing AAA growth and AAA-related events. AAA growth (mm/year) was measured by ultrasound or computed tomography imaging. Meta-analyses were performed using random effects models. A subanalysis was conducted including trials that investigated tetracycline or macrolide antibiotics.

Results Ten randomised controlled trials including 2045 participants with an asymptomatic AAA were included. Follow-up was between 18 and 63 months. Neither blood pressure-lowering medications (mean growth±SD 2.0±2.4 vs 2.3±2.7 mm/year; standardised mean difference (SMD) −0.07, 95% CI −0.19 to 0.06; p=0.288) or antibiotics (mean growth±SD 2.6±2.1 vs 2.6±2.5 mm/year; SMD −0.11, 95% CI −0.38 to 0.16; p=0.418) reduced AAA growth or AAA-related events (blood pressure-lowering medications: 92 vs 95 events; risk ratio (RR) 0.86, 95% CI 0.66 to 1.11; p=0.244; and antibiotics: 69 vs 73 events; RR 0.93, 95% CI 0.69 to 1.25; p=0.614). The subanalysis of antibiotics showed similar results.

Conclusions This meta-analysis suggests that neither blood pressure-lowering medications or antibiotics limit growth or clinically relevant events in people with AAAs.

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[1]Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia
[2]Department of Vascular and Endovascular Surgery, Townsville University Hospital, Townsville, Queensland, Australia

Correspondence to
Dr Jonathan Golledge, Queensland Research Centre for Peripheral Vascular Disease, James Cook University, Townsville, Queensland, Australia;
jonathan.golledge@jcu.edu.au

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JIM Review-Symposium

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Lack of an effective drug therapy for abdominal aortic aneurysm

J. Golledge[1,2,3], J. V. Moxon[1,3], T. P. Singh[1,2], M. J. Bown[4], K. Mani[5] & A. Wanhainen[5]

From the [1]Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University; [2]The Department of Vascular and Endovascular Surgery, The Townsville Hospital; [3]Centre for Molecular Therapeutics, The Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, Qld, Australia; [4]Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK; and [5]Department of Surgical Sciences, Vascular Surgery, Uppsala University, Uppsala, Sweden

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Abstract. Golledge J, Moxon JV, Singh TP, Bown MJ, Mani K, Wanhainen A (James Cook University; The Townsville Hospital, Townsville, Queensland, Australia; University of Leicester, Leicester, UK; Uppsala University, Uppsala, Sweden). Lack of an effective drug therapy for abdominal aortic aneurysm (Review Symposium). *J Intern Med* 2019;https://doi.org/10.1111/joim.12958

Abdominal aortic aneurysm (AAA) rupture is a common cause of death in adults. Current AAA treatment is by open surgical or endovascular aneurysm repair. Rodent model and human epidemiology, and genetic and observational studies over the last few decades have highlighted the potential of a number of drug therapies, including medications that lower blood pressure, correct dyslipidaemia, or inhibit thrombosis, inflammation or matrix remodelling, as approaches to managing small AAA. This review summarizes prior AAA pathogenesis data from animal and human studies aimed at identifying targets for the development of drug therapies. The review also systematically assesses past randomized placebo-controlled drug trials in patients with small AAAs. Eleven previously published randomized-controlled clinical trials testing different drug therapies aimed at slowing AAA progression were identified. Five of the trials tested antibiotics and three trials assessed medications that lower blood pressure. Meta-analyses of these trials suggested that neither of these approaches limit AAA growth. Allocation to blood pressure-lowering medication was associated with a small reduction in AAA rupture or repair, compared to placebo (relative risk 0.94, 95% confidence intervals 0.89, 1.00, $P = 0.047$). Three further trials assessed the effect of a mast cell inhibitor, fibrate or platelet aggregation inhibition and reported no effect on AAA growth or clinical events. Past trials were noted to have a number of design issues, particularly small sample sizes and limited follow-up. Much larger trials are needed to properly test potential therapeutic approaches if a convincingly effective medical therapy for AAA is to be identified.

Keywords: aneurysm, aortic, medication, meta-analysis, systematic review.

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