Development and Validation of Medical Decision Tools in Detection and Treatment of Abdominal Aortic Aneurysm

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A thesis submitted for the degree of Doctor of Philosophy

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December 2016

In memory of Professor Philip J Walker

(8 December 1957 - 31 December 2014)

A true surgeon, academic and mentor

Preface

This work was initially stimulated by a 79-year-old man who presented to hospital with a ruptured abdominal aortic aneurysm. He was in profound shock, was not able to be retrieved and died after 1 hour of hospital presentation. On assessing his available radiological imaging performed 6 years ago, an undiagnosed 3.3cm infrarenal abdominal aortic aneurysm was seen.

Potentially, his aneurysm could have been treated prior to his demise.

Abstract

Abdominal aortic aneurysm (AAA) is a permanent dilatation of the infrarenal segment of the abdominal aorta which can be fatal if the aneurysm ruptures. Ruptured AAA is the second leading cause of global surgical mortality, and prophylactic AAA repair can decrease mortality by a tenfold if surgery is performed as an elective procedure. While screening and repair of AAA could potentially reduce AAA-related mortality, selecting patients that are likely to benefit from repair remains a complex medical decision process which has been compounded by an improved life expectancy of the general population, minimal invasive treatment methods and the increased prevalence of AAA in the elderly.

The overall aim of this thesis was to improve detection and management of AAA and to develop a predictive decision tool that can assist in clinical management. This thesis has been conducted, to shed some light into issues highlighted above using New Zealand and international data. The format of this thesis was categorized into three main domains: First, the prevalence of AAA and the influence of aortic size on late survival was documented in a large cohort of individuals undergoing CT colonography for gastrointestinal symptoms in Canterbury, New Zealand; Second, a systematic review and meta-analysis of prognostic factors that might influence late survival following AAA repair were performed, and the national clinical and administrative AAA repair databases were interrogated to provide epidemiological and outcome data; Third, the factors identified from this review were applied into developing a discrete event-simulation model to predict survival following AAA repair. The model developed has been externally validated against existing national databases of patients undergoing AAA repair and it appears sufficiently accurate to predict five-year survival. The results and conclusions presented throughout this thesis fill some of the gap in AAA knowledge, and such predictive decision-making tools might help improve AAA management.

Acknowledgements

I would like to thank Professor Justin Roake and Associate Professor Gregory Jones for the invaluable supervision and mentorship they provided during this thesis. I would also like to express my gratitude to the Foundation for Surgery- New Zealand Research Scholarship and the University of Otago for funding this research project. A special thank you goes to Department of Surgery, particularly Morwenna Malcolm, for the administrative support, and for the analytical team at the Ministry of Health for providing national data throughout the research period.

There were several researchers that I collaborated with in this work and without whom this project would not be completed: Jonathan Williman, Phil Hider, Ian Thomson, Peter Sandiford, Suzanne Pitama and Giorgi Kvizhinadze, and four medical students: Anshuman Gupta, Mohamud Osman, Michaela Mullen and Heidi Chen.

The automated data-entry for model validation in Chapter 6 was built with the help of my Excel-guru brother Ziad- thank you for the endless hours advising on data problems across continents.

To my parents for the continuous encouragement, and my wife Rasha- I am not sure I could have done this without your support.

To the "vascular and friends" weekly running sessions during the last year of the thesis that kept me sane and focused.

Last but not least, to those patients with an AAA whose data was used to generate this work, in the hope that your experiences might help the lives of others.

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List of Abbreviations

AAA	abdominal aortic aneurysm
AUC	area under curve
AVA	Australasian Vascular Audit
BMI	body mass index
CI	confidence intervals
COPD	chronic obstructive pulmonary disease
CTC	computed topography colonogram
DES	discrete event simulation
EuroSCORE	European System for Cardiac Operative Risk Evaluation
EUROSTAR	EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair
EVAR	endovascular aneurysm repair
GAS	Glasgow Aneurysm Score
HR	hazard ratio
ICD	International Classification of Diseases
ICU	intensive care unit
IHD	ischaemic heart disease
IQR	interquartile range
ITI	inner-to-inner
LELE	leading edge-to-leading edge
MI	myocardial infarction
MRI	magnetic resonance imaging
NAAASP	National AAA screening Programme
NMDS	National Minimum Data Set
NZ	New Zealand
OAR	open aneurysm repair
OR	odds ratio
OTO	outer-to-outer
PAD	peripheral artery disease
RCT	randomised controlled trial
ROC	receiver operating characteristic
SD	standard deviation
SE	standard error
SVS	Society for Vascular Surgery
UK	United Kingdom
US	Ultrasound
USA	United States of America
WA	Western Australia
WHO	World Health Organisation

List of Publications

The list below is for publications directly related to thesis chapters. The full text of these publications is attached in appendix 8.6. Other AAA-related publications are listed in appendix 8.5.1.

1) Khashram M, Jones GT, Roake JA. Prevalence of abdominal aortic aneurysm (AAA) in a population undergoing computed tomography colonography in Canterbury, New Zealand. European journal of vascular and endovascular surgery 2015; 50(2):199-205.DOI:10.1016/j.ejvs.2015.04.023

2) Khashram M, Thomson IA, Jones GT, Roake JA. Abdominal aortic aneurysm repair in New Zealand: a validation of the Australasian Vascular Audit. ANZ journal of surgery. 2016. DOI:10.1111/ans.13702

3) Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Systematic Review and Meta-analysis of Factors Influencing Survival Following Abdominal Aortic Aneurysm Repair. European journal of vascular and endovascular surgery. 2016; 51(2):203-15. DOI: 10.1016/j.ejvs.2015.09.007

4) Khashram M, Hider PN, Williman JA, Jones GT, Roake JA. Does the diameter of abdominal aortic aneurysm influence late survival following abdominal aortic aneurysm repair? A systematic review and meta-analysis. Vascular. 2016. DOI: 10.1177/1708538116650580

5) Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Management of Modifiable Vascular Risk Factors Improves Late Survival following Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-Analysis. Annals of vascular surgery. 2016. DOI:10.1016/j.avsg.2016.07.066

"If we knew what it was we were doing, it would not be called *research*, would it?"

Albert Einstein (14 March 1879 – 18 April 1955)
Died of a ruptured AAA

Chapter 1: Approaches to Detection and Management of Abdominal Aortic Aneurysms

1.1 Introduction to AAA

Infrarenal abdominal aortic aneurysm (AAA) is generally an asymptomatic condition that is potentially fatal if rupture occurs. The term aneurysm originates from the Greek word "aneurysma" meaning dilation or widening. The definition of AAA varies but is usually accepted when the diameter of the abdominal aorta reaches 3cm or greater (1). The natural history of AAA is gradual sac expansion until rupture (law of Laplace) causing death unless the aneurysm is repaired surgically or death from other causes occurs. Repair of ruptured AAA caries a ten-fold increase in operative mortality compared to elective AAA repair, which carries a 2-5% 30-day mortality.

The aetiology of AAA can be classified into three broad categories:

1) Degenerative (atherosclerotic) or late onset
2) Infectious or non-infectious aortitis
3) Connective tissue disease resulting in aneurysm formation

Degenerative AAAs, which are associated with global atherosclerosis, are by far the most common and will be the primary emphasis of this thesis.

Repair of AAA is an established evidence-based treatment that provides life-preserving prophylaxis against death from rupture. The natural history of slow growth and the potential for early detection prior to rupture which results in reduced mortality rates make AAA a condition suitable for population screening to prevent death from rupture. In New Zealand, basic population data on AAA prevalence, management and outcomes are not well documented. The primary aim of this thesis was to obtain information that can aid in the detection of AAA and develop models that may assist in the clinical decision-making of AAA management.

1.2 Abdominal Aortic Aneurysm

1.2.1 Definition

In order to diagnose AAAs, an accepted definition is required. The most commonly used clinical definition for diagnosing an AAA is an aortic diameter of ≥ 3cm. However, other definitions have been proposed (2); for example, the Society for Vascular Surgery (SVS) defines an aneurysm as being 1.5 times that of the expected normal diameter (3). A consensus that provides a standardized definition of AAA is yet to be established and is likely to be adjusted to gender and body measurements. For the majority of clinical practical purposes, an infra-renal abdominal aortic diameter ≥ 3cm is considered an AAA.

1.2.2 Risks for developing AAA

Population studies have consistently identified risk factors that increase the probability of developing AAA. These fall in two groups:

1) Non-modifiable – sex (males), age, family history (genetics) and ethnicity (Caucasians compared to other ethnicities).

2) Modifiable – smoking (current/history), hypertension, ischemic heart disease, peripheral vascular disease and high cholesterol.

These risk factors are similar to those shared with other cardiovascular diseases with the exception of diabetes that appears to be protective against AAA formation (4).

1.2.3 AAA presentation

Patients with AAA generally present to healthcare services in one of two ways: Electively without symptoms often as an incidental finding, or acutely with abdominal pain and/or rupture, which -if occurs- may be responsible for sudden death.

The most common mode of presentation for patients with AAA is as an incidental finding. Patient presentations with AAA steadily increased

between the 1950s-1980s (5), associated with a wider use of radiological modalities and an increase in awareness of the condition and the treatment options available.

The most common acute presentation is with rupture where the overall mortality is approximately 80%, including pre-hospital death in 30% of the cases and preoperative mortality of 50% as represented in Figure 1.1 (6). Of those patients reaching hospital and not undergoing repair, approximately 80% die within 24 hours (7) and virtually all within one month. Preoperative mortality for ruptured AAA remains high but may be improving slowly (8).

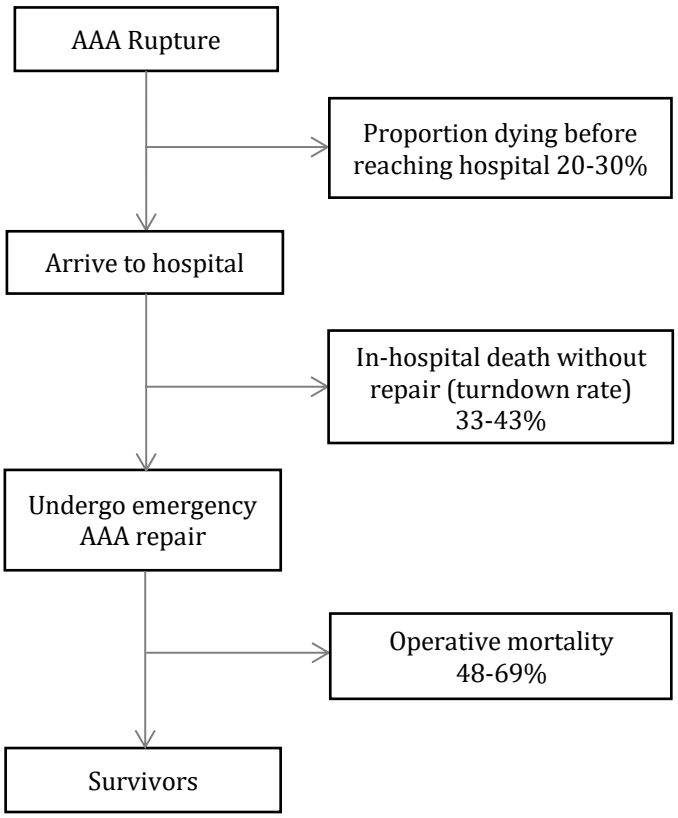


Figure 1.1 Presentation of ruptured AAA and proportion of patients with associated mortality

Data adapted from Reimerink *et al.* Systematic review and meta-analysis of population-based mortality from ruptured abdominal aortic aneurysm (6)

Less commonly acute non-ruptured AAA presentations may include abdominal pain related to the aneurysm, mass effect against adjacent structures, thrombosis and distal embolization. This presentation is usually referred to as 'symptomatic but not ruptured AAA'. This 'symptomatic'

category is a distinctive group in that patients have an operative mortality that is intermediate between ruptured AAA and elective AAA repair (9).

1.2.4 Prevalence of AAA

AAA prevalence is an important determinant of the effectiveness of population screening. Historically, prevalence of AAA was obtained from population studies and autopsy series (10). AAA prevalence rates vary depending on the demographics of the population screened and the geographical location. A meta-analysis of the published AAA prevalence in men and women reported a pooled rate of 4.8% (95%CI: 4.3-5.3). Subgroup analysis revealed that AAA prevalence was 6.0% in males and 1.6% in females (11). AAA prevalence also increases with age, with an odds ratio increase of 5 per 5-year age-category for >55 age groups when compared to those younger than 55 years old (reference category) (12).

1.2.4.1 Change in prevalence

Epidemiological studies from Europe, Australia and New Zealand have suggested that AAA prevalence is changing. One study compared AAA episodes from national administrative datasets from New Zealand, England and Wales between 1991 and 2007 and showed that the age-standardized mortality rate and the deaths from AAA have sharply reduced in these regions (13). Population data from Australia has also suggested that AAA rupture and non-rupture incidences in all age groups have decreased in the last decade (14). With regards to point prevalence, a sub-group analysis from a meta-analysis consisting of 37 studies from Europe showed that AAA prevalence decreased from 6.5% (95%CI: 4.8-8.1) during 1988-1992 to 2.8% (95%CI: 1.4-4.3) during 2011-2013 (11).

However, it may be that AAA burden is shifting to an older age group rather than decreasing. Choke *et al.* highlighted that although the trends of emergency AAA repair and associated mortality have declined, elective AAA cases have not changed in England and Wales during 2001 to 2009. It was also noted that the AAA population has shifted to an older age group (15).

The Aneurysm Global Epidemiology Study on trends in AAA mortality using the World Health Organization (WHO) mortality database from 19 nations showed that there was a decline in AAA mortality in most countries (16, 17). This was associated with improved cardiovascular risk modification in patients (17) and the decrease in smoking patterns (18). However, AAA mortality has increased in Austria, Denmark, Hungary and Romania.

Factors that might have contributed to a decline in AAA prevalence and mortality in the last decade are a decline in tobacco use, screening studies, increased incidental detection and non-operative management of small AAA (<5cm). However, factors that might have led to an increase in reported AAA prevalence and mortality are an improved overall life expectancy in patients who are more likely to have an AAA, advancement in medical management and improved awareness of AAA disease by both individuals and primary care doctors who refer patients for management.

In summary, the prevalence of AAA appears to be changing and the age-standardized mortality rates of AAA are decreasing, but whether the overall crude burden of people with AAA has decreased is debatable. The remarkable changes during the last two decades require better understanding but may be partially explained by a decrease in cigarette smoking habits.

1.2.4.2 Current international prevalence

AAAs are more prevalent in Western countries and Australasia compared to Asia, Africa and South America (11) (19). For example, the prevalence of AAA in Europe and Asia is 5.1% (95%CI: 4.4-5.9) and 0.5% (95%CI: 0.3-0.7) respectively. In Sweden, results of the AAA screening programme in the middle region of the country revealed a prevalence of 1.7% in 22,187 men aged 65 years old. The prevalence increased to 2.2% when men with previously repaired AAA or already on AAA surveillance were included (20). Preliminary data from the United Kingdom (UK) National AAA screening Programme (NAAASP) indicates recent AAA prevalence of 1.2% in 65-year-old men (21). This is considerably different from the 4.9% figure observed

in the MASS trial from 1997 to 1999 (22). Population AAA screening in Denmark in men aged 65 to 74 years reported a prevalence of 3.3% which has decreased slightly during the last 15 years from 4.0% (23). National screening data is likely to be confounded by the age group of men being invited, screening avoidance and the method in which individuals are invited to attend screening. Evidence that AAA prevalence is declining in such populations is convincing but the true magnitude of the fall is unclear.

1.2.5 The burden of AAA on health systems

It was first noted that AAA mortality was increasing at a rapid rate from 1951 to 1968 until it reached a steady plateau through 1981 in the USA (24). This can probably be attributed to an increased clinical awareness of AAA, improved diagnostic methods and the subsequent treatment options that became available during this time.

The Global Burden of Disease study from 2010 documented the mortality of 235 causes of death (25). The deaths related to aortic aneurysm in 1990 and 2010 were 1,319,000 (946,000-1,733,000) and 1,917,000 (1,403,000-2,492,000) respectively, corresponding to a 45.4% increase. However, the age-standardized mortality decreased from 3.3 (2.4-4.3) to 2.9 (2.1-3.8) per 100,000 persons.

The crude annual AAA mortality count reported from the WHO (2010) in the USA, UK, Germany and Italy was 6,289, 5,251, 1,251 and 2,073 respectively (26). The USA population is at least four times larger than the UK and serious underreporting is likely occurring. In Italy and Germany where the population is similar to the UK, the annual mortality is two to three times lower. This inconsistency is likely to influence the recommendations reported from such organizations such as the WHO.

1.3 Natural History of AAA

The natural history of AAA is a gradual progressive increase in aortic diameter. There are well- documented risk factors linked to AAA development and sac expansion. Understanding such risk associated with the development and expansion of AAA may aid in targeted detection of AAA and in clinical decision-making surrounding management and surveillance intervals.

1.3.1 Risks of small AAA expansion

The predictors of growth of individual AAA are not fully understood, probably due to the complex behaviour of the biology of AAA expansion. There is a general acceptance that most AAAs steadily increase in diameter with time and several studies have reported a mean expansion rate of approximately 2.5mm/year (27, 28). However, this figure is neither absolute nor linear for all patients with AAA and several factors influence the rate. Some AAAs have erratic or stepwise non-growth periods (29). Three general patterns of growth have been described: linear, accelerated and uncategorized growths (27).

The best information available with regards to the natural history of AAA expansion and rupture comes from the RESCAN study, which is a large collaborative collection of >15,000 individual patient data points from published and unpublished datasets (8).

The initial AAA diameter is the most important predictor of growth, which means that in general larger AAAs grow more rapidly than smaller AAAs (RESSCAN). The most important modifiable factor associated with an increase in AAA expansion found in the RESCAN meta-analysis was smoking. The “current use” of tobacco was a dominant factor affecting AAA expansion associated with a 0.35mm increase in growth rate per annum (8, 30). The only factor that has been shown to decrease expansion rates is diabetes (8). Pharmacological medications such as statins, beta-blockers and antiplatelet therapy individually do not appear to influence expansion in adjusted analysis (8). In another study an increase in expansion was reported in

patients with family history of AAA compared to those patients without a family history (31).

1.3.2 Risks of AAA rupture

There is consistent agreement that AAA diameter at initial presentation/assessment remains the strongest predictor of rupture. After adjusting for baseline AAA size, the RESCAN study reported that women had a hazard ratio (HR) of 3.76 (95%CI: 2.58-5.47) for rupture compared to men, and smokers had a HR of 2.02 (95%CI: 1.33-3.06) compared to ex-smokers and never smokers (8). Other factors that are reported to be associated with an increased rupture risk are age, lower BMI and hypertension (32).

The European and the USA Society for Vascular Surgery (SVS) guidelines have reported annual rupture risks to guide clinicians with management options (33, 34). These guidelines report slightly different predicted rupture risks. The estimated annual rupture risk stratified according to 10mm-AAA-diameter categories is shown in Table 1.1.

Table 1.1: Annual AAA rupture risk by diameter

European Vascular Society guidelines (33)		**USA SVS guidelines (34)**	
AAA diameter (mm)	**Annual rupture risk (%)**	**AAA diameter (cm)**	**Annual rupture risk (%)**
30-39	0	<4	0
40-49	1	4-5	0.5-5
50-59	1-11	5-6	3-15
60-69	10-22	6-7	10-20
>70	30-33	7-8	20-40
		>8	30-50

SVS: Society of Vascular Surgery, adapted from referenced guidelines

There is agreement in the literature that the rupture risk for small AAA (<5cm) is very small and regular surveillance is the safest and most cost-effective option.

There is limited data on the natural history of rupture in AAA >5cm in diameter. Collection of such information is difficult and indeed unethical, as the majority of such patients should undergo AAA repair, with the exception of those with severe co-morbidities. The rupture risk of AAA >5cm is confounded by the presence of multiple co-morbidities and hence a higher overall background mortality. A meta-analysis attempted to quantify the risk of rupture of larger AAAs and it was noted that the pooled cumulative yearly rupture risk for AAAs of 5.5-6cm, 6.1-7cm and >7cm was 3.5%, 4.1% and 6.3% respectively (35). This information should be interpreted with caution as autopsy confirmations of the diagnosis were not obtained and therefore the information most probably underestimates the true rupture risk.

1.4 Measurement and Detection

Clinical examination with physical palpation of the aorta to diagnose the presence of an AAA is the simplest and least expensive method of diagnosing AAA. However, the primary limitation of this strategy is the low sensitivity particularly with small AAA (36). This makes it an unacceptable test for mass screening. The gold standard tool for detecting AAA is ultrasound (US), with reported sensitivity of >85% and specificity of >99% (37). An aortic US scan is non-invasive and is not associated with any physical risks. It is relatively cheaper than other radiological modalities such as CT and MRI. The examination can be performed accurately in less than 10 minutes.

1.4.1 Variations in methods of measurement

Generally, measurement errors can be caused by differences in methodological techniques of the same measurement (intra-observer error) or by measurements being performed by different individuals (inter-observer error). Measuring aortas accurately is required to diagnose aneurysms since the definition of AAA is based on a measured diameter.

Factors contributing to errors in AAA diameter measurement include: irregular AAA shape, aortic wall thickness, phase at cardiac cycle,

magnification, resolution of acquired images and imaging modality used. As expected, each radiological modality will inherit some variations in AAA measurements.

Radiological modalities such as catheter angiograms and magnetic resonance imaging (MRI) have a tendency to underestimate the true AAA diameter because these techniques rely on intra-luminal flow, therefore aortic wall thickness, calcium deposition and the presence of thrombus formation can potentially be underestimated (38). On the other hand, computed topography (CT) scans may overestimate the diameter of the aorta when the readers do not account for aortic tortuosity and angulation.

US remains the most suitable tool for accurate AAA measurements due to the ability of the technologist/sonographer to correct the US probe to maintain a true cross-sectional view of the aorta (39). A review by Long and colleagues documented the wide range of different methodologies used in the existing AAA prevalence and surveillance literature (40). Of 10 studies that reported guidelines for screening of AAA using US, only three studies described specific details of measuring techniques.

Caliper Position

There is no universally accepted measurement technique for AAA. The aortic wall is composed of three distinct layers and their respective thicknesses can vary between different aortas and variations of 5mm may occur (41). There are three accepted methods of positioning calipers during measurement: Outer-to-outer (OTO), inner-to-inner (ITI) and leading edge-to-leading edge (LELE) (Figure 1.2).

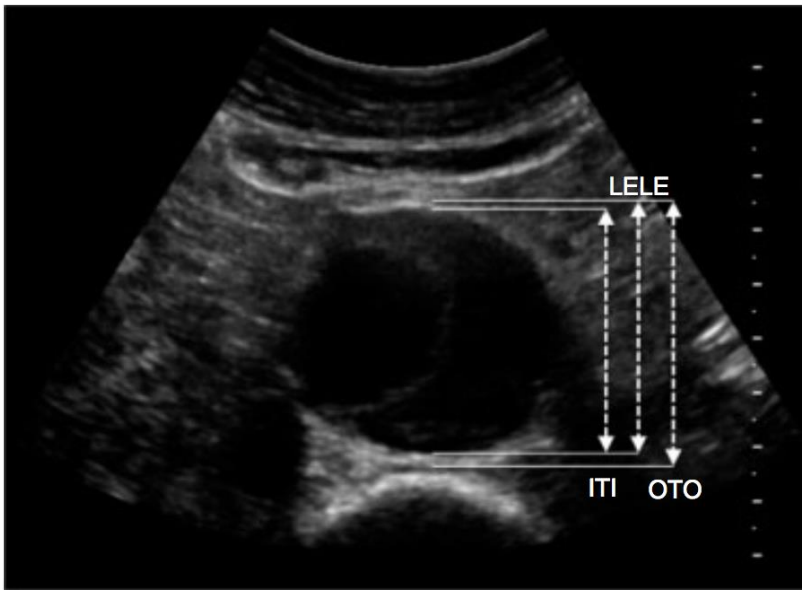


Figure 1.2: Different methods of measuring abdominal aortic diameters

Inner-to-inner (ITI) and outer-to-outer (OTO) aortic wall measurements may differ by a mean difference of 4.2mm (42). ITI measurement may be associated with better reproducibility (43) (useful when multiple personnel are performing scans), but may exclude a group of people with AAA from diagnosis and surveillance— a potentially hazardous omission particularly in younger patients with a long life-expectancy.

The National AAA Screening Programme (NAAASP) in the UK has replicated the aortic measurement methodology used in the Multicentre Aneurysm Screening Study (MASS) which was based on the ITI, whereas the Swedish AAA screening program used the LELE methodology (41, 43). This difference in measurement must be considered when combining AAA datasets and comparing prevalence of AAA between studies.

1.4.2 Detection of AAA by serendipity or screening

AAA prevalence is one of the key parameters in determining the likely effectiveness of population screening. A second determinant is the proportion of non-screen detected AAA prior to screening or outside the screening recommendation— principally (incidental) findings of abdominal imaging for unrelated diagnostic purposes. This figure is reported to range

from 35-46% (44). In the MASS, 277 patients in the control group had undergone elective AAA repair for incidentally identified AAA, compared to 600 patients in the screened group. In the Western Australian (WA) Health in Men study, 54 men in the control group had an elective repair compared to 86 men in the screened group. With this high rate of background AAA detection in the WA study, AAA screening in men was not effective (45).

In the absence of a formal AAA detection program, vascular surgery health care units managing AAA disease depend on radiological modalities for diagnosis and clinician referrals of people with AAA.

1.5 Management of Established Asymptomatic AAA

Once an AAA is detected and presence has been confirmed by appropriate radiological imaging, three management options could be considered:

1. Non-intervention if treatment is unlikely to offer significant benefit due to low life expectancy or high operative risk.
2. Surveillance until AAA reaches the size threshold for repair (5.5cm diameter).
3. Repair with either open aneurysm repair (OAR) or endovascular aneurysm repair (EVAR).

1.5.1 Surveillance of small AAA

Surveillance is a well-established strategy in the management of small AAA. The frequency of US intervals differs depending on the size of the initial AAA. Serial scans are used to measure the aorta at agreed surveillance intervals depending on the initial AAA diameter. Stather *et al.* summarized the global AAA surveillance experience from expert representatives at an international meeting (46). The majority of screening strategies reduced intervals when AAA diameter increases (Table 1.2). However, some of the reported intervals from some countries are not accurate; for example, it has been reported that the surveillance interval in NZ for >3cm AAA is 12 months, which is not an accurate reflection for the majority of vascular units in NZ.

Table 1.2 Summary of US surveillance intervals

Aortic diameter (cm) SVS (47)	Frequency intervals (months)	NAAASP (UK)(33)	Frequency intervals (months)	UK SAT(30)	Frequency intervals (months)
2.5-2.9	60	-	-	3-3.9	24
3-3.4	36			4-4.5	12
3.5-4.4	12	3-4.4	12	4.5-5	6
4.5-5.4	6	4.5-5.5	3	>5	3

NAAASP: National AAA screening program; SAT: small aneurysm trial

1.5.2 AAA repair of small AAA (<5.5cm)

In the mid-1990s, prior to the establishment of screening programs, there was a suggestion that patients with small AAAs (4 to 5.4cm) might benefit from early repair to prevent the devastating high mortality of rupture. Four randomised trials (two open vs. surveillance and two EVAR vs. surveillance) have been conducted to answer the question "if AAAs are repaired at a smaller size, would AAA rupture and hence overall mortality be reduced?"

Initially two RCTs, one from the UK (UK Small Aneurysm Trial, UK SAT) and the other from the USA (Aneurysm Detection and Management study, ADAM) randomised patients into early repair vs. surveillance. Their results showed that there was no survival difference observed among patients who underwent immediate AAA repair versus surveillance. This difference was maintained even after 12 years of follow up (48). Approximately a decade later, two further EVAR trials were conducted: Comparison of surveillance versus Aortic Endografting for Small Aneurysm Repair (CAESAR, Italy) and the Positive Impact of endoVascular Options for Treating Aneurysm earLy, (PIVOTAL, USA) (49, 50). The argument for conducting the EVAR trials was that the 30-day mortality with EVAR is much lower than OAR and hence EVAR would be a more suitable treatment and the benefits of intervention to prevent rupture would be elucidated. Both trials concluded that there was again no difference in overall mortality with early treatment compared to surveillance. A systematic review and meta-analysis of these four trials concluded that there were no benefits of early repair (51). In addition, the

US and European guidelines have recommended against early repair for small AAA.

1.5.3 AAA repair of large AAA (>5.5cm)

To date, there are no known specific drug therapies that have been effectively shown to reduce AAA expansion (52). Therefore, repair of the aneurysm is the only effective treatment to exclude AAA and prevent rupture. The repair could be achieved with open AAA repair or by endovascular stent insertion. Each approach comes with its unique advantages and limitations.

1.5.3.1 History

Until the 1950s, ligation of the aneurysm was the adopted surgical treatment available. This remained the case until 1951 when Dubost performed the first successful AAA open repair with a homograft (53), and restoration of blood-flow continuity was achieved. It became widely noticed that non-operated AAA had a poorer survival than operated AAA, and resection was recommended (54, 55). Hence, there were no trials comparing AAA repair versus no repair conducted in that era. During the late 1980s, independent reports by Volodos (56) in the Soviet Union and Parodi *et al.* (57) in Buenos Aries, Argentina, were the first to report AAA treatment using a stent graft for treating AAA disease. This technique later became known as EndoVascular Aneurysm Repair (EVAR).

1.5.3.2 Open AAA repair

The AAA is usually approached via either a laparotomy (transverse or midline incision) or using a left retroperitoneal exposure. The extent of the AAA is defined and control of the AAA proximally and distally is achieved with clamps. The aorta is then cross-clamped, the aneurysm sac is entered, aneurysm contents (thrombus) evacuated, and a prosthetic graft is sewn *in-situ* as a tube graft if the AAA was confined to the aorta or as a bifurcated graft if the disease extends into the iliac or femoral arteries. Then the aortic

sac is used to cover the graft to isolate the foreign material from the bowel cavity (Figure 1.3).

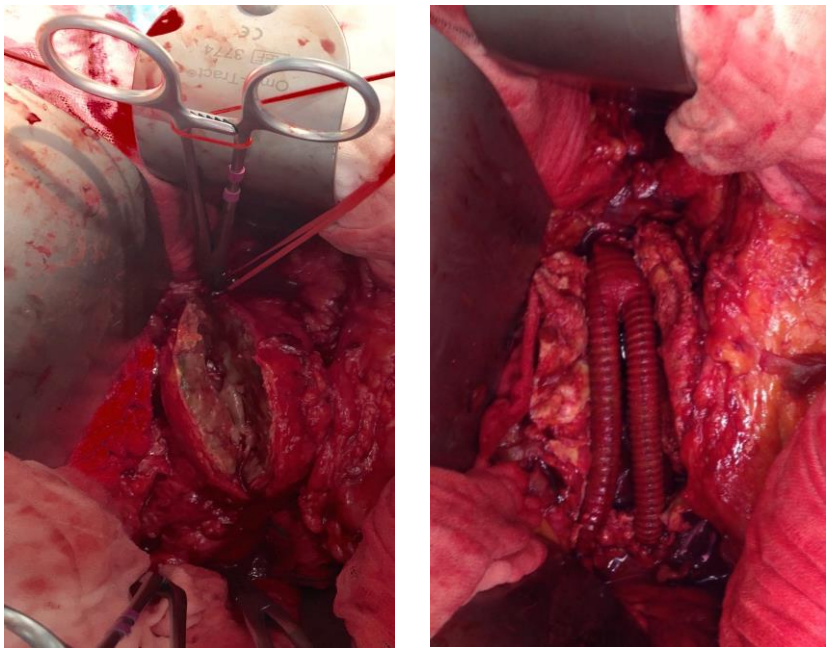


Figure 1.3 Intraoperative images of OAR

Left: the aorta and iliac arteries are clamped and AAA sac opened. Right: a bifurcated Dacron graft sewn from the infra-renal aorta to the iliac arteries

1.5.3.3 Endovascular aneurysm repair

EVAR is an alternative minimal invasive method of excluding AAA with a prosthetic stent graft inserted through the femoral arteries using fluoroscopic guidance. The stent is positioned and deployed, and the presence of contrast (blood) reperfusing the AAA sac is checked. Technical success of the procedure can be defined as the absence of sac perfusion and restoration/preservation of blood flow to major organs (Figure 1.4). If contrast is seen outside the stent, the term "endoleak" is given, which is subsequently classified into 5 types (58):

Type 1: Flow origination from the proximal or distal seal

Type 2: Retrograde blood vessel flow into sac

Type 3: Structural graft failure

Type 4: Graft fabric porosity

Type 5: Endotension (presence of endoleak without an identifiable cause)

Given that EVAR is relatively a new technology, life-long stent graft surveillance is still recommended to monitor the presence of endoleak, sac expansion and stent graft complications such as migration, dislocation or kinking. Hence, endoleaks are the main drawback of EVAR and are seen by many as the 'Achilles heel' of this technology.

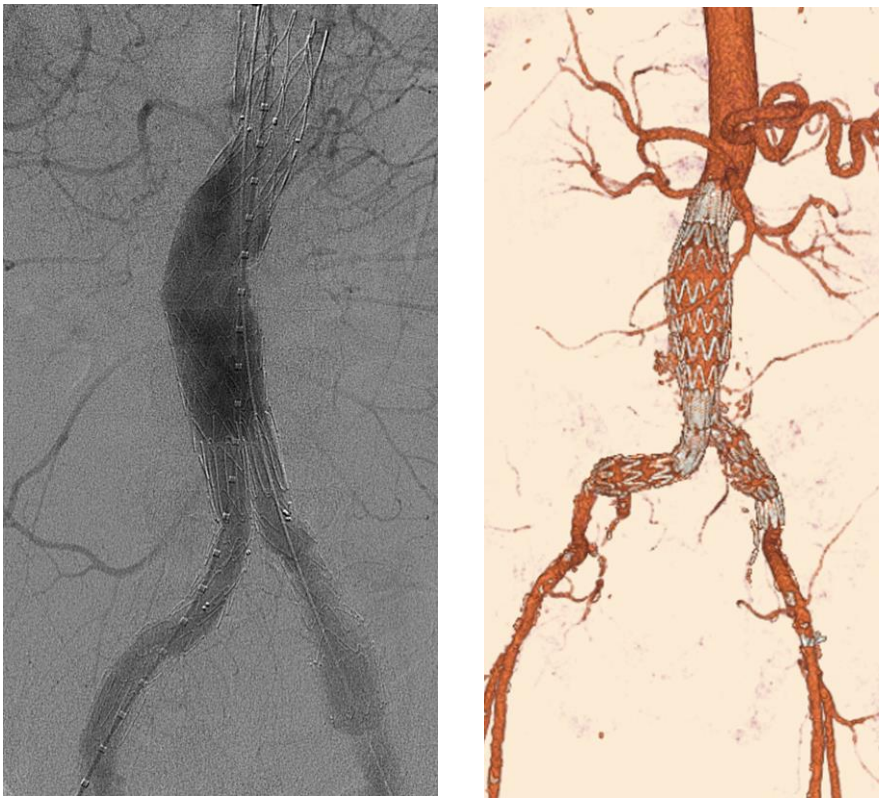


Figure 1.4 Abdominal aortic aneurysm treated with EVAR

Left: Completion Digital Subtraction Angiography during an EVAR. Right: 3D CT Angiogram reconstruction of EVAR at 3 months follow-up showing no endoleak

1.5.3.4 Results of RCT comparing OAR and EVAR

Historically, the "gold standard" and mainstream strategy for treating AAA was with open surgery. However, since the introduction of a minimal invasive option (EVAR), there have been four randomised controlled trials (RCTs) conducted to compare EVAR with the more open aneurysm repair (OAR) for the treatment of large AAA. The first trials from the UK (Endovascular Aneurysm Repair EVAR-1) and the Netherlands/Belgium

(Dutch Randomised Endovascular Aneurysm Management, DREAM) were very comparable and reported their initial findings in 2004. EVAR-1, DREAM and the Open Versus Endovascular Repair (OVER) from the USA reported very similar findings in short- and long-term outcomes. The most recent RCT Aneurysme de l'aorte abominale: Chirugie versus Endoprothese (ACE) from France randomised low- to moderate-risk patients to EVAR or OAR. The ACE investigators reported no difference in 30-day or up to 3-year mortality between the two modalities, but EVAR was associated with more re-interventions. The ACE trial ended after the 3-year follow-up and no long-term data is expected *(personal communication with principal author)*. Two meta-analyses of the RCTs concluded that EVAR had significantly lower 30-day mortality compared to OAR but long-term survival was very similar for both approaches. However, re-intervention rates in the EVAR group were significantly higher (59, 60). Despite this, EVAR utility has reached 70-75% in the United States and Australia between 2010- 2011 (61, 62). Summaries of the trial results are presented in Table 1.3.

Table 1.3 Short- and long-term results of four randomised controlled trials comparing OAR and EVAR

	Year of 1st public-ation	No. participants	Country	30-day deaths		Long-term survival (%)		Freedom from re-intervention	
				OAR	EVAR	OAR	EVA	OAR	EVAR
EVAR-1	2004	1047	UK	24 (4.7)	9 (1.7)	54	54	90	72
DREAM	2004	345	Netherlands & Belgium	8 (4.7)	2 (1.2)	69.9	68.9	81.9	70.4
OVER	2009	881	USA	13 (3)	2 (0.5)	60	58%	NR†	NR‡
ACE	2011	299	France	1 (0.6)	2 (1.3)	86.7	86.3	85.8	76.1

† ACE 3 years, EVAR-1 8 years, DREAM 6 years, OVER 9 years
‡ Only reported as a combined freedom of re-intervention and death

Numbers in parenthesis indicate percentages

1.5.4 Long-term results

Three of the randomized trials have published follow-ups longer than 5-years. The results of a meta-analysis that included four randomised controlled trials (RCT) comparing open AAA repair (OAR) with endovascular aneurysm repair (EVAR) showed that the modality chosen for AAA repair does not influence survival at 4 years (OR 0.92, 95% CI: 0.75-1.12) (59). When the results from three propensity-score matched studies were included in the meta-analysis, the main conclusion did not change (HR 0.97, 95% CI: 0.9-1.04) (63). In a selected large Medicare population which included 39,996 propensity-matched patients who underwent EVAR or OAR from 2001 to 2008, no difference in survival was observed between the types of repair (64).

The crossover point between EVAR and OAR was observed in the trials between 2 to 4 years following repair, were EVAR "lost" the early survival advantage and the long-term survival was unchanged. In RCTs with an intention to treat analysis, the baseline selection bias is "non-existent" and the treatment allocated is the primary outcome.

There is a suggestion that operative mortality has improved with time, particularly with the advancement in endovascular technology (64, 65), but even in contemporary series, overall survival does not appear to have changed.

1.5.5 Cost estimates of AAA repair

In this era where health expenditure is increasing, cost effectiveness analyses have become an important element when treatment options are compared. In order to justify a national AAA screening program advocating repair with one type of repair or another or balancing repair with quality of life gained, the economics of AAA management costs should be considered. This information can be divided into three components analysed in the following sections.

1.5.5.1 The cost of AAA repair versus no repair

The actual costs of conservative treatment without repair are relatively inexpensive compared to AAA surgical repair-related treatment costs. The well-established treatment management for most fit patients with AAA precludes a trial designed to determine cost-effectiveness of AAA repair versus no AAA repair. Actuarial costs have been described from the EVAR-2 trial where patients who were deemed not physically fit to undergo OAR were randomised into EVAR or no repair. The costs of the EVAR were more expensive than the no-repair group. However, there was no statistical difference in survival between the two groups (66).

1.5.5.2 Costs of treatment – OAR vs. EVAR

The comparative costs between EVAR and OAR have been mostly derived from the RCTs. Since elective and emergency procedures differ significantly between each type of presentation, cost information will be discussed separately below.

Elective setting

Randomized trials comparing OAR and EVAR have provided some evidence on cost differences between each treatment approach. In the short term, EVAR was more expensive than OAR despite the significantly shorter hospital stay, less blood requirement and less intensive care unit (ICU) costs associated with EVAR (67). This is largely due to the upfront cost of the endovascular device. A meta-analysis and Markov-based modelling of the four trials concluded that OAR was also more cost effective than EVAR in the long-term in the European-based studies but not in the OVER trials (USA) (68).

Acute or emergency setting

In contrary to scheduled aneurysm repair, endovascular treatment was found to be associated with lower costs than open repair for emergency procedures in one trial (69) but not in another trial (70). Reasons for the contradictory findings might be related to the randomization process in including patients and differences in the cost of stent devices (71).

1.5.5.3 Costs of elective versus rupture AAA repair

Despite the higher mortality associated with ruptured AAAs, the costs of emergency repair are significantly higher than elective repair driven primarily by an increase in ICU length of stay, blood products and a higher complication rate. In a study using a Markov model, Patel *et al* showed that the costs incurred from a ruptured AAA (despite the associated high morbidity and mortality) was cost-effective as it led to an improvement in quality adjusted life years (QALY) compared to immediate deaths without any repair (72).

A local study of 169 consecutive patients who underwent AAA repairs at Christchurch Hospital revealed that the costs (NZ dollars) of repairing a ruptured AAA were significantly more expensive than elective AAA ($38,804 *vs*. $28,019, 95% CI for mean difference: $249-$21,321). This finding was consistent with similar studies published two decades ago (73).

1.5.6 Long-term survival following AAA repair

Given the association of AAA with cardiovascular risk factors, it is expected that life expectancy of patients with AAA would be lower than a matched "normal" population. A review from 2001 revealed that the 5-year crude estimated survival following AAA was 70% and the expected survival for matched population was about 80% (74). Furthermore, a meta-analysis published in 2015 reported that the crude observed estimated 5-year survival following elective AAA repair (OAR and EVAR) was 69% (95%CI: 67-71), and this figure has not changed during the last 40 years (75) despite the decrease in 30-day operative mortality.

1.5.7 Factors influencing late survival

As operative experience accumulated during the last century, it became apparent to surgeons that certain groups of post-AAA-repair patients had a reduced survival compared to others (76). Multiple risk factors were associated with worse survival, including an increase in age, hypertension and heart disease. As more follow-up data was gathered, further predictors

were described and differences in predictors between the types of repair were reported.

However, predictors that influence survival have not been consistent among the studied population and the follow-up period varied. Obtaining accurate assessments for such predictors might provide better estimates of the relative influence of each predictor and its impact on survival. In Chapter 4 of this thesis, a comprehensive review of the literature will be presented to provide the best estimates for each of the factors that influence late survival following AAA repair.

1.5.8 AAA-related death

Despite treatment or exclusion of AAA by repair, patients have a lifelong ongoing risk of AAA-related complications and death. The mechanisms of such complications can be broadly categorized as 1) device or graft material failure, 2) biological factors causing aneurysmal formation in proximal or distal segments that can expand, 3) erosion of the prosthetic into adjacent structures (i.e. duodenum) and 4) a life-long risk of prosthetic infection.

Fortunately, such aortic complications are uncommon and by far the majority of deaths following AAA repair are due primarily to cardiovascular and oncological conditions (77). Such causes of death are also the same causes of death in an age-matched population without AAA disease (78). Despite the fact that prosthetic-graft-related complications are estimated to be in the range of 2-3% (79), such complications confer a high risk of mortality and morbidity.

The most catastrophic scenario is a rupture of a previously-repaired AAA by either EVAR or OAR. The rupture rates following EVAR have been reported to be significantly higher than after OAR. Data from the UK EVAR 1 and 2 trials indicate that from a total of 1,442 patients, 27 (3.2%) ruptures occurred in the EVAR group and 0 ruptures occurred in the OAR group after a mean follow-up of 57.6 months (80). A meta-analysis estimated that the incidence of late rupture after EVAR was 0.9% with a mean time to rupture of 3 years from the index procedure (81).

1.5.9 Quality of life after repair

The RCTs comparing EVAR and OAR as well as some observational studies have provided information on the relatively short-term post-operative period extending to 5 years. The general summary from the trials was that both types of repair had a similar return to baseline for lifestyle activities and quality of life at 1 and 2 years post repair. 5-year follow-up from the DREAM trial showed that patients who underwent EVAR had a worse health-related quality of life than patients who underwent OAR (82).

There is a paucity of long-term quality of life data following AAA repair (83), particularly in this era when the morbidity and mortality from both types of repair are declining and the proportion of octogenarians who are offered repair is increasing.

1.6 Screening for AAA

1.6.1 History of screening

AAA screening could theoretically detect patients with aneurysms and prevent AAA-related complications and death (84). As AAA's health-burden increased through greater detection and better-established, safer surgical repair, interest in large-scale AAA screening developed -especially in Europe and Australia- in the early 1990s.

1.6.2 AAA screening trials

There have been four RCTs that compared US screening for AAA with unscreened controls, these are summarised in Table 1.4. The first RCT was conducted in Chichester, UK and was the only trial that included females, but given the lower prevalence of AAA detected in women, they were excluded from future trials. A meta-analysis of the screening trials concluded that AAA screening reduced AAA-specific mortality (rupture) in asymptomatic men over the age of 65, OR 0.60 (95%CI: 047-0.78) (85) and was associated with a trend to decrease overall long-term mortality in men (86).

The main conclusion from the trials was that US screening for AAA in men reduced death from AAA by 40%, was safe and cost effective and could be recommended. It was first adopted at a national level in England in 2009. Other countries have initiated national AAA screening programs, although protocols differ between countries (46).

Table 1.4 – Summary of the four AAA RCT screening trials

Study/ year	Country	Years	No. invited for screening	No. screened	Controls	Age	Preva-lence (%)	Screened (%)
Chichester 1995	UK	1988-1994	M 3,205 F 4,682	3,205 3,052	M 3,228 F 4,660	65- 80	M 7.6 F 1.3	M 73 F 65
MASS 2002	UK	1997-1999	33,839	27,147	33,961	65- 74	4.9%	80%
Viborg 2002	Denmark	1994-1995	6,339	4,843	6,319	65- 73	4.0%	69%
Western Australia 2004	Australia	1996-1998	19,352	12,213	19,352	65- 79†	7.2%	63%

† Expected age at midpoint of the study, *M:* males, *F:* females

The studies were fairly similar in design but the higher prevalence seen in the Western Australian and Chichester studies could be due to their inclusion of >75 year old men, compared to the other two studies.

There appeared to be some other benefits of screening from these studies; men who underwent AAA repair from the screening arm of the RCT had lower postoperative mortality compared to men in the control group who underwent AAA repair (87). This could be due to the medical treatment and risk-factor modification initiated during AAA surveillance. This finding also supports the notion that screening for AAA is beneficial.

Outcome data outside the RCTs differed from that observed within the AAA screening programs. The longest reported AAA program has been running in Gloucestershire, UK since 1990. This program reported a decrease in AAA rupture during the study period thought to be related to the screening program (88). On the other hand, in Malmo, Sweden, Otterhag and colleagues have suggested that the incidence of AAA rupture has been

decreasing between 2004-2010 prior to the introduction of the national AAA program in late 2010 (89).

Compared to other cancer screening programs, AAA screening reduces death by 4 per 1000 (21) (breast cancer screening reduces death by 0.7 per 1,000 and colorectal cancer screening reduces death by 1.5 per 1,000). The number of people needed to be screened to save one life from death by AAA is 217 (86).

1.6.3 Established screening programmes

The overall prevalence from the NAAASP in England from the first 700,000 screened men was 1.34% and the mean uptake was 78.1% (range: 61.7-85.8%). Interestingly, during the same study period, there were 27,421 men over 65 years who self-referred and their AAA prevalence was 2.8%. This may simply be due to AAA prevalence increasing with age, or other individual reasons such as having a family history of an AAA or having higher risk factors (90).

In Sweden, the screening program started in one county in 2006 and was introduced throughout the country in 2010. The overall prevalence of AAA in 65-year-old men was 2.2%, including 0.5% of the eligible population with a known or previously repaired AAA (20).

In the United States, following a meta-analysis of published AAA screening studies (91), a recommendation for screening all men and women aged 65-75 who had ever smoked or those with a known family history of AAA was introduced as a package by Medicare (92). The uptake of this program has generally been very low (93) and outside AAA screening recommendations (92, 93). The prevalence of AAA from a single Veterans Affairs centre was relatively high at 7.2%, perhaps reflecting the impact of smoking (94).

In Denmark, a second RCT trial- the Viborg Vascular (VIVA) has been completed to determine if AAA screening in this decade is still considered beneficial. Preliminary data suggests that the prevalence of AAA in men

(aged 65-74 year) is 3.3% (95). The mortality outcomes for both groups have not been reported to date.

1.6.4 Cost effectiveness of AAA screening

Cost effectiveness of an AAA programme is defined as the comparison of the costs of the proposed screening program compared to the *status quo* in AAA clinical management. This relies on the costs encountered for this treatment or strategy divided by the health utility or quality of adjusted life years gained or lost (96).

The following parameters are required to be met to determine the cost effectiveness: prevalence of AAA, mortality rates, cost associated with treatment and the quality of life of patients. Data from RCTs have provided the costs and quality of life for AAA patients that had not undergone screening (i.e. had their AAA diagnosed incidentally).

There are two types of AAA screening cost-effectiveness evidence models discussed within the literature; 1) actual costs from prospective trials, 2) predictive models based on published studies that can test a range of estimates. Estimating costs for any screening program is a complex process and has to be modified to accommodate local practices and health expenditure. There is some disagreement regarding the cost-effectiveness of screening programs (97), and the method of economic modelling used can have limitations and impact the conclusions drawn (98).

Contemporary national AAA screening programmes have reported lower AAA prevalence rates. Despite the lower prevalence of AAA being detected in the UK after the introduction of the NAAASP, a revised and updated cost-effectiveness model using current data and long-term data from the MASS trial showed that the AAA screening programme remained hugely cost-effective (99, 100). This finding has also been observed in Sweden where the prevalence of AAA was estimated to be 1.3% (101). In another cost-effectiveness model from Sweden, screening for AAA remained cost-effective even with a low prevalence of 0.3, provided the background incidental AAA detection remains low (<30%) (44).

1.6.5 Reasons for lack of screening

AAA burden is not evenly distributed around the globe and mainly affects Caucasians in Western countries. In continents such as Africa and Asia, AAA disease is very uncommon and therefore AAA screening programs would very likely to be less beneficial and non-cost-effective. In addition, the screening can be costly to nations with health budget constraints.

Another reason for the slow uptake of screening programs is related to the suggestion that the incidence of AAA is decreasing, therefore it is deemed unnecessary to implement screening. A potentially important but perhaps less reported reason for not implementing AAA screening is due to the costs to healthcare in an era where constraints to governing health authorities are already stretched.

1.7 Challenges

From the information presented to date, several challenges in the management of AAA have been encountered, and despite the intensive research in this field, many questions remain unanswered. It is important to note that the majority of previous studies were conducted 20-30 years ago and there is a need for more contemporary data to inform discussion given the rapid evolution in our understanding and treatment of AAA.

1.7.1 Women and AAA disease

The screening and management of AAA in women is a particular challenge, primarily because the majority of AAA research has included more men. Traditionally, woman have been excluded from AAA screening trials as the prevalence of AAA in women is 4-5 times less than men. Only one RCT included 4682 women invited for screening and 4600 women included in the control group. There were 3052 women that attended aortic screening and an overall prevalence of 1.3% was documented. Interestingly, the acceptance rates for women were lower across all age categories when compared to men. This study did not show a benefit for screening AAA in women (102).

A study from Sweden that invited 6,925 women of which 5,140 accepted and attended an AAA screening had an overall prevalence in non-smokers of 0.03% and 2.1% for current smokers (103). This strongly suggests that women who never smoke should not be included in screening programs. Also, women with a history of smoking have a higher incidence than men who have never smoked (104).

The second challenge that arises with this gender difference is that women presenting with an AAA rupture present approximately 6 years older than men. Although women in the general population have a longer life expectancy than men, when AAA disease is present, this relationship inverses and women seem to have higher mortality following repair. In a meta-analysis, the pooled 30-day mortality after elective AAA repair is significantly higher in women following OAR and EVAR with adjusted odds ratios for age being 1.28 (95% CI: 1.09-1.49) and 2.41 (95% CI: 1.49-3.88) when compared to men (105). The influence of gender on long-term survival following AAA repair is still controversial.

1.7.2 AAA in the elderly

Life expectancy in the developed world is increasing and health services are observing the increased costs of delivering health care. With regards to AAA, prevalence increases with age in both genders. The average age of patients with AAA presenting to hospitals is increasing (15).

This has also been shown from a decade of AAA presentations in Australia where the trend of non-rupture AAA in men over the age of 80 has increased (14). Elderly men >75 years old who undergo AAA repair and survive confer the most benefit and have lower standardized mortality ratio than the normal population (48).

With a lower 30-day mortality with EVAR, some elderly patients who prior to the EVAR trials would have been deemed unfit for the conventional repair, might benefit from EVAR particularly if death caused by AAA rupture is prevented.

Although an increase in age is associated with worse short-term and long-term outcomes, the actual association (in isolation) is small compared to other predictors such as cardiac, respiratory or renal disease.

1.7.3 Targeted screening

Targeted or selected screening can be defined as focused strategies to increase the efficacy or yield of a screening program. The proposed AAA screening programs in the UK, Sweden, USA and others are considered targeted/selective, as men over the age of 65 years old in the UK and men or woman with a history of smoking 100 or more cigarettes during a lifetime (as part of a Medicare package) in the USA are eligible for screening. As AAA predominantly affects men >60 years old, there is no doubt that the screening is targeted to a certain degree to remain effective.

In order to improve detection and increase the yield of AAA screening, a more targeted approach has been suggested. Owing to the well-established risk factors for AAA development, selecting patients according to age, smoking history and the presence of cardiovascular risk can all be factored into screening targeted groups.

The drawbacks of such approaches include the fact that selecting people with higher risk factors who might have a lower relative survival might cause the overall benefits of AAA treatment not be observed. Moreover, there are ethical implications if fit patients are not offered screening when the chances of developing an AAA are still 1 to 3%.

The prevalence of AAA increases in patients with IHD (106, 107) and in one study this relation was proportional to the number of coronary vessels involved (108). Another relatively simple and selective screening is to scan all patients referred to the vascular US laboratory for an AAA. This approach has demonstrated a strong association of AAA presence with patients who have significant lower extremity, carotid artery stenosis and renal artery stenosis (109).

Inviting men at 65 years of age will not diagnose all men with AAA in the community. This is supported by data from Finland, which included 587 patients presenting with a ruptured AAA over a 12-year period. The authors showed that 18.3% of patients with ruptured AAA were in fact younger than 65 years of age. Of these, 21.4% were males less than 65 years of age and 3% were females (110). This indicates that within the most commonly proposed AAA screening program paradigm, inviting men on their 65th birthday, one in five affected men would potentially have an AAA rupture prior to screening.

Data from the Western Australian AAA screening randomised controlled trial revealed that if AAA screening was targeted to the known risk factors, 25% of patients would be missed, thereby improving the specificity of AAA detection, but with a trade-off in detection sensitivity (111). Another limiting issue within targeted screening approaches is the likely selection of older patients with AAA, as has been observed in the Western Australian (111) study and other studies (108). These examples highlight the potential issues that might arise if more targeted AAA screening programmes were to be applied.

1.7.4 Barriers to AAA screening

Information on AAA population screening is now available from national programmes. Some of the identified barriers to AAA screening in men were: recent immigration, low income and education levels, being single or divorced and having to travel long distances (112). Two studies from different regions in Scotland, where the reported uptake of each program was >85%, identified that an increase in deprivation decile was associated with lower attendance to AAA screening (113-115).

1.7.5 Who to target for AAA screening?

AAA screening has traditionally been targeted towards men at 65 years of age and this was the strategy used by governmental health authorities during the mid-1990s to the mid-2000s. Emerging evidence has revealed

that the change in AAA epidemiology, lower preoperative mortality with repair and improved life expectancy should be considered rather than the adaptation of the same screening guidelines.

Many developed cities have an overrepresentation of multicultural and ethnic societies, which could underestimate AAA prevalence, as the disease is less common in non-white persons. In the UK, men from the following ethnic backgrounds: Asian, Black and Chinese have very low prevalence of AAA and had higher attendance rates compared to white British males (21). Therefore, the number needed to be screened increases when non-White men are screened. This has also been seen in the USA where ethnic minorities had a lower prevalence of AAA.

In addition, a family history of AAA increases the chances of having an AAA in both males and females (116). This group of patients has a higher prevalence of AAA than the general population and present at a younger age (117).

1.8 New Zealand Specific AAA Data

National health bodies are investigating the implications of an AAA screening program in NZ and local national data is required to assist with this process. Population screening to estimate the prevalence of AAA in New Zealand has never been conducted. However, there are indications that the disease burden is significant. A study of ruptured AAAs in Auckland from 1993-1997 reported a 6.1 per 100,000 per year (118), which is in the mid- range of the reported incidence of ruptured AAA from a systematic review that included 22 studies ranging between 2.9 to 14.1 per 100,000 persons per year (6).

In New Zealand (NZ), where there are several ethnic groups including the indigenous people of NZ – Māori, it is important to know what the prevalence of AAA is as Māori have higher health disparities than NZ Europeans. With regards to AAA risk factors, Māori have high smoking rates particularly in Māori women.

Māori in general have a higher mortality after AAA repair and present at a younger age than non-Māori (119). Māori women appear to have AAA mortality rates almost comparable to NZ European males and substantially greater than NZ European females (120). The drivers of this high mortality have not been well documented.

Specific research on AAA burden in NZ is limited to a few studies. Therefore, obtaining local national data is vastly important so a decision on the appropriateness of an AAA screening program can be made. In New Zealand, it is estimated that 236 deaths per year can be attributed to AAA (121). This figure does not include the number of people with ruptures that do not present to hospital and do not undergo emergency repair. Contemporary data regarding burden of AAA, workload, and annual mortality rates in NZ is lacking.

Estimating prevalence of AAA in New Zealand will be the primary focus of Chapter 2 in this thesis. In chapter 4, interrogation and validation of the available NZ data on AAA will be presented.

1.9 Academic Papers

This doctoral thesis has been completed with the publication of ten articles, five of which contributed directly to chapters and the remaining five as supplementary or exploratory work. However, the amount of repetition was kept to a minimum. The summary of the five publications, author contribution and reference is outlined in Table 1.5.

Permission has been granted by journal publishers to include this content and some of the published figures in this thesis.

Table 1.5 Summary and contribution of published articles included directly into chapters

Chapter	Paper title	Authors	Contribution of candidate	Journal	Status
2	Prevalence of Abdominal Aortic Aneurysm (AAA) in a Population Undergoing Computed Tomography Colonography in Canterbury, New Zealand	Khashram, Jones & Roake	Candidate synthesised findings and wrote the manuscript. Co-authors provided guidance on interpretation and had editorial input into final drafts	Eur J Vasc Endovasc Surg	2016: 50 (2) 199-205
4	Abdominal Aortic Aneurysm Repair in New Zealand: A Validation of the Australasian Vascular Audit	Khashram, Thomson, Jones & Roake	Candidate designed the study and wrote the manuscript. Co-authors provided guidance and editorial input into final drafts	ANZ J Surg	Date: 2016 Aug 4 doi: 10.1111/ans.13702
5	Systematic Review and Meta-analysis of Factors Influencing Survival Following Abdominal Aortic Aneurysm Repair	Khashram, Williman, Hider, Jones & Roake	Candidate designed, conducted and analysed search and wrote the paper. Co-authors assisted in data interpretation and reviewed manuscripts	Eur J Vasc Endovasc Surg	2016; 51(2):203-15
5	Management of Modifiable Vascular Risk Factors Improves Late Survival following Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-Analysis.	Khashram, Williman, Hider, Jones & Roake	Candidate designed, conducted and analysed search and wrote the paper. Co-authors assisted in data interpretation and reviewed manuscripts	Ann Vasc Surg	2016 Sep 22 doi: 10.1016/j.avsg.2016.07.066.
5	Does the Diameter of Abdominal Aortic Aneurysm Influence Late Survival Following Abdominal Aortic Aneurysm Repair? A Systematic Review and Meta-Analysis	Khashram, Hider, Williman, Jones & Roake	Candidate designed, conducted and analysed search and wrote the paper. Co-authors assisted in data interpretation and reviewed manuscripts	Vascular	2016;24(6):658-667

1.10 Structure of Thesis

This thesis will focus on the methods of detection and management of AAA disease. The thesis will provide prevalence of AAA in a large selected population undergoing CT colonography (chapter 2). The definition and risk factors of developing AAA and how the aortic diameter influences survival will be provided in chapter 3. Data relevant to AAA treatment and outcomes in New Zealand will be collected and analysed to describe the burden of AAA in New Zealand (chapter 4). The prognostic factors that influence survival following AAA repair will be documented and quantified from a systematic review and meta-analysis of the published literature (chapter 5). Predictors of short- and long-term survival will be then fitted into a prognostic model that will inform the gains (or losses) in survival of AAA repair for an individual patient. This model will be validated with established databases (chapter 6). Finally, chapter 7 discusses and summarises the entire thesis and highlights directions for future research and limitations encountered.

"There is no disease more conducive to clinical humility than aneurysm of the aorta"

William Osler 12 Jul 1849 - 29 Dec 1919

Chapter 2: The Use of CT Colonography to Determine the Prevalence of AAA

2.1 Overview

Due to the fact that abdominal aortic aneurysm (AAA) rupture has an overall mortality exceeding 80%, elective AAA repair is one of the most effective surgical procedures for prevention of premature death from AAA rupture. This necessitates an effective method of detection, as aneurysms are usually asymptomatic.

Interest in AAA screening initially started in the 1980s following a better understanding of the natural history of AAA and the increased mortality associated with non-operative management in AAA > 5cm. In addition, the use of ultrasound (US) scan provides a relatively cheap and safe method for AAA detection.

Four studies randomised men over the age of 65-80 to an AAA US scan versus no scan and demonstrated a reduction in AAA-related mortality in the screened group. Denmark has undertaken a second randomized trial (Viborg Vascular screening trial, VIVA) to determine whether AAA screening is still beneficial in 65-74 year old men in the context of an apparent reduction in AAA prevalence. The medium- to long-term results are not published yet but a prevalence of 3.3% has been reported (95) and it is likely that screening will remain cost effective within Europe.

In New Zealand (NZ), a large national randomised study is unlikely to be undertaken given well-established evidence provided by the international studies. The costs of such a trial would potentially be better used for the development of an AAA detection program. However, NZ lacks even basic local information on AAA including prevalence.

To provide AAA prevalence information, an observational study was undertaken in the Canterbury region of the South Island of NZ.

The questions that arise from this in relation to AAA screening in NZ are:

1) What is the prevalence of AAA in the general population?
2) What are the predictors for AAA presence and demographics of patients with AAA disease?
3) In those people with AAA, how does the life expectancy match the general population?

2.2 Contribution

In this project, I was the principal investigator for the research. I performed all measurements of the AAA from the CTC images stored on the Picture Archiving and Communication System (PACS), then collected demographical, clinical risk factor and outcome data on patients with AAA. I performed the data analysis and noted some inaccuracies in death records. An application to the Ministry of Health was made to obtain accurate and current survival statuses of the included patients.

2.3 Publication

Khashram M, Jones GT, Roake JA. Prevalence of Abdominal Aortic Aneurysm (AAA) in a Population Undergoing Computed Tomography Colonography in Canterbury, New Zealand. *European journal of vascular and endovascular surgery.* 2015; 50 (2):199-205

2.4 Background

Abdominal aortic aneurysm (AAA) screening using an abdominal ultrasound has been shown to reduce AAA mortality in asymptomatic men over the age of 65 (85). The uptake of national screening programs has been slow for several reasons. These include changing epidemiology (18, 122), lack of funding or awareness and varying AAA prevalence among different populations and ethnicities. In NZ, the true prevalence of AAA is unknown and detection still relies on incidental findings from radiological modalities and referrals from other physicians. The global AAA burden has diminished between 1990 and 2010 but the AAA prevalence remains relatively high in

Australasia and Oceania (19). However, there is some evidence of decreasing age-specific mortality from AAA in NZ (13).

2.4.1 Surrogate screening with CT colonography

To determine the prevalence of AAA in Canterbury, the wide-spread use of CT colonography (CTC) acted as a surrogate for detecting AAA. The use of CTC for detection of colorectal diseases and colonic surveillance has gained popularity in our region as an alternative to optical colonoscopy due to constraints on the public health system in providing colonoscopy for symptomatic patients (123). It has also been used when colonoscopy could not be completed and in surveillance of colonic diseases. A CTC (also referred to as virtual colonoscopy) is a non-invasive, low dose CT that assesses the entire colon by inflating air via the rectum to allow distension of the colon and visualisation of colonic pathology. Other potential advantages of CTC include detection of extra-colonic pathologies, such as AAA, at no additional cost or radiation risk. CT also permits assessment of the entire aorta (usually descending thoracic aorta to femoral bifurcation) and precise measurement of the aortic wall without hindrance from bowel gas or obesity.

2.4.2 Selection process

A pathway to triage patients with gastrointestinal symptoms was introduced in 2008. Depending on clinical symptoms, physical examination findings, family history and laboratory results, a higher score will direct referrals towards an endoscopic colonoscopy, while a low score will direct referrals to a CTC first approach (123). The point system and decision tree is included in appendix 8.1.

2.4.3 CTC and AAA detection

The retrospective options to document the prevalence of AAA would be to use radiological imaging modalities (such as US, CT or MRI) to measure aortic diameters. The reasons for choosing CTC as opposed to the other modalities were: first, there are mutual risk factors and demographics (age groups) between AAA and CRC; second, patients referred for CRC

investigations with the primary aim of detection are likely to benefit from treatment should abnormal pathology be detected; and third, as CTC has been used as a screening test, it is likely to capture a group of patients from primary care whose medical conditions were not severe enough to warrant tertiary hospital care.

Previous Markov-simulation-modelling studies revealed that dual screening for colorectal cancer and AAA using CTC was more cost-effective in a hypothetical population when compared to optical colonoscopy and an abdominal aortic ultrasound (124, 125). While AAA screening randomised trials used an US to measure abdominal aorta in the absence of a national US screening programme, the aim of this study was to use CTC as a surrogate for US to document the prevalence of AAA.

2.5 Objectives

The primary objectives of this research was to document the prevalence of AAA in the population undergoing CTC examination in the Canterbury region of the South Island and to determine the predictors of developing AAA and the factors that influence overall survival.

2.6 Methods

This was a retrospective observational study. From 1st of January 2009 to 1st of April 2013, consecutive CTC performed in the Canterbury, West Coast and Timaru regions of the South Island of NZ were retrieved from the PACS database. The retrospective nature of the study precluded individual patient consent. The study was approved by the national Health and Disability Ethics Committee and the Canterbury District Health Board approved locality assessment.

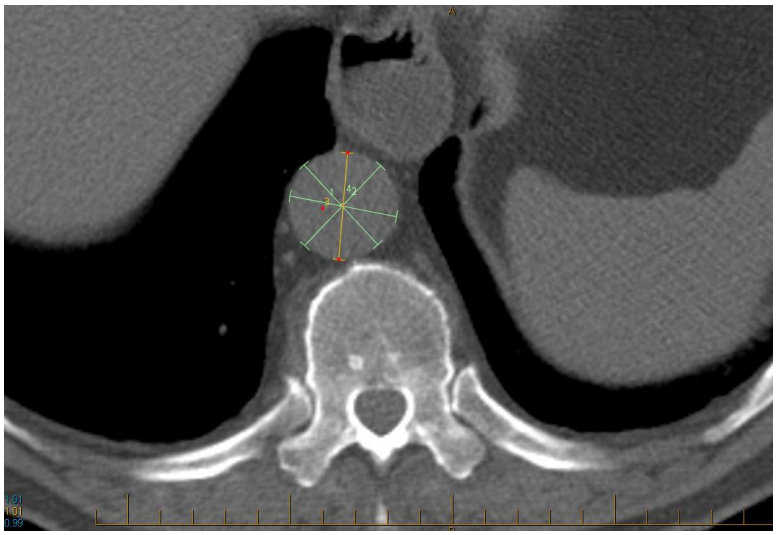
The CTC examination was performed at seven different centres with similar imaging protocols. A rectal or stomal tube was inserted for air inflation, and a helical CT with 2.5mm slices was performed in prone and supine positions with a large field of view. Intravenous contrast was used if the diagnosis of

malignancy was known or as indicated clinically. The presence of a distended distal bowel and rectal tube or a stomal tube ensured that the scan was a CTC.

2.6.1 Measurements

The entire available aorta from the series (usually from the descending aorta into the femoral bifurcation) was meticulously assessed. Measurements were performed with a digital magnified view, at eye level to avoid any parallax, using outer wall to outer wall diameters and fine electronic calipers also ensuring the line of measurement passed through the centre of the aneurysm (Figure 2.1) (126). Maximum short axis diameters were recorded to 0.1mm. The presence of thoracic and abdominal aorta $\geq$30mm, iliac and femoral arteries $\geq$20 mm and visceral artery $\geq$15mm were recorded. The presence of previous aortic prosthetic grafts or endovascular stent grafts was also documented. All measurements were carried out by the same investigator (MK).

A



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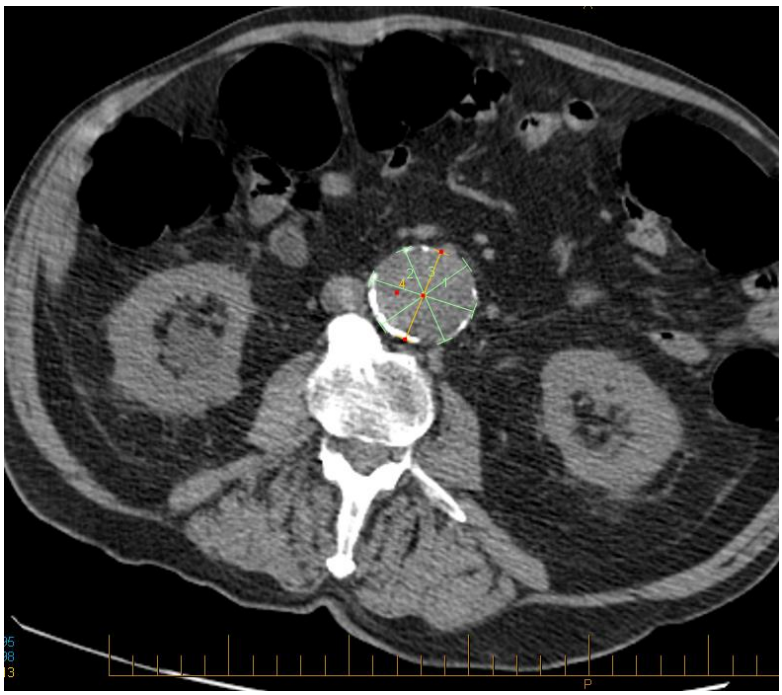


Figure 2.1 CTC transverse sections of the aorta with variations in diameter measurements

(A) Aortic measurement performed in four different axes showing very similar AAA diameters between 3.30 and 3.39cm

(B) An irregular-shaped AAA with diameters ranging between 3.95 and 4.48cm

2.6.2 Patient data collection

Death data was obtained from the hospital electronic database and ambiguous dates were checked by phone interview with patients or their family practitioner. It was noted that death records were not always accurate using the hospital's patient-management software. Therefore, dates of death, deprivation status and ethnicity data were requested and obtained from the Ministry of Health National Minimum Data Set.

Deprivation index was defined as the measure of the socioeconomic status of geographical areas based on the NZ 2013 census data where 1 is least deprived and 10 is most deprived (57). Clinical risk factors, aneurysm location, CRC diagnosis and causes of death were collected from patients with aneurysms or previous aortic surgery. CTC radiologist reports were viewed to determine whether the presence of aneurysms was commented on and patients were on an AAA surveillance program. The largest aneurysm diameter was defined as the primary aneurysm and other aneurysms detected were referred to as secondary. Estimated predicted life-expectancy figures were obtained from the New Zealand life tables 2010-2012 (www.stats.govt.nz) for a fictive population matched to age and sex (127).

2.6.3 Validation of AAA measurement with CTC and USS

Patients with AAA who had an US scan within 6 months before or after the index CTC study were identified. Maximum anterior-posterior diameter measurements were recorded as measured independently by the radiologist or sonographer at the time of the scan. At the time of the AAA measurement from the CTC, the investigator was blinded to the AAA US measurement.

2.6.4 Statistical analysis

Continuous variables were described as either mean (standard deviation, SD) or median (range or interquartile range, IQR) as appropriate, and categorical variables as percent frequencies. Preliminary analysis indicated that the continuous explanatory variables (age and deprivation) were related to AAA presence (binary) on a linear rather than a logarithmic scale,

therefore linear regression models were used to calculate unadjusted and adjusted rate differences (128). Risk ratios were also calculated for categorical variables using Poisson regression with robust standard errors due to non-convergence of log binomial models (129). Kaplan-Meier methodology was used for survival analysis and log-rank test was used for univariate group comparison. Cox proportional hazard models were used to calculate adjusted and unadjusted hazard ratios (HR) for variables influencing survival. Survival data was censored on the 1st of October 2014. The Pearson's R test was used for correlation of a sample of patients that had a CTC and US of the AAA within a 6 months period. Statistical significance and 95% confidence intervals (CI) were calculated with an alpha of 0.05. Statistical analyses were performed using SPSS 22 for Mac (SPSS Inc., Chicago, IL).

2.7 Results

During the study period, 4915 CTC scans were performed on 4665 individuals. Of these scans, 22 where coded on the PACS database as CTC studies but either were not a CTC when the scans were reviewed or the raw axial images were not stored and hence were excluded from any further analysis. Therefore, 4893 scans on 4644 patients with a male to female ratio of 1: 1.4 and a median (range) age of 69.2 (17.4 to 97.4) years were reviewed. No AAA was detected in 925 people aged <55 years old and this group has been excluded from any subsequent analysis (Figure 2.2). Median (range) age of the remaining 3719 individuals was 72.9 (55.0 to 97.4) years. There were 289 patients who had either an aneurysm in any location or a previous abdominal aortic prosthetic graft inserted. The location of aneurysms and abnormal aortas detected are summarized in Table 2.1.

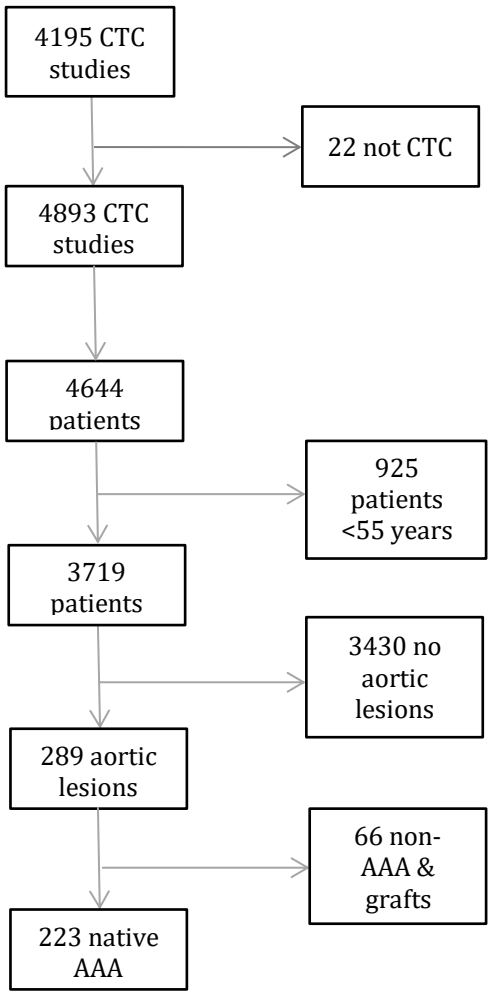


Figure 2.2 Flow diagram representing the patient identification process

Table 2.1 Proportion of ≥3cm thoracic/abdominal aneurysms and ≥2cm iliac/ femoral/ visceral aneurysms in 289 patients

Location	N
AAA, native	223 (77.2%)
AAA, graft †	26 (9.0%)
Iliac	23 (8.0%)
Thoracic	5 (1.7%)
Femoral	1 (0.3%)
Prosthetic graft ‡	9 (3.1%) (6 open, 3 EVAR)
Visceral	2 (0.7%)

†, Graft diameter ≥3cm, ‡ graft diameter <3cm (EVAR: endovascular aneurysm repair)

2.7.1 Patient Demographics

There were 223 patients with a native AAA and 3,496 without an AAA. Patients with an AAA were seven years older and more likely to be male than those without an AAA . The proportion of patients with IHD, COPD, diabetes, hypertension, receiving a statin and have a smoking history was higher in the AAA group. The creatinine serum levels were similar between both groups. On the other hand, individuals without an AAA had a higher proportion of a cancer history than patients that had an AAA. The deprivation scores and ethnic composition were similar between both groups. The demographics and risk factors are presented in Table 2.2.

Table 2.2 Demographics and baseline characteristics of patients undergoing CTC

	AAA	No AAA
Age/ years, median (range)	79.7 (57.4-96.2)	72.2 (55-97.4)
Males, n (%)	166 (74.4)	1387 (39.7)
Ethnicity, n (%)		
NZ European/European	210 (94.2)	3243 (92.8)
Māori	4 (1.8)	75 (2.1)
Other/unknown	9 (4.0)	178 (5.1)
AAA diameter / cm, median (range)	3.3 (3-9.4)	NA
AAA neck location, n (%)		NA
Infra-renal	203 (91.0)	
Juxta-renal	14 (6.3)	
Suprarenal	6 (2.7)	
IHD, n (%)	113 (50.7)	683 (19.5)
Statin, n (%)	139 (62.3)	1180 (33.8)
Hypertension, n (%)	195 (87.4)	1822 (52.1)
COPD, n (%)	51 (22.9)	354 (10.1)
Creatinine/ µmol/L, mean (SD)	106.7 (34.6)	89.0 (40.0)
Diabetes, n (%)	43 (19.3)	455 (13.0)
Cancer history, n (%)	19 (8.5)	484 (13.8)
Smoking, n (%)		
Never	49 (22.3)	2125 (60.8)
Ex-smoker	137 (62.6)	951 (27.2)
Current	33 (15.1)	238 (6.8)
Deprivation index, n (%)		
1-2 (better SES)	30 (13.5)	476 (13.6)
3-4	36 (16.1)	727 (20.8)
5-6	46 (20.6)	825 (23.6)
7-8	91 (40.8)	1146 (32.8)
9-10 (worse SES)	21 (9.4)	309 (8.8)
AAA in surveillance, n (%)	84 (37.3)	NA
Secondary aneurysm, n (%)	20 (9.0)	NA
AAA reported, n (%)	158 (70.9)	NA

Number of patients = 3719

IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease, SES: socioeconomic status, NA: not applicable

Two hundred and fifty eight individuals had either a ≥3cm AAA or an abdominal aortic graft present. Of those, 223 had a native AAA, 26 had either a dilated prosthetic graft or a residual post-EVAR AAA sac ≥ 3cm, and 9 had a <3cm aortic graft. The CTC identified 165 (74%) new incidental AAA and

the rest had a known AAA on prior imaging. The median (range) age was 79.7 (57.4-96.2) years, while 74.4% of those with AAA were male and 94.2% were of NZ European or European ethnicity. Native AAA in the infrarenal position was the most common aneurysmal site.

2.7.2 AAA prevalence

The overall prevalence (95%CI) of all AAA ≥ 3cm was 258 amongst 3719 individuals (6.9%, 95% CI: 6.1-7.8). After excluding 35 prosthetic AAA grafts, the prevalence was 223/3684 (6.1%, 95% CI: 5.3-6.9). The prevalence of native AAA in males and females 55-64.9, 65-74.9, 75-84.9 and ≥85 years of age was 1.3, 9.1, 16.8, 22.0% and 0.4, 2.0, 3.9 and 6.2% respectively (Figure 2.3).

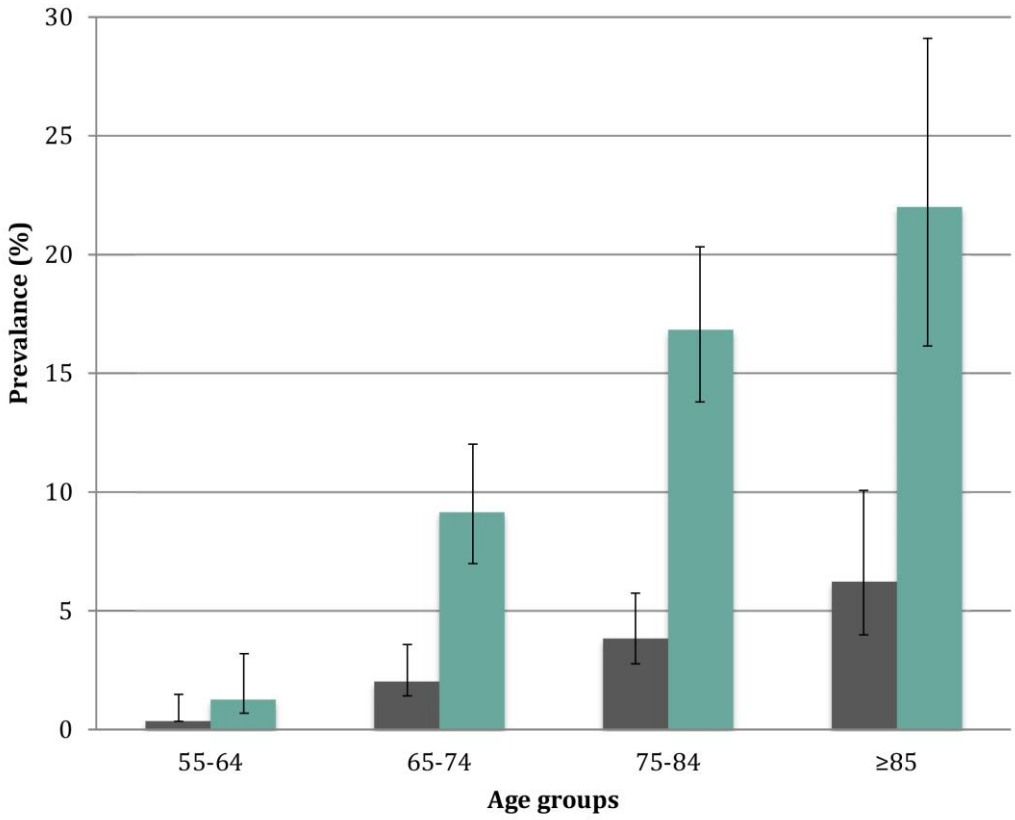


Figure 2.3 Prevalence of AAA stratified to age bracket and sex

Number of patients = 233. Error bars present 95% confidence intervals. Blue bars indicate males, grey bars indicate females

The distribution of native AAA diameter according to sex is presented in Figure 2.4. Regardless of gender, 72.2% (161/223) of AAA patients had a 3-3.9cm aneurysm and 10.3% (23/223) had a ≥5 cm AAA.

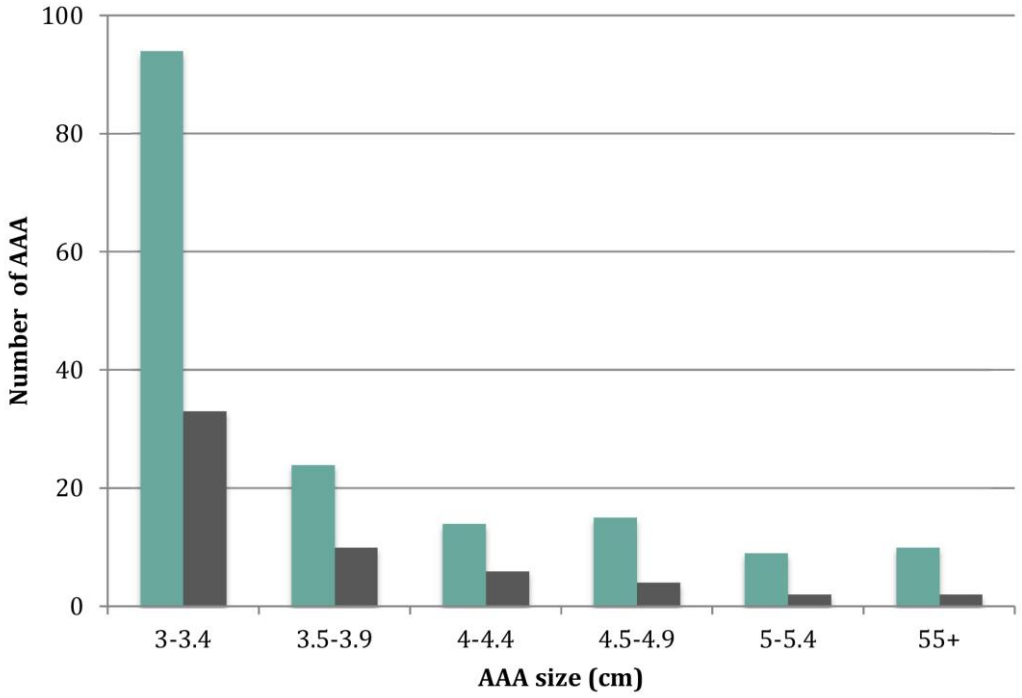


Figure 2.4 Distribution of AAA diameter stratified to sex

Number of patients = 223. Blue bars indicate males, grey bars indicate females

2.7.3 Predictors for AAA presence

There was a significant association between presence of an AAA and advanced age (>55 years), with an increase in prevalence rate of 4% (95% CI: 3.0-5.0, P < 0.001) for each 10-year increase in age. Male gender was also a strong predictor for AAA presence with a risk ratio of 4.08 (95% CI: 3.1-5.4, P < 0.001). Patients with a higher deprivation index (≥5) were weakly associated with AAA at a univariate level (P<0.03). Ethnicity was not a significant predictor of AAA presence in this model (Table 2.3).

Table 2.3 Predictors of AAA presence using a linear regression model

		Unadjusted			Adjusted †		
Continuous Variables	**Median (IQR)**	**Risk difference**	**95% CI**	**P**	**Risk difference**	**95% CI**	**P**
Age	79.7 (73.8-84.1)	4%	3.0-5.0	< 0.01	4.0%	3.0-5.0	< 0.01
Deprivation	6 (5)	0.3%	0-0.6	0.08	0.16%	-0.1-0.5	0.2
Categorical variables	**AAA prevalence n (%)**	**Risk Ratio**	**95% CI**	**P**	**Risk Ratio**	**95% CI**	**P**
Age							
55-64	7 (0.7)	1 (ref)	-	-	1 (ref)	-	-
65-74	59 (5.0)	6.7	3.1-14.6	<0.01	6.8	3.1-14.6	< 0.01
75-84	123 (9.2)	12.5	5.8-26.7	< 0.01	12.3	5.8-26.2	< 0.01
85-94	48 (11.9)	16.1	7.3-35.2	< 0.01	16.7	7.6-36.5	< 0.01
Sex							
Male	166 (10.7)	4.06	3.0-5.5	< 0.01	4.08	3.1-5.5	< 0.01
Female	57 (2.6)	1 (ref)	-	-	1 (ref)	-	-
Deprivation							
1-5	91 (5.1)	1 (ref)	-	-	1 (ref)	-	-
6-10	132 (6.9)	1.4	1.0-1.8	0.02	1.3	1.0-1.6	0.08
Ethnicity							
NZ European	210 (6.1)	1 (ref)	-	-	1 (ref)	-	-
NZ Māori	4 (5.1)	0.8	0.3-2.2	0.55	1.5	0.6-3.8	0.6
Other/& Unknown	9 (4.8)	0.8	0.4-1.5	0.51	0.9	0.5-1.7	0.8

IQR: interquartile range, CI: confidence intervals, ref: reference, † Adjusted for other variables in the model

2.7.4 Location of patients undergoing CTC

The number of CTC scans performed annually from 2009 to 2012 was 1039, 1174, 1169 and 1178 respectively. Patients had their CTC examinations performed at four main locations: Timaru 2561 (55.1%), Christchurch 1113 (24.0%), Ashburton 806 (17.4%) and the West Coast 164 (3.5%).

Of the 3719 individuals analysed, 2012 had their CTC scans performed in Timaru, 936 in Christchurch, 648 in Ashburton and 123 in the West Coast region. The prevalence of AAA in each of the four geographical locations was

6.1% (95%CI: 5.10-7.19), 6.3% (95%CI: 4.92-8.05), 5.09% (95%CI: 3.65-7.07) and 6.5% (95%CI: 3.89-13.32) respectively.

2.7.5 Fate of patients with a native AAA

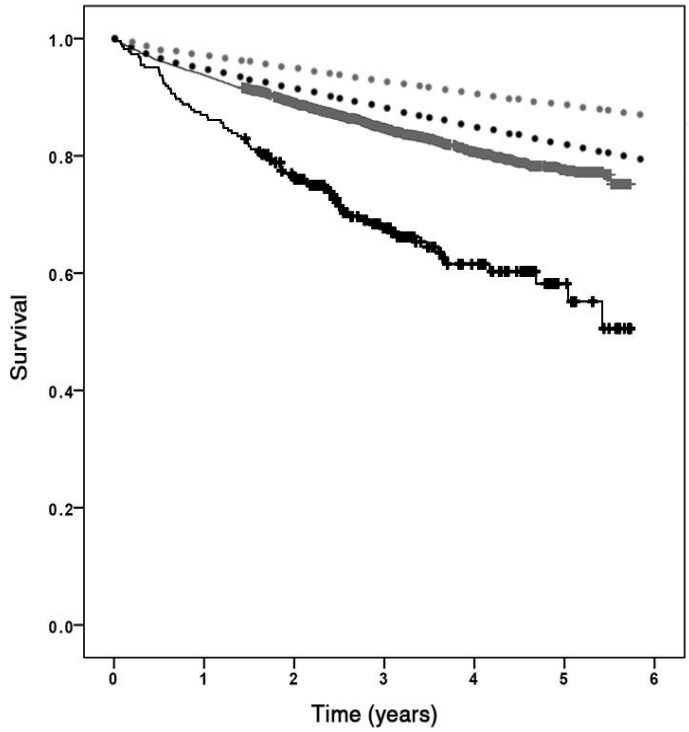
Of the 223 individuals identified with a native AAA, 23 (10.3%) had an AAA greater than 5cm and of these, 12 subsequently underwent AAA repair (9 open and 3 EVAR) during the follow-up period. Nine patients were thought not to benefit from repair; five due to medical comorbidities (primarily cognitive impairment), and four due to suprarenal extension of the aneurysm therefore deemed unfit for complex aortic procedures. Two patients were on surveillance (AAA <5.5cm). In all, 13 (56.5%) of those participants with a >5cm AAA were still alive at the completion of the study. Six died without repair, three died post-repair (>30days post operatively) and one died of an AAA rupture without repair.

2.7.6 Late survival of the population

The median (IQR) follow-up period was 3.2 (2.1-4.4) years. The Kaplan-Meier survival curves for study participants with AAA compared to those without AAA is shown in Figure 2.5 and Table 2.4. The 5-year observed survival of those with AAA was 55.1% (standard error 5.0), compared to 77.4% (0.9) in those without AAA (log-rank, P<0.0001). When adjusted for age and sex, the presence of AAA did not influence late survival, HR 1.24 (95%CI: 0.97-1.58, P=0.086). Estimated predicted life-expectancy figures from the New Zealand life tables 2010-2012 were plotted on the same graph for comparison.

There were 78 deaths in the AAA group. The causes of death during the study period were: 25 unknown causes, 19 cardiovascular, 14 cancer-related, 11 respiratory, 5 multi-organ failures, 2 sepsis and 2 AAA ruptures in female patients (3.8 and 9.4cm AAA).

A



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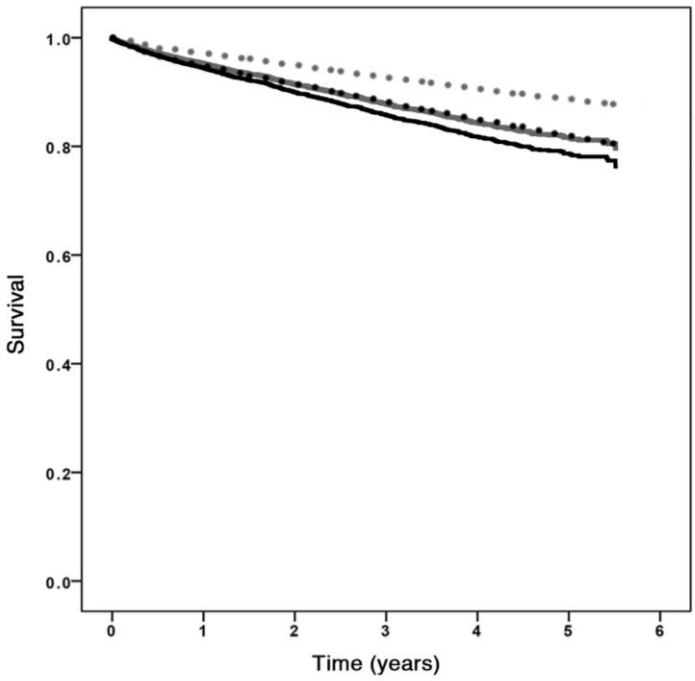


Figure 2.5 Survival analaysis of individuals with and without AAA

(A) Kaplan Meier observed (solid) and expected (dotted) survival curves of people with AAA (black line) and without AAA (grey line) (B) Cox proportional hazard of adjusted (age and sex) survival with expected (dotted) survival curves HR 1.24 P<0.086

Table 2.4 Cox proportional hazard model of variables affecting late survival

	Unadjusted			Adjusted †		
Variable	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age per decade	2.46	2.25-2.69	<0.001	2.46	2.25-2.70	<0.01
Sex (female)	0.61	0.53-0.71	<0.001	0.59	0.51-0.69	<0.01
AAA presence	2.28	1.8-2.88	<0.001	1.24	0.97-1.58	0.083
Deprivation per decile	1.02	0.99-1.06	0.16	1.00	0.97-1.03	0.83
Ethnicity						
NZ European	Ref	-		Ref	-	-
NZ Māori	0.82	0.46-1.45	0.49	1.35	0.76-2.4	0.30
Other & Unknown	0.52	0.33-0.82	0.005	0.66	0.42-1.04	0.073

HR: hazard ratio; CI: confidence intervals; Ref: reference † Adjusted for other variables in the model

2.7.7 CTC versus US measurement study

Of the 223 patients with a native AAA, 41 patients (18.4%) had undergone an US of the AAA within 6 months of the CTC examination. The investigator measuring AAA diameters using CTC was blinded to the results of the prior US scan. The median CTC and US AAA diameters were 4.1 and 4.2 cm respectively and there was excellent correlation between the two modalities (Pearson's R Correlation coefficient r=0.96, P <0.001). The potential source of bias in measuring AAA between CTC and US was tested using the Bland-Altman methodology. The mean difference was -0.06cm (limits of agreement: -0.56 to 0.56) (Figure 2.6).

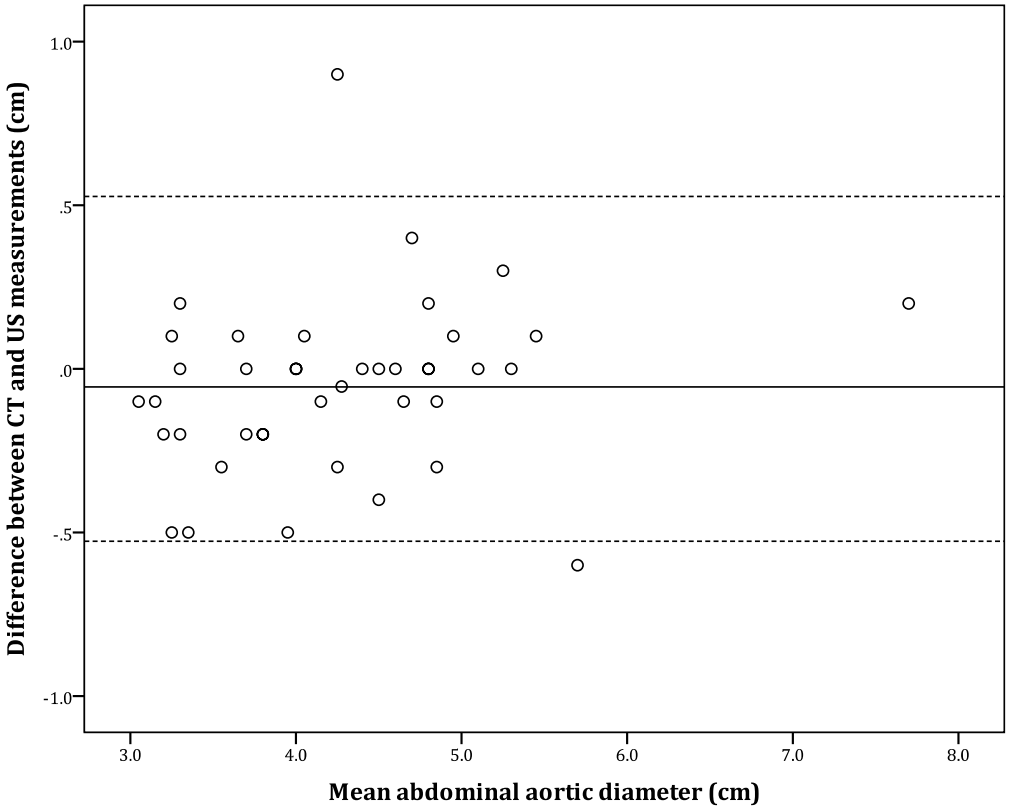


Figure 2.6 Bland- Altman plot showing the differences in aortic measurements between CTC and US

2.8 Discussion

In this study the prevalence of AAA in patients undergoing investigation with a CTC in the South Island of New Zealand was documented. A prevalence of 6.1% of AAA in individuals aged ≥55 was observed. This was similar to the prevalence that was observed with the randomized controlled screening trials that were conducted approximately 10 to 20 years ago in Western Australia (Health in Men Study, 7.2%) and the UK (MASS trial 4.9% and Chichester study, 7.6%) (22, 45, 130).

This study specifically aimed to use CTC to determine AAA prevalence. Previous studies reporting extra-colonic findings from CTC varied with respect to AAA prevalence, ranging from 1.4% to 5.4% despite similar demographics of groups included (131-133) as shown in Table 2.5. In contrast to previous studies which did not primarily focus on the status of the abdominal aorta, our current study represents the largest series to date specifically detecting AAA within a CTC patient cohort.

Table 2.5 Reported AAA prevalence from CTC studies

Author	Setting	Year of publication	N	Age	Male (%)	Prevalence (%)
Cash (131)	USA	2012	1410	75 (NR)	58	0.5
Moore (132)	NZ	2012	2142	59 (19-87)	47	1.4
Hellstrom (133)	Sweden	2004	111	66 (19-86)	59	5.4
Current (134)	*NZ*	*2015*	*4644*	*69 (17-97)*	*43*	*4.8*

NZ: New Zealand, NR: not reported, N: number

2.8.1 AAA NZ prevalence

In NZ, prior to a very recent study, the prevalence of AAA in the population was unknown. In the study by Majeed and colleagues published in 2015, 10,403 patients undergoing a transthoracic echocardiogram were also examined by an US for the presence of AAA. In men aged 65-74 years the AAA prevalence was 4.7% and rose to 8.5% in those 75-84 years (135). In this current study, the age-specific AAA prevalence rate detected by CTC was similar to that in patients undergoing echocardiography. Although increased AAA prevalence has been reported in association with severe (angiographically confirmed) coronary artery disease (108), the large proportion of angiographically normal subjects under evaluation for valvular disease in an 'echo-cohort' would most-likely mask a coronary-disease-driven prevalance effect. In addition, some of the differences between the echo-studied population and this study might be due to differences in AAA measurement between CT and US. Nevertheless, both studies highlight the relatively high burden of AAA prevalence in NZ as shown in Figure 2.7.

2.8.2 Combining all AAA prevalence studies from NZ

On the 3rd and 4th of July 2015, the NZ AAA screening working group met in Christchurch to discuss the existing knowledge of AAA prevalence, implications of a national program and translating contemporary evidence to areas where research is required. The results of six independent selective

groups revealed a consistent high prevalence of AAA among the studies (135, 136). The prevalence ranged between 3.2-6% depending on the average age of the group and the method the population was selected or invited. The prevalence from each study stratified to sex is presented in Figure 2.7.

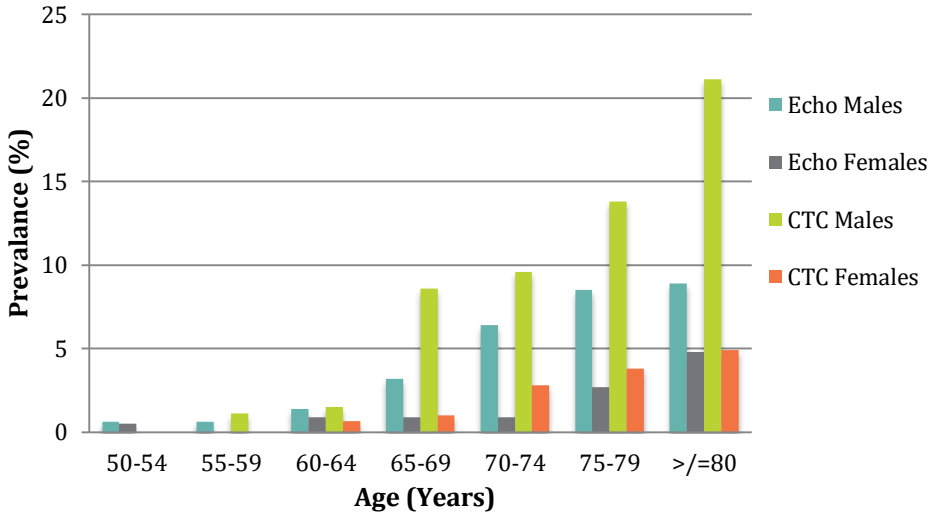


Figure 2.7 Prevalence of AAA from the CTC and transthoracic echo studies stratified by age and sex

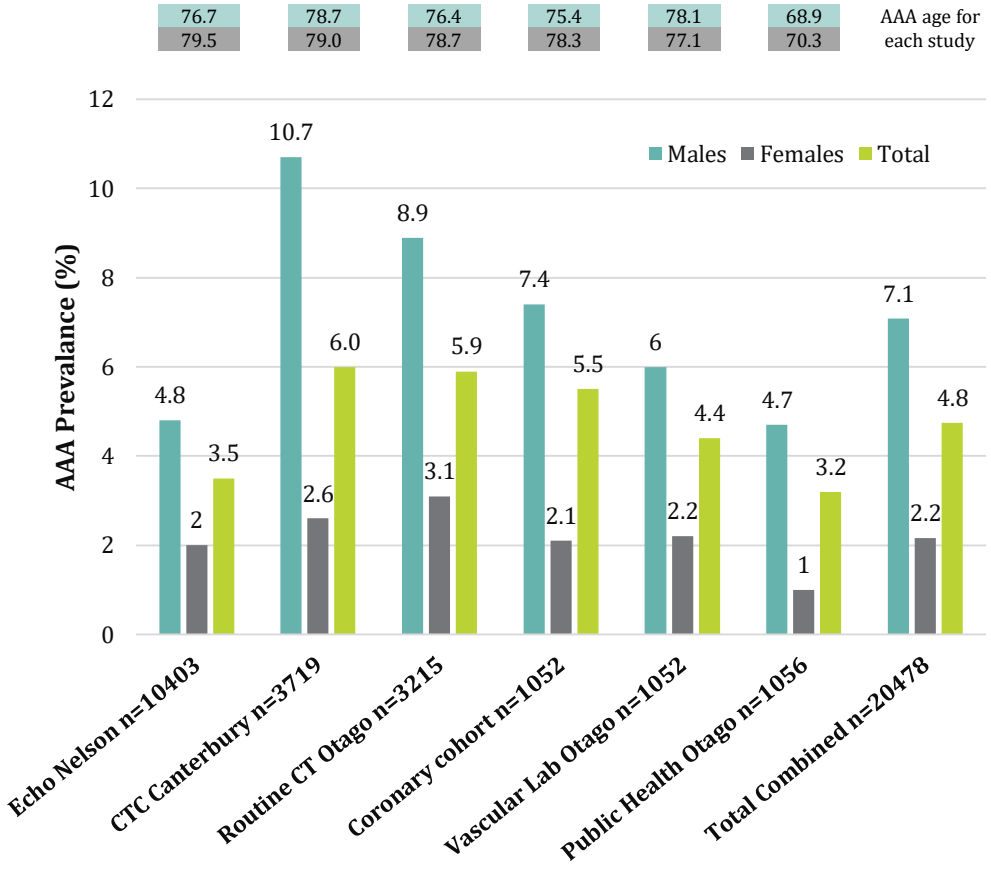


Figure 2.8 Prevalence of AAA in each study group stratified into sex

The average age (in years) for males and females for each group is reported above the bar chart

2.8.3 International AAA prevalence

A systematic review and meta-analysis of 14 AAA screening population studies revealed a prevalence range of 4.2 to 14.2% in men and 0.35 to 6.2% in women (137). Our estimated prevalence is similar to previous population studies. In this study, 942 people were over the age of 80 years, of which 554 (58.8%) were female. This particular group has not been included previously in the screening trials. Data from this study has extended the knowledge of AAA prevalence in octogenarians; a group with an improved life expectancy that hasn't been included in previous population AAA studies. It is expected, given that the prevalence of AAA increases with age, that more people will require management in terms of risk factor modification, decision surrounding screening and surveillance and counselling family members for AAA screening.

Variations within international AAA screening programs include differences with respect to the targeted population, interval of surveillance scans and size prior to consideration for surgical treatment (46). The epidemiology of AAA is changing globally with a decrease in AAA mortality observed in countries such as England, Australia and New Zealand, whereas an increase in mortality has been reported from Hungary, Denmark, Austria and Romania (17). Despite a lower AAA prevalence reported from Sweden and England, screening for AAA appears to remain cost-effective (101).

It is unclear whether the study population is truly representative of the general South Island NZ population. A direct "cause and effect" between CRC and AAA prevalence has not been established but it has been estimated that approximately 0.3-3.8% of AAA will have a concomitant CRC present at the time of the diagnosis (140). CRC and AAA share some risk factors such as smoking, age and male gender. Cardiovascular risk factors for the people without an AAA and the prevalence of CRC were not available to allow such analysis. In this AAA group, the prevalence of CRC was 8.5%, higher than previously estimated, which is likely to be due to the selection process of undergoing a CTC.

2.8.4 The impact of CTC on AAA detection

In Canterbury, the use of CTC has gained popularity as an alternative to colonoscopy due to constraints in the public health sector. Between October 2010 and February 2016, there were 568 patients with small aneurysms seen in a nurse-led aneurysm clinic in Christchurch Hospital. Of these, 97 (17.1%) patients were diagnosed with their AAA by a CTC and the remaining were diagnosed by other radiological modalities. The patients diagnosed by a CTC were on average two years older, but there were no major baseline differences in comorbidities between the CTC cohort and patients referred by other radiological modalities (141). This further supports that this apparent potential bias for selecting individuals undergoing a CTC does not appear a marker of a higher risk profile.

The survival following elective AAA repair was lower than the expected survival of the age- and sex-matched population (142), and the presence of AAA itself appeared to be an independent predictor of reduced survival. Previous studies have reported that non-AAA-related deaths are more common in patients undergoing small AAA surveillance than AAA-related deaths (143). Our current study is consistent with these observations, with the leading causes of death amongst patients with AAA undergoing CTC being cardiovascular and oncological conditions.

CT was used for AAA detection in this study, whereas the randomised screening studies used an US and in some, a targeted aortic US scan was used. The advantages of a CT for screening AAA was noted in this study with detection of 23 isolated iliac aneurysms, 5 thoracic aneurysms, 2 visceral aneurysms and late graft complications following AAA repair. A study from a Veteran Affairs (VA) centre where dedicated vascular technicians included the iliac arteries in AAA-screening ultrasound scans detected a 0.1% isolated iliac aneurysms (92). Our results revealed an isolated iliac aneurysm in 23/3719 (0.6%) of patients undergoing CTC.

2.8.5 Other potential advantages from the CTC

Amongst the 4644 individuals identified in this study, 65 (1.4%) of the AAA detected did not have a formal diagnosis or comment on the presence of AAA during the CTC-reporting process. Such underreporting of incidental AAA has been observed previously in 4112 patients undergoing CT of which 53 (1.3%) patients did not have the aortic dilatation recognised or reported (144). Based on these findings, it is recommend that the abdominal aorta should be specifically screened for an AAA when people undergo abdominal CT scans particularly in those over the age of 55 years.

Therefore, in this current study, the primary general practitioners of patients with an aneurysm incidentally detected from the CTC who were not initially diagnosed or not followed were informed of the diagnosis, and US surveillance scan was initiated for patients who might benefit from repair should the AAA reach threshold.

2.9 Limitations

2.9.1 Population studied

In this study, the CTC population selected to act as a surrogate for AAA prevalence might not represent the true sample of the general population. This population was relatively older and included a high proportion of women which differs from the population screening AAA studies.

CRC shares some mutual risk factors with AAA disease- age (although five years younger in CRC), a smoking history and being a male. Other "weaker" association include poor diet (less fruits and vegetables) and higher deprivation (low SES). Therefore, the high prevalence of AAA observed in this study might be due to the selection process.

This study and the other AAA prevalence cohorts were all based in the South Island and hence might not be generalizable to the overall NZ population as the certain demographics such as a higher proportion of people who identify as a NZ European or of European descent. This was noted in this study since the proportion of Maori was only 2%, which is less than the 6-7% expected population in this geographical region.

The pathway and indications for obtaining a CTC includes examination findings such as abdominal pain and palpable masses, which both might be present with an AAA. Therefore this might steer physicians to refer patients to a CTC. This selection bias might partially explain the high prevalence of AAA observed in this study.

In addition, this cohort had a lower observed survival than that expected of the total population, and some of the patients might have a reduced life expectancy due to a cancer diagnosis as demonstrated by 8.5% of AAA patients having a history of cancer and 13.5% in the non-AAA group.

The selection process of patients into this study was different to population screening studies. This population of this study sought medical attention due to symptoms or clinical concerns which are different from those of invited participants included in other aneurysm screening studies. This was

reflected by a representative sample from all socioeconomic groups. This is relevant given that it is widely accepted that people with lower socioeconomic status and/ or living in more deprived geographical areas have lower attendance rates to AAA screening and appear to be more likely to have the condition (145).

2.9.2 Measurement differences

Variations in diameter measurements between CT and US have been reported with CT measurements reporting a larger diameter, which might not represent the "true" maximal difference (138). During an US measurement, the transducer can be tilted to measure a true diameter even in the presence of aortic tortuosity. In addition, the cardiac cycle phase during a CT is unknown and is not routinely controlled for. The use of CT to measure AAA might lead to underestimation of AAA size due to the unknown phase of the cardiac cycle. US measurements carry a 1.9mm average difference between systolic and diastolic peak recordings (139). Despite the well-documented differences between the two modalities (US and CT), the methods used in this study appeared to have minimized these differences and similar AAA diameters were attained.

2.9.3 Retrospective nature

This was a retrospective study and therefore the collection of clinical risk factors could only be as accurate as that documented on electronic medical charts and health records. A prospectively designed study with direct patient assessment would have been more ideal. However, the study time duration, costs and resources required to conduct such a prospective longitudinal study are important constraining factors that need to be considered.

2.10 Conclusions

In conclusion, the prevalence of AAA in a population undergoing CTC for gastrointestinal symptoms in the South Island of NZ is relatively high and warrants further evaluation. The prevalence of AAA both in males and

females rose steeply with age. The results acquired in this observational study seem to support a national population AAA-screening program in men and possibly in women in the light of European cost-effectiveness data in a context with lower AAA prevalence.

2.11 Further Work

Using the CTC program, I was able to provide information on the prevalence of AAA in this selected population residing in the South Island of New Zealand. The presence of AAA did not appear to influence survival when age and sex were adjusted for. This selected population might represent a group that would benefit from AAA screening.

Since aortic diameters are a continuous variable, it is important to determine whether a change in aortic diameter increases mortality and if there are any differences in certain subgroups stratified to age, ethnicity or gender.

However, the aortic diameter of this population should be known to assist in defining the AAA. In addition, demographics, ethnicity and cardiovascular risk factors might influence aortic size and need to be taken into account.

Chapter 3: The Definition of Abdominal Aortic Aneurysm: Predictors for Developing AAA and Effects on Long-Term Survival

3.1 Overview

The diameter of the aorta is a continuous variable. The threshold to define an aortic aneurysms is usually set at certain cut-offs but variables influencing the diameter of the aorta have been reported in some populations. There are three key factors which influence the stage at which an AAA is clinically defined to be present, these being: the radiological modality used, the aortic wall anatomical reference points used to measure the diameter and the precise definition of what constitutes an AAA.

The normal age, gender and ethnicity-specific aortic dimensions have not been documented within the New Zealand population. With a multi-ethnic society, determining the "normal" aortic diameter is important for diagnostic and therapeutic purposes. Māori New Zealanders, being of Polynesian descent, may have aortic diameters that differ from New Zealanders of European ancestry. Ideally, any formal aortic-screening programme should base its aneurysm definition on local reference-group data, rather than data from different populations or historical sources.

Differences in aortic diameter between genders have also been well documented. However, studies rarely separate analysis into gender sub-groups. Throughout this chapter, data is presented and analysed according to gender groups to provide a better understanding of AAA disease in males and females.

In chapter two, the prevalence of AAA in a selected population has been determined. In this chapter the focus is on the normal aorta and definition of AAA, predictors of AAA development and the effect of AAA diameter on survival.

3.2 Contribution

In this chapter, my responsibility was to collect, measure and analyse the data presented. There were two medical students that formally assisted in collecting some of the data presented in this chapter as part of the 2015 summer studentship programme. M Osman assisted in acquiring some of the risk factors data and A Gupta measured some of the normal aortas.

3.3 Publications

Abstract – Conference proceedings

Khashram M, Gupta A, Osman M, Jones G, Roake J. Evaluation of Aortic Diameters in a Population Undergoing CT Colonography: Prevalence and Effect on Survival. Journal of Vascular Surgery. 62(2):537.

3.4 Background

3.4.1 The "normal" aorta and definition of AAA

The definition of an AAA varies in the reported literature as normal aortic diameters differ with respect to age, sex, ethnicity and body size. There are, however, four generally well-accepted definitions of AAA reported in the literature: $\geq$3cm of the infra renal aorta (146), $\geq$1.5x suprarenal aorta (147), $\geq$4cm or exceeding the suprarenal segment by $\leq$0.5cm (148) or $\geq$1.5x the normal predicted infrarenal diameter (3).

The first attempt to document the diameters of the normal abdominal aorta was reported by Steinberg and colleagues in 1965 (146). Following injection of intravenous contrast, an anteroposterior radiological film was performed and the abdominal aorta was measured at different locations. Aortic diameters $\geq$ 3cm were defined as an aneurysm in both males and females and the authors also noted significant differences in diameters between genders.

A further method proposed by Sterpetti *et al.* using a transabdominal ultrasound measured the diameter of the aorta in the segment above the

aneurysm (suprarenal) and the maximum AAA diameter to provide a ratio of the measurements (147). Using this approach requires accurate measurements of the suprarenal aorta, which can be technically challenging for sonographers and has not been routinely measured in large AAA population or screening studies.

The Society for Vascular Surgery (SVS) and the International Society of Cardiovascular Surgery suggest using 1.5 times the predicted normal diameter. However, data on predicted aortic values have been limited and not widely used. Sonesson *et al.* were the first to present nomograms predicting aortic size from 146 healthy white male and female volunteers. It was noted that the aortic diameters positively correlated with body surface area (149). These findings were not reproducible when a larger study including 69,905 veterans from the USA with an infrarenal diameter of <3cm was conducted. The American study found that there was a very small association (0.1cm change) between body size, ethnicity and gender (150) and suggested that a simple definition of AAA (≥3cm) should be used.

To put these differences in AAA definitions into clinical practice, a study from the Norsjö municipality (northern Sweden) measured the aneurysms of 504 individuals aged between 65 and 75 years old and the various definitions were used. The prevalence of AAA ranged between 6.9% to 16.9% in males and 1.2% to 9.8% in females (151).

Variations of normal aortic diameters between different ethnicities have also been observed. For example, the Multi-Ethnic Study of Atherosclerosis reported that Hispanic, African and Chinese Americans had smaller infrarenal aortic diameters than Caucasian Americans after adjusting for body size measurements (152). Data on normal aortic diameters from non-Western countries is very limited. A cross-sectional study of Chinese hypertensive adults reported an average infrarenal aortic diameter of 1.55cm in males and 1.38cm in females (153). A study from three centres in South Korea using an US to measure the abdominal aorta of 1218 individuals reported a mean infrarenal aortic diameter for males and females of 1.90 and 1.79cm respectively (154). The only study reported from India examined

142 individuals and documented a mean aortic diameter of 1.46 and 1.33cm for males and females respectively (155). These differences might influence how AAA is defined and managed when setting thresholds for surveillance or treatment in different ethnic groups.

3.4.2 Aortic diameter and influence on survival

Aortic diameter differences between genders has been well documented but due to aortic aneurysmal disease being more prevalent in males and a tendency to report overall rather than gender-specific data, the impact of this gender difference is not well-understood. An index referred to as the aortic size index (ASI), which is calculated by dividing the aortic diameter by the body surface area, has been proposed to standardize such differences. This index was first reported to predict thoracic aneurysm rupture or dissections (156) and subsequently has been shown to be a better predictor of AAA rupture in females compared to absolute AAA diameter (157).

Individuals with aortic sizes smaller or larger than the average normal aortic diameter appear to be at a greater risk of death. The Western Australian AAA screening study (Health in Men Study) including 12,203 men revealed that aortic diameters of 10-18mm had an increased risk of mortality (hazard ratio HR of 1.23 (95% CI: 1.03-1.46)) compared to men with aortic diameters of 19-22mm (158). The Cardiovascular Health Study showed that the presence of AAA was an independent risk of cardiovascular disease events and mortality (159). A further population-based study from the Tromsø, Norway, including 6640 individuals with a 10-year follow-up revealed that the presence of AAA and an increase in aortic diameter were independent predictors of overall and cardiovascular mortality.

3.5 Objectives

The objectives of this chapter were to document the normal abdominal aorta diameter for a large New Zealand population and to compare the aortic diameters of Māori and non-Māori individuals, to determine predictors of

increased aortic size and those associated with AAA development and finally to report the influence of aortic diameter on overall patient survival.

3.6 Methods

Ethical approval was granted by the HDEC and the local hospital board also approved the study (Ref 13/STH/190/AM01).

3.6.1 Study population

Consecutive patients undergoing CT Colonography (CTC) for gastrointestinal symptoms in the Canterbury region of the South Island from January 2009 to April 2013 were identified from the PACS database.

3.6.2 Aortic measurements

The methods of aortic measurements have been covered in chapter 2. Briefly, the aorta was digitally magnified and measurements were performed at eye level to avoid parallax. Fine electronic calipers were placed on the outer to outer diameter of the aortic wall passing through the centre of the aorta in the maximum short axis plane. Careful attention was applied to ensure that the origins of the mesenteric and renal vessels were not included in the measurement.

Two investigators measured the aortic diameters: MK, principal investigator (PI) and AG, medical student. The student was blinded to the principal investigator's measurements and was not aware of the aortic diameters or of which patients had a prior diagnosis of aneurysm.

3.6.2.1 Levels of aortic measurement

The aorta was measured at five levels:

- **Supraceliac** (distal descending thoracic aorta) proximal to the crux complex within 1cm
- **Suprarenal** within 1cm from the renal arteries (proximal)
- **Infrarenal** within 1cm from the lowest renal artery (main artery, not accessory)

- **Mid infrarenal aorta** or the maximum dilatation point
- **Distal aorta** 1cm prior to the bifurcation

3.6.2.2 Validation of measurements

All aortas with a change in diameter were measured (chapter 2). A second investigator who was trained in measuring aortas recorded the diameter of the remaining aortas after multiple sets of validations.

It was noted that the descending/ supraceliac aortic segment anatomically changes diameter and direction with a marked difference in anteroposterior and lateral measurements. Therefore, all aortic diameters taken at this level which measured >2.5cm were re-measured taking into account this anatomical course, and the aortas at the infrarenal level which were >2.7cm were also re-measured by the PI for quality assurance. In addition, some scans which had no arterial contrast, no aortic calcification or a very subtle demarcation of the diaphragmatic crux were referred to the PI for measuring.

3.6.3 Definitions

Comorbidities were collected from hospitals' electronic medical records and primary health records. In addition, further departmental databases were interrogated to assist and improve comorbidity-reporting accuracy: cancer, cardiology diagnostic/interventional and spirometry databases.

Cardiovascular risk-factors and patient co-morbidities were defined as following: Cancer history was defined as having a cancer diagnosis prior to the CTC or having the cancer diagnosed by the CTC, and benign skin/cutaneous skin (non-melanoma) lesions were not included. Diabetes was defined as using oral hypoglycaemic or insulin therapy. Hypertension was defined as being treated with any anti-hypertensive agent rather than blood-pressure recordings. Statin use or the use of other lipid modifying agents was defined as being treated with a cholesterol-modifying medication around the time of the CTC. Ischaemic heart disease (IHD) was defined as the presence of coronary disease based on symptoms (angina), angiography

findings, coronary events (myocardial ischaemia) or coronary interventions (coronary artery bypass grafting/percutaneous coronary interventions). Chronic obstructive pulmonary disease (COPD) was defined clinically or by the means of spirometry tests. Serum creatinine levels were recorded from the day nearest to the CTC study and renal impairment was defined as creatinine $\geq$150mmol/L. Weight and height recordings were measured from clinical records, departmental databases and primary general-practitioner records to the nearest records. For the purposes of this study, it was assumed that height did not change but weight recordings used were obtained closest to the time of the study as possible. Subsequent body surface area (BSA) using Du Bois method (BSA= 0.007184 x $Weight^{0.425}$ x $Height^{0.725}$) and body mass index (BMI) were used to calculate anthropologic measurements (BMI=weight (kg)/$height^2$ (m)). The aortic-size index (ASI) was calculated by BSA/maximum infrarenal aortic diameter (cm/m^2).

3.6.4 Data acquisition of aortic diameters in Māori

As noted in chapter 2, the overall number of Māori from the CTC cohort was relatively smaller than to provide meaningful conclusions on aortic size. An enquiry was made into other vascular surgery departments in NZ requesting data on measured aortas of Māori older than 40 years. There were four independent datasets provided from three geographical locations:

- **Waikato Hospital** – Consecutive Māori CT abdomen scans from a tertiary centre performed February 2014 - October 2015.
- **Waitemata primary health group**- Māori primary care staff screening with an ultrasound in May-June 2016 as part of a pilot study to investigate the prevalence of AAA in Māori
- **Waitemata (Northshore) Hospital**- Consecutive CTC performed on Māori from June 2007 to Dec 2014
- **Otago primary health group**– Māori with known AAA or who had an elevated 5-year cardiovascular disease-risk assessment >10% were invited for an abdominal aortic US scan.

Māori ethnicity was based on self-identification or identification from electronic health records. Since this data was requested retrospectively, demographics and comorbidities were missing for ~40-50% participants. The additional aortic diameters from Māori were only used in this chapter to determine the age and sex adjusted normal aortic diameter and this was compared to the aortic diameters of patients identifying as NZ European.

3.6.5 Statistical analysis

The NHI for each individual was linked to the Ministry of Health National Minimum Data Set. Deprivation, ethnicity and survival status were added into the CTC database. Continuous variables were expressed as mean (SD) or median (range, interquartile range) and categorical variables were presented as absolute values (percentages, %) where appropriate. Data was considered normally distributed if z-scores were within ±2.58. Limits of agreement between the measurements by the two investigators were calculated using the Bland-Altman technique (160).

A univariate and multivariate linear regression model using the aortic diameter as the dependent variable determined the relationships between infrarenal aortic diameter and age, sex and ethnicity for the added Māori data. Clinically important predictors of AAA presence were entered into a logistic regression model and odds ratio (OR) for each variable was calculated. Univariate analysis was assessed individually, then statistical-significant and clinical-relevant variables were included into the multivariable model where appropriate. A time-to-event survival analysis was undertaken to determine predictors of survival. Cox proportional hazard models were used to define predictors of survival and risks of mortality presented as hazard ratios (HR). Individual status (alive or dead) was censored on the 14th of March 2016. Statistical significance was set at $P<0.05$ and analyses were performed using SPSS 23 for Mac (SPSS Inc., Chicago, IL).

3.7 Results

In all 4,644 patients were included in this study with a median (range) age of 69.2 (17-97) years of which 2711 (58.4%) were females. The demographics and comorbidities stratified into sex are presented in Table 3.1.

Table 3.1 Baseline demographics and comorbidities of the CTC cohort

	Males n= 1933	Females n=2711	Total	Missing (%)
Median age, years (IQR)	69.0 (58.1-78.3)	69.3 (57.9-78.2)	69.2	0
Ethnicity				0
NZ European	1753 (90.7)	2505 (92.4)	4258 (91.7)	
NZ Māori	43 (2.2)	80 (3.0)	123 (2.6)	
Pacific Island	8 (0.3)	7 (0.3)	15 (0.3)	
Asian	20 (1.0)	47 (1.7)	67 (1.4)	
Other	109 (5.6)	72 (2.7)	181 (3.9)	
Deprivation				16 (0.3)
1-5 (less deprived)	944 (49.0)	1342 (49.7)	2286 (49.4)	
6-10 (more deprived)	984 (51.0)	1358 (50.3)	2342 (50.6)	
Smoking history				
Past smokers	669 (36.3)	579 (22.6)	1248 (28.3)	234 (5.0)
Current	207 (11.2)	259 (10.1)	466 (10.6)	
Weight, kg (SD)	83.4 (16.9)	72.3 (18.1)	76.9	1352 (29.1)
Height, cm (SD)	173.8 (7.0)	160.7 (6.6)	160	2261 (48.7)
BSA, m^2 (SD)	2.0 (0.2)	1.8 (0.2)	1.9 (0.2)	2264 (48.8)
BMI, kg/m^2 (SD)	27.9 (5.1)	28.6 (6.8)	28.3 (6.1)	2241 (48.3)
ASI median (IQR)	1.02 (0.93-1.16)	0.97 (0.87-1.09)	0.99	2264 (48.8)
IHD	413 (22.0)	412 (15.7)	825 (17.8)	133 (2.9)
COPD	227 (12.1)	198 (7.6)	425 (9.4)	143 (3.1)
Renal impairment	128 (6.6)	57 (2.1)	185 (4)	0
Diabetes	248 (13.2)	296 (11.3)	544 (12.1)	135 (2.9)
Hypertension	1187 (50.2)	1225 (46.6)	2169 (48.1)	137 (3.0)
Statin use	692 (36.8)	721 (27.4)	1413 (31.4)	138 (3.0)
Cancer history	298 (15.4)	265 (9.8)	563 (12.1)	0

Numbers in parenthesis are percent unless stated otherwise.

BSA: body surface area, BMI: body mass index, ASI: aortic size index, IHD: ischaemic heart disease, COPD: chronic pulmonary obstructive disease, IQR: interquartile range, SD: standard deviation.

3.7.1 Aortic diameters

There was a general decrease in median aortic diameter at each anatomical level in both males and females. The median (IQR) of aortic diameters at the supraceliac, suprarenal, proximal infrarenal, mid infrarenal and aortic bifurcation are presented in Table 3.2.

Table 3.2 Aortic diameters for each anatomical site among males and females

Anatomical level	Males	Females	Total
Supraceliac	2.59 (2.42-2.72)	2.39 (2.21-2.56)	2.47 (2.28-2.65)
Suprarenal	2.26 (2.09 2.43)	2.00 (1.85-2.18	2.11 (1.92-2.30)
Proximal infrarenal	2.03 (1.87-2.22)	1.77 (1.62-1.93)	1.87 (1.70-2.08)
Mid infrarenal	2.00 (1.84-2.23)	1.70 (1.57-1.86)	1.82 (1.65-2.03)
Aortic bifurcation	1.92 (1.77-2.11)	1.62 (1.50-1.77)	1.74 (1.57-1.95)

All diameters in centimetres. Numbers in parathesis are interquartile range

The mid infrarenal aorta was the only aortic segment that dilated with an advanced age in males and to a lesser extent in females as shown in Figure 3.1.

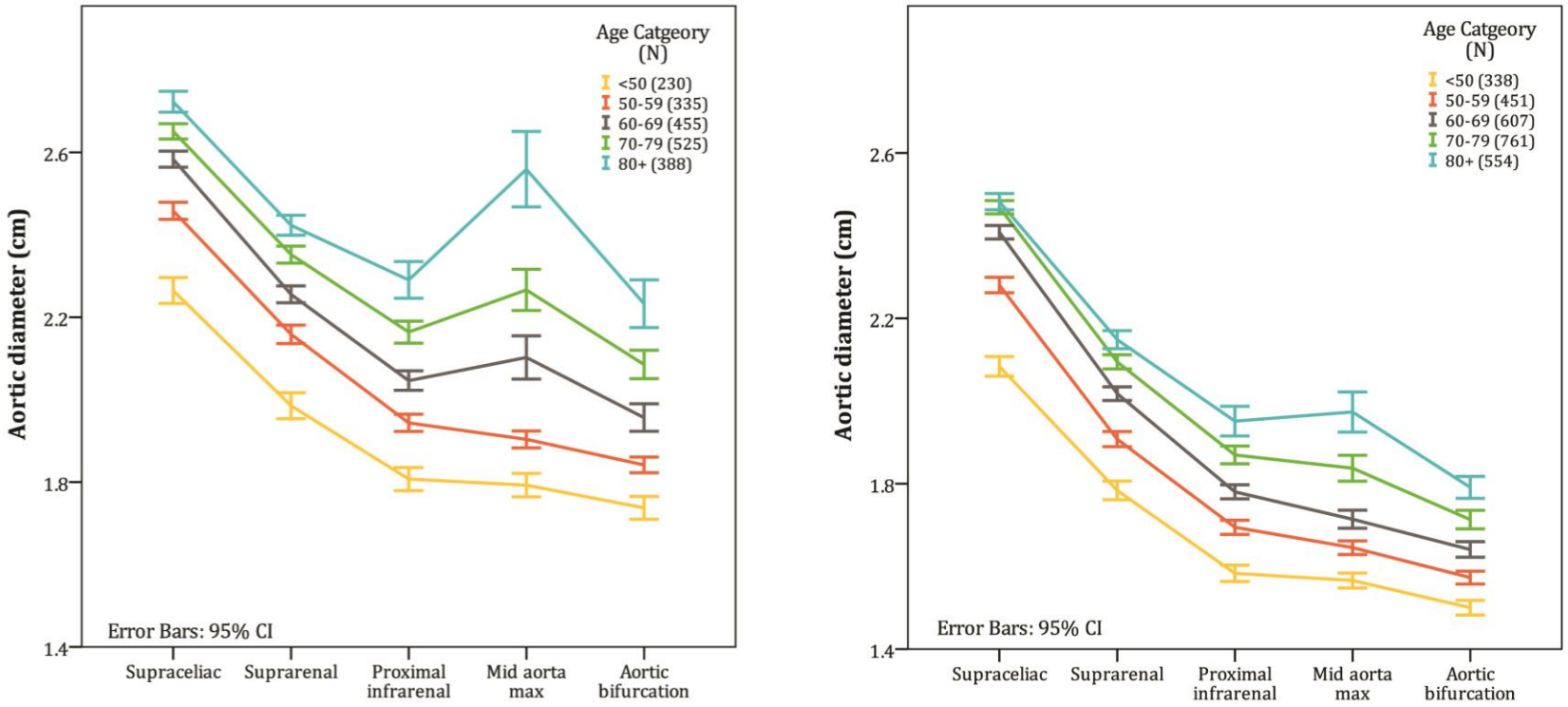


Figure 3.1 Aortic diameter at each segment stratified into age groups

Left: Male, Right: Female. Values are mean and error bars are 95% confidence interval

3.7.2 Infrarenal aortic diameters

The infrarenal aorta diameter was not normally distributed as assessed by Shapiro-Wilk's test (P<0.001) in both males and females and it was positively skewed in both males (z=3.36) and females (z=5.63). The median (Q1-Q3) aortic diameter for males and females was 2.00 (1.84-2.23) and 1.77 (1.57-1.86) respectively. Percentile plots of the infrarenal aorta revealed different distributions for males and females and an exponential rise around the 87.5th to 90th percentile in males and the 92.5th to 95th percentile in females (Figure 3.2).

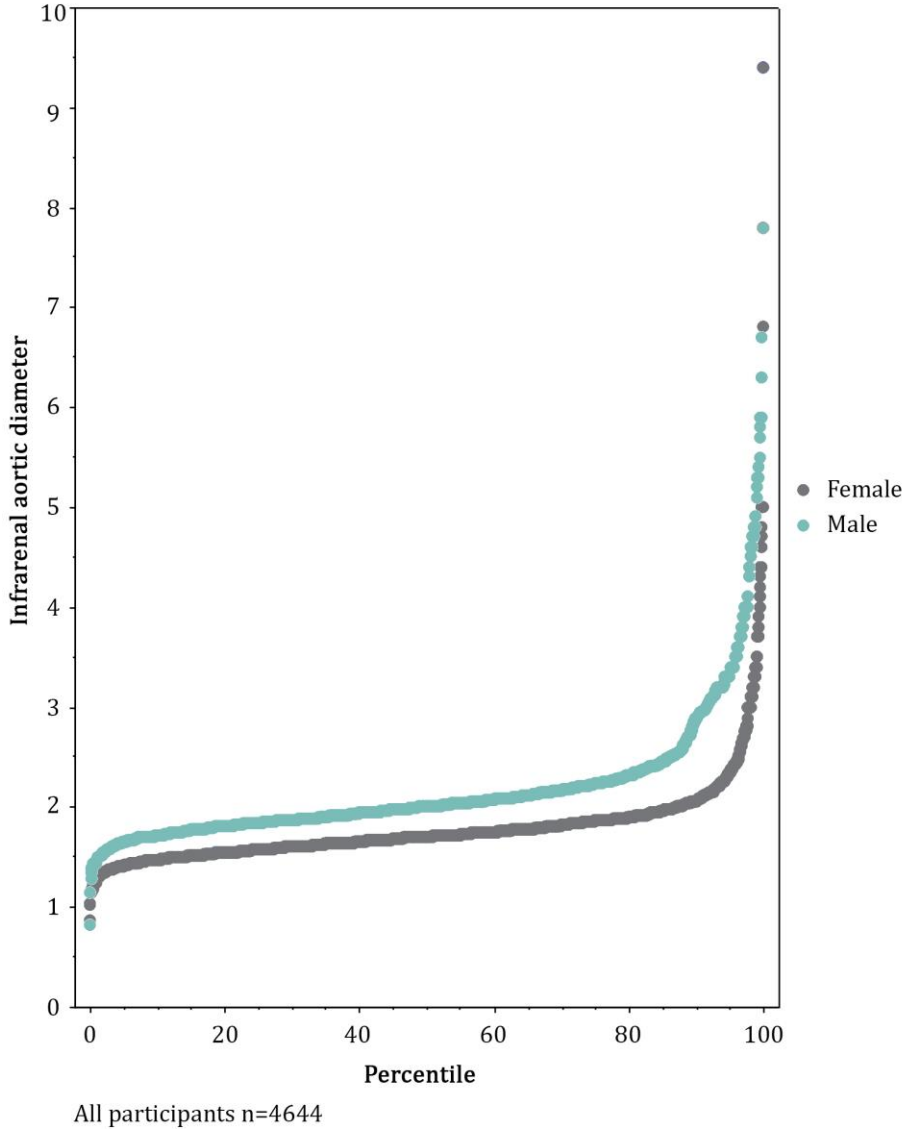
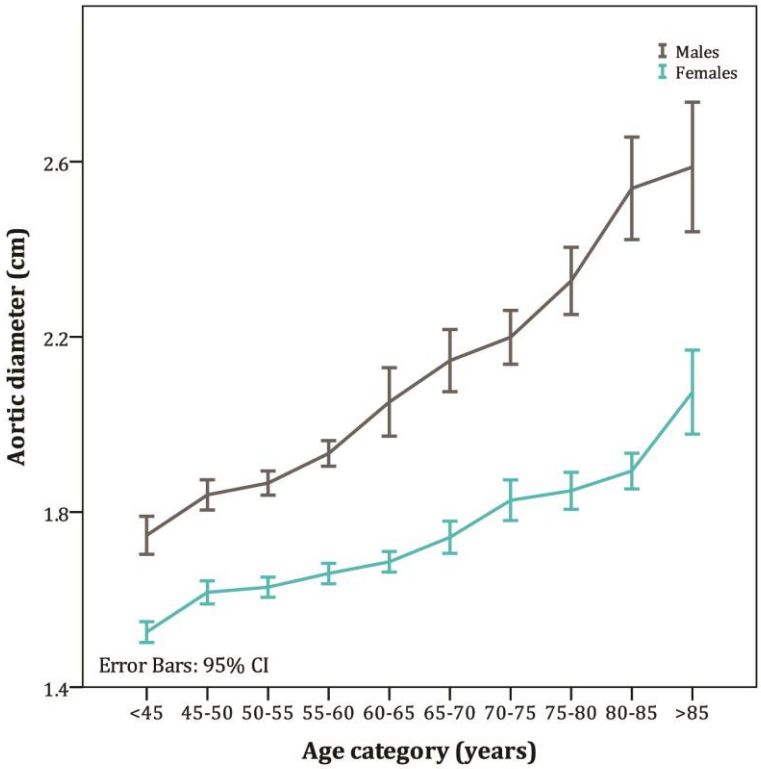


Figure 3.2 Percentile plot of the infrarenal aortic diameter of males and females

3.7.3 Influence of age and sex on infrarenal aortic diameters

The aortic diameter of subjects increased with age and males had a larger aorta in all age groups compared to females. For males, the median (IQR) in <45, 45-54, 55-64, 65-74, 75-84, >85 years was 1.66 (1.52-1.75), 1.85 (1.73-1.97), 1.93 (1.81-2.07), 2.03 (1.88-2.23), 2.16 (1.98-2.50) and 2.25 (2-2.94) respectively. The corresponding values for females were: 1.47 (1.39-1.59), 1.61 (1.51-1.72), 1.65 (1.55-1.77), 1.72 (1.61-1.86), 1.78 (1.63-1.98) and 1.87 (1.69-2.16), as shown graphically with statistical confidence intervals in Figure 3.3.



	<45	45-50	50-55	55-60	60-65	65-70	70-75	75-80	80-85	>85
Males	116	114	150	185	209	246	251	274	230	158
Females	189	150	206	244	307	300	394	367	309	245

Figure 3.3 Median infrarenal aortic diameter stratified according to age groups and sex

Number of patients in each category is shown below

3.7.4 Sub-group analysis of Māori Aortic Diameters

After combining the five data sets of Māori aortic diameters, there were 1086 individuals with infra renal aorta measured. The median (range) age was 62.2 (40.0-96.7) years and 591 (54.4%) were females. The data comprised of 688 patients from Waikato, 112 from Canterbury, 100 from North Shore Hospital, 73 from Otago and 51 from Waitemata public health screening. There were 62 (5.7%) Māori with greater than or equal to 3.0 cm aortas and these were excluded from the model building, and there was one patient who had a previous EVAR stent-graft and was also excluded. To allow comparison, consecutive patients ≥40 years old identified as NZ European were extracted from the CTC group.

3.7.4.1 Population Demographic

The NZ Maori cohort was on average younger and had a higher proportion of current smokers, diabetes, renal impairment and IHD. Statin use was lower in NZ Maori and hypertension was similar between the NZ Maori and NZ European individuals (Table 3-3).

Table 3.3 Baseline demographics and clinical profile of Maori and European subgroup

	Maori Males	NZ European Males	Maori Females	NZ European Females	Missing
Number in cohort	456 (9.3)	1521 (31.0)	568 (11.6)	2362 (48.1)	-
Age, years (SD)	62.4 (9.9)	67.7 (12.5)	61.1 (11.5)	68.8 (12.5)	-
Diabetes	117 (26.9)	185 (12.5)	139 (26.8)	259 (11.3)	213 (4.3)
Hypertension	224 (51.7)	714 (48.2)	249 (46.2)	1098 (48.0)	165 (3.4)
Smoking history					255 (5.2)
Non-smoker	182 (42.4)	829 (57.0)	213 (39.9)	1540 (68.9)	
Ex-smokers	123 (28.7)	486 (33.4)	186 (34.8)	504 (22.6)	
Current	124 (28.9)	139 (9.6)	135 (25.3)	191 (8.5)	
Renal impairment	38 (11.9)	94 (6.2)	27 (6.3)	52 (2.2)	276 (5.6)
Statin use	86 (27.0)	525 (35.4)	100 (23.4)	642 (28.1)	391 (8.0)

Numbers in parenthesis are percentages (unless otherwise stated)

3.7.4.2 Comparison of aortic diameters amongst NZ European & Māori

The CTC cohort contributed to the NZ European aortic diameter data and there were 4135 NZ Europeans older than 40 years, of which 2426 (58.7%) were females. 249 (6.0%) individuals had a ≥ 3cm infrarenal aorta and were excluded from this analysis.

The demographic data for the non-aneurysm participants are shown in Table 3.4, and the age- and gender-stratified infrarenal aorta median diameters in Table 3.7.

Table 3.4 Demographics comparing infrarenal aortic diameters in Māori and NZ Europeans

	Māori Males	NZ European Males	Māori Females	NZ European Females
Number in cohort (%)	456 (9.3)	1523 (31.0)	568 (11.6)	2362 (48.1)
Age, years (SD)	62.4 (9.9)	67.7 (12.5)	61.1 (11.5)	68.8 (12.5)
Mean aortic diameter, cm (SD)	2.05 (0.29)	2.02 (0.26)	1.80 (0.27)	1.74 (0.24)
Median aorta diameter, cm (IQR)	2.03 (1.84-2.23)	1.99 (1.84-2.16)	1.79 (1.62-1.96)	1.71 (1.58-1.85)

SD: standard deviation, IQR: interquartile range.

3.7.4.3 Predictors of larger aortic diameters

The relevant predictors of larger aortic were entered into a linear regression model as independent variables. Univariate analyses indicate that older age, males, hypertension and renal impairment were significant in both Maori and NZ Europeans. A history of smoking and statin use was associated with larger aortic diameters in NZ European but not in NZ Maori (Table 3.5).

Table 3.5 Univariate variables associated with a larger aortic diameter

	NZ Maori n=1024			NZ European n= 3883		
	Intercept	**Unstandardised coefficients (SE)**	**P**	**Intercept**	**Unstandardised coefficients (SE)**	**P**
Age (per year)	1.482	0.007 (0.001)	<0.001	1.366	0.007 (0)	<0.001
Males	1.799	0.248 (0.017)	<0.001	1.738	0.278 (0.008)	<0.001
Diabetes	1.892	0.033 (0.022)	0.136	1.844	0.040 (0.014)	0.004
Hypertension	1.879	0.065 (0.019)	0.001	1.812	0.076 (0.009)	0.001
Smoking history	1.916	-0.009 (0.020)	0.655	1.829	0.054 (0.010)	0.001
Renal impairment	1.887	0.094 (0.41)	0.022	1.840	0.180 (0.023)	0.001
Statin use	1.882	0.052 (0.027)	0.051	1.828	0.068 (0.010)	0.001

After adjustment, only older age and males remained significant predictors of larger infrarenal aortic diameters in both NZ Maori and NZ European. A history of smoking remained a predictor in NZ European individuals but not in Māori (Table 3.6).

Table 3.6 Multivariate linear regression model of aortic diameters

	NZ Maori Adjusted R^2 = 0.201		NZ European Adjusted R^2 = 0.351	
	Unstandardised coefficients (SE)	***P*-value**	**Unstandardised coefficients (SE)**	***P*-value**
Age per year	0.05 (0.001)	<0.001	0.007 (0)	<0.001
Males	0.242 (0.021)	<0.001	0.279 (0.008)	<0.001
Diabetes	0.016 (0.026)	0.525	-0.004 (0.012)	0.736
Hypertension	0.040 (0.023)	0.090	0.001 (0.008)	0.870
Smoking history	-	-	0.030 (0.008)	<0.001
Renal impairment	0.015 (0.038)	0.689	0.028 (0.020)	0.151
Statin use	-0.012 (0.027)	0.646	0.008 (0.009)	0.373
Intercept	1.444 (0.058)	<0.001	1.217 (0.022)	<0.001

Table 3.7 Median infrarenal aortic diameter of individuals stratified into age

	Māori Males		NZ European Males		Māori Females		NZ European Females	
Age, years	**Aortic diameter**	***N***	**Aortic diameter**	***N***	**Aortic diameter**	***N***	**Aortic diameter**	***N***
<60	1.97	*173*	1.87	*444*	1.71	*261*	1.63	*606*
60-64	2.03	*105*	1.94	*173*	1.75	*102*	1.67	*284*
65-69	2.10	*71*	1.97	*201*	1.90	*81*	1.69	*273*
70-74	2.10	*62*	2.03	*205*	1.82	*54*	1.73	*359*
75-79	2.09	*24*	2.07	*215*	1.92	*33*	1.76	*334*
80+	2.10	*21*	2.14	*285*	2.00	*37*	1.82	*507*

N= number of individuals

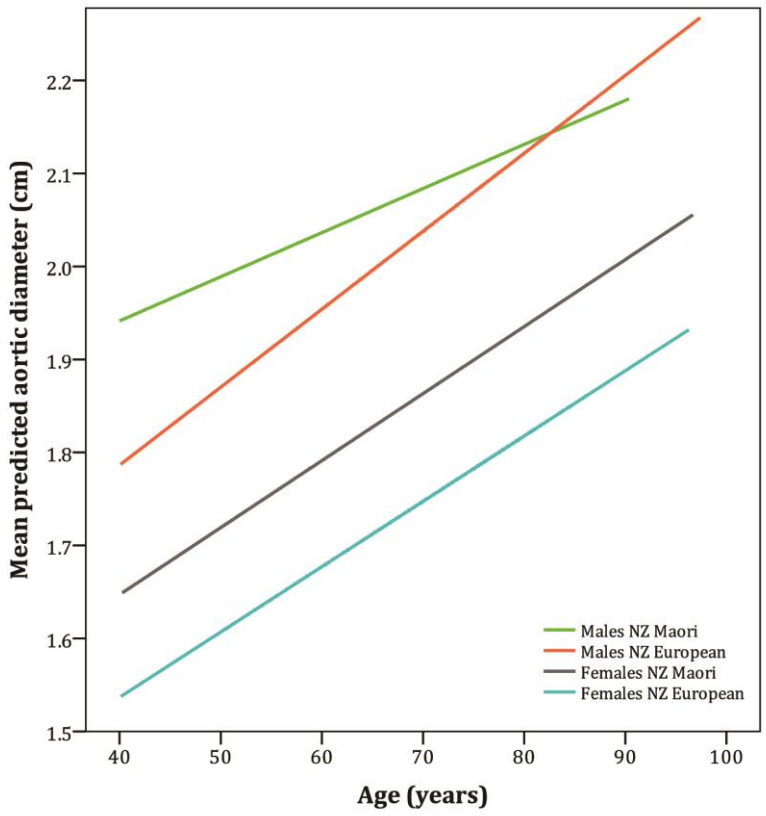


Figure 3.4 Predicted linear model of infrarenal aortic diameters in Māori and NZ European by age

As shown in Figure 3.4, the median aortic diameter increased with age in both Māori and NZ Europeans. The predicted aortic diameter of Māori females remained larger than NZ European females by 0.12mm throughout the investigated age range. In males, the difference in average aortic diameters was inconsistent and the slopes converged with increasing age.

The predicted aortic diameter for a 67-year-old NZ European male, Māori male, NZ European female and Māori female was 2.01, 2.07, 1.73 and 1.84 cm respectively (Table 3.8).

Table 3.8 Slope and intercept of the predicted aortic diameter

	Māori Males	NZ European Males	Māori Females	NZ European Females
Intercept aortic diameter	2.07 (2.04-2.10)	2.01 (2.00- 2.02)	1.84 (1.82 - 1.87)	1.73 (1.72 - 1.74)
Slope	0.05 (0.02- 0.07)	0.08 (0.07 - 0.09)	0.07 (0.05 - 0.09)	0.07 (0.06 - 0.08)

Intercept at 67 years old (average age)

3.8 Predictors of a larger aorta

For patients undergoing CTC, a linear regression model was built using aortic diameter as the dependent variable and clinically important variables as possible predictors for all individuals greater than or equal to 50 years old with an infrarenal aortic diameter less than 3.0cm.

Univariable analyses indicate that advanced age, height, BSA, IHD, statin use, hypertension and smoking history were associated with an increase in aortic diameter in both genders (Table 3.9). In males only, an increase in weight was associated with larger aortic diameters.

Table 3.9 Linear regression of predictors stratified into gender (univariate)

	Males n=1511			Females n=2306		
	Intercept	**Unstandardised coefficients (SE)**	**P**	**Intercept**	**Unstandardised coefficients (SE)**	**P**
Age per decade	1.42	0.087 (0.006)	<0.001	1.21	0.077 (0.004)	<0.001
Deprivation per decile	2.05	-0.013 (0.013)	0.346	1.75	0.003 (0.010)	0.751
Weight per 10kg	1.88	0.019 (0.005)	<0.001	1.71	0.005 (0.003)	0.158
Height per 10 cm	1.98	0.004 (0.001)	0.001	1.74	0.005 (0.001)	<0.001
BMI per unit	1.86	.006 (0.002)	<0.001	1.73	0.001 (0.001)	0.583
BSA per unit	1.62	0.205 (0.045)	<0.001	1.58	0.094 (0.035)	*0.006*
IHD	2.02	0.072 (0.016)	<0.001	1.74	0.077 (0.014)	<0.001
Statin use	2.01	0.047 (0.014)	<0.001	1.74	0.024 (0.011)	0.028
Hypertension	1.99	0.073 (0.013)	<0.001	1.72	0.059 (0.010)	<0.001
Smoking history	2.01	0.038 (0.014)	0.006	1.74	0.024 (0.011)	0.032
COPD	2.02	0.049 (0.021)	0.019	1.74	0.037 (0.019)	0.052
Diabetes	2.03	0.017 (0.019)	0.379	1.75	0.023 (0.016)	0.143
Cancer history	2.03	0.02 (0.18)	0.257	1.75	-0.008 (0.016)	0.643

Numbers in parenthesis represent standard error (SE), BSA: body surface area, BMI: body mass index, IHD: ischaemic heart disease, COPD: chronic pulmonary obstructive disease, IQR: interquartile range.

On multivariable analysis, age, smoking history and an increase in BSA remained independent predictors of larger aortic diameters in both genders (Table 3.10). However, a history of IHD was predictive of larger aortic diameters in women but not men (P=0.043).

Table 3.10 Multivariate regression model of aortic diameter

	Males Adjusted R^2 =0.179		Females Adjusted R^2 =0.140	
	Unstandardised coefficients (SE)	**P**	**Unstandardised coefficients (SE)**	**P**
Age (per decade)	0.103 (0.009)	<0.001	0.091 (0.007)	<0.001
IHD	0.018 (0.022)	0.419	0.037 (0.018)	0.043
Statin use	-0.011 (0.019)	0.543	-0.008 (0.015	0.593
Hypertension	0.019 (0.019)	0.323	-0.014 (0.014)	0.333
Diabetes	-0.035 (0.023)	0.134	-0.030 (0.019)	0.127
COPD	0.026 (0.025)	0.310	0.023 (0.024)	0.342
Smoking history	0.048 (0.017)	0.006	0.055 (0.015)	<0.001
BSA	0.365 (0.044)	<0.001	0.238 (0.034)	<0.001
Intercept	0.561 (0.121)	<0.001	0.676 (0.089)	<0.001

Numbers in parenthesis represent standard error (SE), BSA: body surface area, BMI: body mass index, IHD: ischaemic heart disease, COPD: chronic pulmonary obstructive disease, IQR: interquartile range.

3.8.1 Predicting the presence of AAA

A logistics regression model was built by using clinically known parameters that have been previously reported to be associated with AAA disease. The model only included data from individuals over 50 years of age, with younger individuals being excluded as there were no aneurysms observed in this subgroup. Variables missing >10% of data points were not included in the model. Univariate predictors stratified into gender are presented in Table 3.11.

Table 3.11 Predictors of AAA presence (univariate analysis)

	Males		Females	
	OR (95%CI)	**P**	**OR (95%CI)**	**P**
Age, per year	1.10 (1.08 to 1.13)	<0.001	1.09 (1.05 to 1.13)	<0.001
Smoking history		<0.001		<0.001
Never	Reference		Reference	
Ex-smoker	4.50 (2.97 to 6.84)		2.62 (1.46 to 4.70)	
Current	10.56 (5.59 to 20.00)		7.03 (3.14 to 15.80)	
IHD	1.33 (0.91 to 1.93)	0.137	2.95 (1.70 to 5.12)	<0.001
COPD	1.22 (0.81 to 1.85)	0.346	2.26 (1.17 to 4.35)	0.015
Renal impairment	0.96 (0.57 to 1.63)	0.876	0.43 (0.09 to 2.00)	0.342
Diabetes	1.05 (0.67 to 1.63)	0.842	1.04 (0.52 to 2.06)	0.919
Hypertension	2.19 (1.36 to 3.52)	<0.001	3.12 (1.36 to 7.16)	<0.001
Statin use	2.17 (1.49 to 3.17)	<0.001	1.79 (1.03 to 3.12)	0.039
Cancer history	1.10 (0.71 to 1.70)	0.668	1.50 (0.68 to 3.31)	0.315

AAA: abdominal aortic aneurysm, IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease.

Males and females shared similar predictors for developing AAA including age, history of smoking and hypertension. However, a history of IHD and COPD were independent predictors of AAA presence in females but not in males as shown in Table 3.12.

Table 3.12 Univariate and multivariate predictors of AAA presence

	Number with AAA (%)	Unadjusted odds ratio	P	Adjusted odds ratio	P
Age. per year	_	1.09 (1.07-1.10)	<0.001	1.10 (1.07-1.12)	<0.001
Males (%)	166 (74.4)	4.39 (3.23-6.00)	<0.001	3.30 (2.35-4.62)	<0.001
Smoking history					
Never	48 (21.6)				
Ex-smoker	139 (62.6)	6.60 (4.72-9.24)	<0.001	4.23 (3.00-6.10)	<0.001
Current	35 (15.8)	5.83 (3.71-9.16)	<0.001	10.10 (6.00-17.01)	<0.001
IHD (%)	115 (51.6)	4.65 (3.53-6.12)	<0.001	1.72 (1.25-2.38)	<0.001
COPD (%)	57 (25.6)	3.20 (2.32-4.40)	<0.001	1.47 (1.02-2.11)	0.040
Renal impairment	24 (10.8)	2.78 (1.77-4.37)	<0.001	0.74 (0.44-1.26)	0.268
Diabetes	44 (19.7)	1.66 (1.2-2.34)	0.004	1.08 (0.73-1.60)	0.702
Hypertension	197 (88.3)	7.29 (4.82-11.04)	<0.001	2.80 (1.78-4.41)	<0.001
Statin use	141 (63.2)	3.46 (2.61-4.58)	<0.001	2.00(1.43-2.77)	<0.001
Cancer history	36 (16.1)	1.26 (0.87-1.82)	0.221	1.11 (0.74-1.67)	0.624

AAA: abdominal aortic aneurysm, IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease.

3.8.2 Aortic size index and effect on survival

There were 956 (20.6%) individuals who died by the end of the follow-up period, with a median (range) length of follow-up being 54.4 (0.02-86.23) months. Preliminary analysis indicated that having a history of cancer and being octogenarian were factors that competed with the background mortality rate (hazard ratio >3) and were therefore associated with reduced survival. For these reasons, two analyses were carried out, one including all the cohort (Table 3.13) and the other excluding cancer patients and those older than 80 years old (Table 3.14).

Table 3.13 Multivariate analysis of factors associated with overall survival in patients ≥50 years old

	Males HR (95%CI)	P	Females HR (95%CI)	P
Age per year	1.07 (1.05-1.09)	<0.001	1.06 (1.04-1.08)	<0.001
Diabetes	1.40 (1.02-1.93)	0.036	1.56 (1.08-2.26)	0.019
COPD	2.39 (1.77-3.22)	<0.001	2.27 (1.56-3.30)	<0.001
Statin use	0.93 (0.70-1.23)	0.603	1.02 (0.75-1.40)	0.893
IHD	1.09 (0.80-1.48)	0.590	1.18 (0.83-1.66)	0.363
Renal impairment	2.32 (1.62-3.32)	<0.001	2.55 (1.46-4.45)	<0.001
Aortic size index	1.10 (0.81-1.49)	0.544	*1.69 (1.22-2.33)*	0.002
Cancer history	2.73 (2.07-3.61)	<0.001	3.27 (2.38-4.54)	<0.001

HR: hazard ratio, CI: confidence interval, COPD: chronic obstructive pulmonary disease, IHD: ischaemic heart disease

Advanced age, the presence of comorbidities (diabetes, COPD, renal impairment) and a history of cancer were predictors of reduced survival in this model. ASI was among the predictors associated with a lower survival in females, with a HR of 1.69 (95%CI: 1.22-2.33), but not in males (HR 1.10 (95% CI: 0.81-1.49)). Restricting the analysis to individuals without a history of cancer and patients aged between 50 to 80 years old revealed that ASI remained a significant predictor in females only (Table 3.14).

Table 3.14 Multivariate analysis of factors associated with overall survival for 50-80 year-old patients excluding those with a cancer history

	Males HR (95%CI)	P	Females HR (95%CI)	P
Age per year	1.11 (1.07-1.14)	<0.001	1.06 (1.03-1.09)	<0.001
Diabetes	1.26 (0.78-2.02)	0.339	1.49 (0.86-2.56)	0.155
COPD	2.27 (1.43-3.61)	<0.001	3.22 (1.98-5.21)	<0.001
Statin use	0.79 (0.50-1.23)	0.291	0.79 (0.81-2.05)	0.728
IHD	1.13 (0.69-1.85)	0.621	0.75 (0.43-1.30)	0.302
Renal impairment	3.33 (1.85-6.00)	<0.001	3.00 (1.40-6.45)	<0.001
Aortic size index	1.39 (0.77-2.49)	0.273	1.74 (1.07-2.84)	0.025

HR: hazard ratio, CI: confidence interval, COPD: chronic obstructive pulmonary disease, IHD: ischaemic heart disease

3.8.3 Adjusted effect of infrarenal aortic diameter on survival

Within the group which excluded those patients with a cancer history, two further models were investigated. The aortic diameter was kept as a continuous variable in the first model and as a categorical covariate in the second to determine if the aortic diameter predicted overall mortality. In males, the aortic diameter was categorized into four strata according to the <12.5, 12.5 to 62.5, 62.6 to 87.5 and >87.5 percentiles since the distribution was positively skewed. The IQR can be compared to the 'tail ends', and the largest category (12.5 to 62.5) represented the reference category (161, 162).

When the group was separated into these aortic size strata, the adjusted analysis suggested that amongst males a bimodal mortality association was present in those with smaller (<1.78cm, <12.5 percentile) and larger than average (>1.78cm, the highest 35.5 percentiles) aortic diameters when compared to the 50% of the population in the 1.78-2.12cm aortic size range (Table 3.15). When the aorta was left as a continuous variable, an increase by 1cm was associated with a non-significant HR of 1.12 (95%CI: 0.98- 1.27).

Table 3.15 Adjusted analysis of aortic size on overall survival in males

Aorta category (cm)	Number of deaths	HR (95% CI)*	P Value
<1.78	27/181 (14.9)	1.71 (1.11-2.62)	*0.015*
1.78-2.12	112/709 (15.8)	Ref	-
2.12-2.67	113/346 (32.7)	1.43 (1.10-1.87)	*0.009*
>2.67	74/176 (42.0)	1.39 (1.02-1.88)	*0.035*

Adjusted to age, ischaemic heart disease, statin use, renal impairment, smoking history and chronic pulmonary obstructive disease

For females, when the aorta was kept as a continuous variable, an increase in aortic diameter per 1cm was associated with a HR of 1.26 (95%CI: 1.05-1.51). However, categorizing the aorta was not associated with any significant effect on survival.

3.8.4 Validity of CT measurements (Inter-observer error)

A potential source of bias in measuring aortic diameters might be the inter-observer error between the two investigators and this association was tested using the Bland-Altman methodology. After training the investigator in measuring aortic diameters, a validation of "normal" aortic diameters (<2.5cm) was conducted. The mean difference in the first set of validation was 0.15cm (limits of agreement: -0.08 to 0.38). A further refinement in measuring technique was conducted and a second validation comprising of 42 aortic diameters revealed an improvement in aortic difference of 0.02cm (limits of agreement: -0.15 to 0.15). The results of the validation were well in the range of the accepted intra-observer measurement error reported in the literature (+/- 0.4cm) (158).

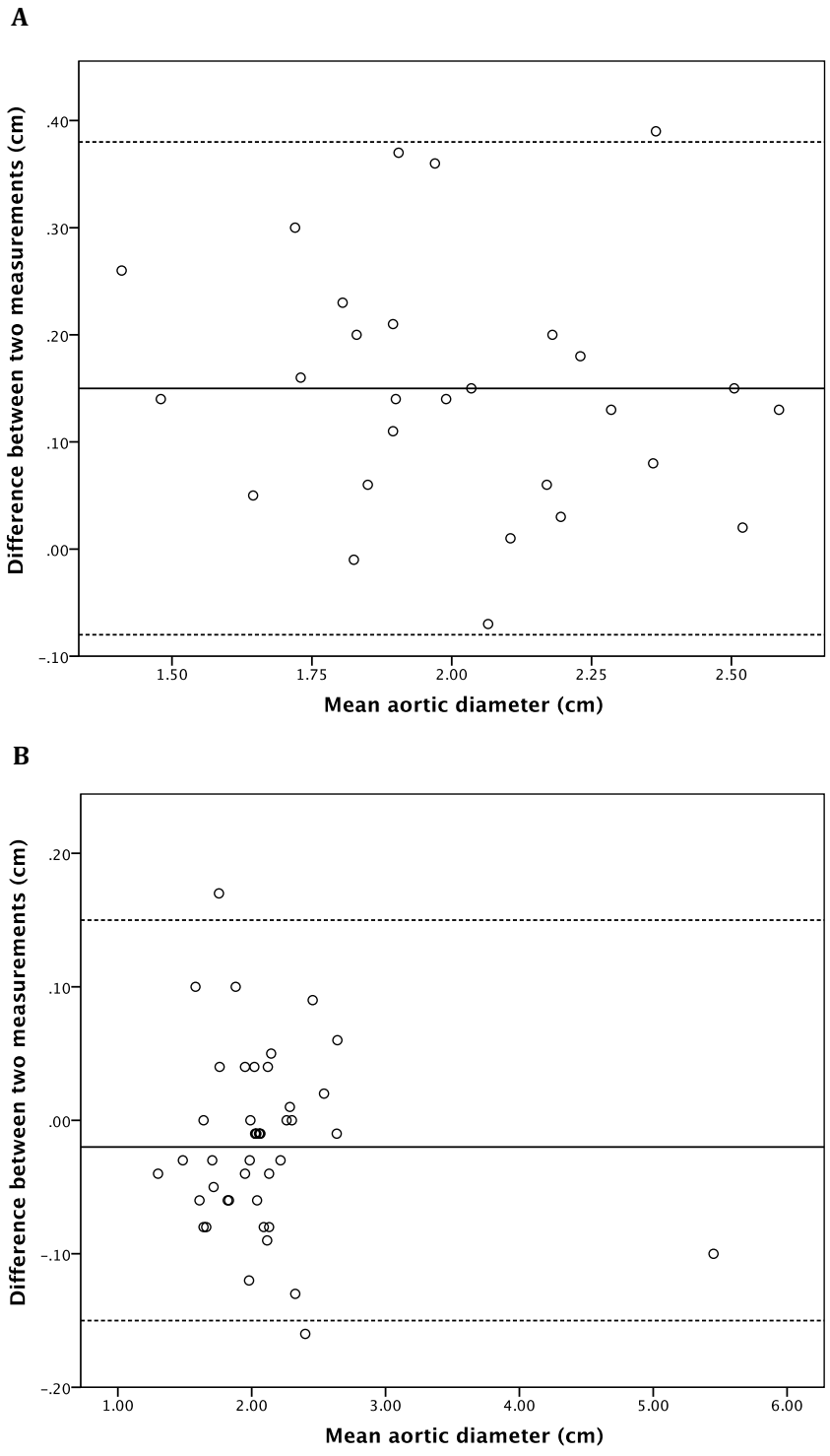


Figure 3.5 Bland-Altman plot showing the differences in aortic measurements between the investigators.

Top (A): first validation (n=28) and bottom (B): final validation (n=42)

Dashed lines indicate limits of agreement (1.96*standard deviation)

3.9 Discussion

In this study, the abdominal aortic diameters from a large population were measured at five levels and predictors of developing a larger aortic diameter and an AAA were determined. Some of these predictors were also prognostic factors independent of reduced overall survival.

In New Zealand, the indigenous Māori people are of Polynesian descent and are believed to have migrated to NZ around 12th -13th century. To date, there is very limited information on the normal aortic diameter in Māori and this data is important as Māori appear to have an increased mortality related to AAA (120). In this chapter, the infrarenal aortic diameter of Maori was slightly larger (1-2mm) than NZ European after age and sex adjustment. This finding highlights that Māori do not appear to have small aortic diameters as observed in the Asian population.

While smoking was found to be an independent predictor of larger aortic diameters in the NZ European population, this association was not observed in the Maori population. This might be due to the higher baseline proportion of Māori with a smoking history included in the combined datasets. The slightly larger diameters observed in Māori might be explained by the overall higher burden of comorbidities. Due to the well-established effects of smoking on AAA development, the aortic diameters are likely to decrease if the prevalence of smoking falls in Maori. The time taken for this affect to occur is an area of where further research is required.

Obtaining information on contemporary aortic sizes is required in order to improve the management of abdominal aortic aneurysms and to provide reference groups should AAA screening become established in New Zealand. Data from Gloucestershire, United Kingdom indicate that the mean aortic diameter in men has decreased from 2.1 cm (0.56) in 1990 to 1.7 cm (0.35) in 2009 (88). Updated data from the NAAASP report a mean aortic diameter of 1.8cm (115). The reasons for this apparent decline may be related to changes in smoking patterns (18, 163), the ultrasound-measuring

techniques used (42) and increased rates of diabetes which itself has an inverse association with aortic diameter dilatation (164).

The aortic diameters presented in this study are consistent with previous population studies. Aortas measured by CT scan from the Framingham Heart Study revealed a mean aortic diameter of the mid abdominal aorta and aortic bifurcation of 1.93 and 1.87 for males and 1.67 and 1.60cm for females respectively (165). In comparison, the aortic diameters recorded in this study (when similar age limits were applied) were 2.01 and 1.92 for males and 1.70 and 1.62 for females respectively. In a study of patients undergoing coronary calcium scanning the descending thoracic aorta diameter in males and females was 2.56 and 2.30 respectively (166) (*cf.* supra celiac artery 2.52 in males and 2.35 cm in females in this current study).

In addition, the AAA risk-factor associations and resulting odds ratios presented in this study were consistent with previous results reported in two other meta-analyses (11, 137) (Table 3.16). Although the current study observed the odds ratio for smoking history as being almost twice as high as the previous studies, this might be due to the relatively smaller numbers of patients included in the study as reflected in the wide confidence intervals. The results of both meta-analyses for smoking were inconsistent as evident by significant heterogeneity within the studies included (11, 137). This could be related to the population selected for AAA screening.

Table 3.16: Two meta-analysis with pooled OR of risk factors influencing the presence of AAA

	Cornuz *et al.* (137)		Li *et al.* (11)		*Current study*
	N of Studies	**OR (95%CI)[1]**	**N of Studies**	**OR (95%CI)†**	**OR (95%CI)**
Sex (Males)	6	5.69 (3.36-9.64)	NR	NR	*3.30 (2.35-4.62)*
History of MI	6	2.28 (1.90-2.74)	10	1.82 (1.65-2.00)	*1.72 (1.25-2.38)*
PAD	8	2.50 (2.12-2.95)	3	3.00 (1.74-5.19)	*NR*
Smoking history	11	2.41 (1.94-2.01)	11	2.07 (1.87-2.28)	*5.08 (3.58-7.21)*
Hypertension	9	1.33 (1.14-1.55)	12	1.26 (1.15-1.39)	*2.80 (1.78-4.41)*
Diabetes	6	1.02 (0.81-1.29)	10	1.04 (0.90-1.19)	*1.08 (0.73-1.60)*

MI: Myocardial infarction, PAD: Peripheral artery disease

† Random-effect model due to expected heterogeneity between studies

In this study, IHD and COPD were associated with AAA presence in females but not in males. This finding has not been previously reported and might be due to the background comorbid profile of this cohort. If these gender-specific predictors can be validated, they could be potentially useful to help identify 'at risk' women and thereby improve detection of AAA in this group.

This study might differ from other AAA screening or population studies in that the population sought medical attention for symptoms or health concerns. This is evident by an equal proportion of individuals living in more deprived and less deprived locations. In addition, this population had a higher prevalence of baseline health conditions as observed by the higher prevalence of diabetes and cancer history compared to other population studies.

Since body measurements appear to affect aortic diameters, the search for a tool to express aneurysm size and a morphometric measurement to index this relationship has been proposed. Ouriel *et al.* was the first to use morphometric measurements in an attempt to predict AAA rupture (167). Lumbar vertebral body diameter was used as an index to patient body-size to predict AAA rupture. More recently, Sconfienza *et al* proposed the use of wrist circumference as a surrogate for body build and reported that the use

of this body size adjustment resulted in an improved definition of AAA. These authors evaluated 1200 patients and correlated wrist circumferences with mid infrarenal diameters. An aortic diameter to wrist circumference ratio of greater than 0.15 was thought to be a more useful definition of AAA (168).

In this current study, due to its retrospective nature, morphometric measurements were limited to BSA and BMI. Previous studies have used anatomical landmarks such as femur and pelvic measurements, in order to perform body size adjustments (169). Obtaining such measurements from the available CT investigations was challenging, as these measurements require additional 3-D reconstruction. The other hindrance in using the CTC data was that the air insufflation distorts the abdominal anatomy and the amount of body-wall and anatomical changes are variable amongst individuals. With the large number of individuals missing height and weight recordings, it was challenging to develop such tools. A prospective clinical study correlated with radiological imaging might provide such information.

In this study, the influence of aortic size and ASI differed between genders. In females, larger aortic diameters and ASI were independent predictors of death. However, in males, this association was not clearly evident and it was not possible to confirm that the aortic diameter influenced survival in a bimodal fashion as previously reported by Norman and colleagues in the Western Australian Health in Men Study (162). Information on aortic diameter and association with survival has been limited to a small number of studies (Table 14). All these studies recruited patients more than 10 to 20 years ago, which has implications on the generalisability of these findings in current clinical practice where cardiovascular modification has improved and life expectancy has risen. ASI has only been previously investigated as a marker of aneurysm rupture but not as a surrogate marker of mortality as demonstrated in this study (156, 157).

Table 3.17: Summary of studies reporting on the effect of aortic diameter on survival

Region	N	Age	Sex	Study duration	Follow-up	Aorta categorisation	Outcomes
Scotland (170)	8146	70.3 (2.9)	Males only	April 2001 to March 2004	7.4, IQR (6.9-8.2)	<24,25-29 & >30	Increased mortality & hospital admission
Western Australia (158)	12203	72.6	Males only	1996-1999	5 year	<10-18,19-22, 23-26,27-30, 31-34, 35-38, 39-42,43-46, 47-50, 51-95	Bimodal Aorta <18 And >24mm
Four Medicare states, USA (159)	4734	74 (65-98)	M=1953 F=2781	1992-1993	4.5 years	<2 2-3, 3-3.5 & >3.5cm	Larger aortas associated with greater CVD events
Tromso, Norway (171)	6640	58-65	M=3394 F=3498	1994-1995	10 year	<18, 18-20, 21-23, 24-26, 27-29, 30-34	Larger aortas CVD death & overall mortality
Current study	3528	70.5 (10.8)	M=1412 F=2116	Jan 2009 to April 2013	Median 4.6 years Max 7.2 years	Continuous & Categorical M=12.5% F=2.5%	M= smaller & larger diameters F= AAA presence and aortic size

Numbers in parenthesis represent standard deviation or as otherwise stated, M=males, F=females All aortic diameters are in mm.

As anticipated, there are limitations to the studies presented in Table 3.17), relating in particular to the group-selection criteria and age-range limits which were included in the analysis. In addition, there were differences in the way that the various studies stratified aortic diameters.

3.10 Limitations

The relatively large cohort with data on aortic diameters in a NZ context and a relatively long survival follow-up are strengths of this study. However, some limitations need to be discussed.

Firstly, the retrospective nature of the design prevented a complete capture of all demographical and clinical data, particularly noted in the high percentage of missing height recordings. However, we attempted to estimate the weight and height recordings from other databases. Comparing the

weights and heights of 9,000 patients (from the same geographical catchment) with an average age of 65.1 years who underwent coronary interventions or percutaneous cardiac procedures revealed an average weight and height of 83.7 kg and 169.7cm respectively. Other more useful measures such as waist to hip ratios, which might be more useful to predict cardiovascular risks, were not available.

Secondly, the potential selection bias of such a cohort meant that some of the observations should be interpreted with caution, particularly in the survival analyses. Where possible, the competing effects of cancer and advanced age were excluded to improve the generalisability of the findings to a community-based population. Unlike other studies, the age included in the regression analysis was limited to $\geq$ 50 years old.

In the Canterbury region, Māori comprise of about 8-9% of the population but they were underrepresented in this study (2.2%). This has limited the generalisability of reporting ethnic data. To overcome this, data from other regions were gathered to provide the best current data on Māori aortic diameters. This approach in itself might have introduced bias with measuring aortas and identification of Māori. Furthermore, other possible confounders and adjustments could not be performed as risk profiles for the datasets were not available or the definitions were not consistent. Furthermore, although patients were included consecutively from each centre, the selection process and indication for obtaining the radiological scan differed between volunteers in the general population as in the Waitemata primary health group and those with gastrointestinal symptoms undergoing a CTC. Furthermore, other possible confounders and adjustments as body size measurements could not be performed as risk profiles for the datasets were not available or the definitions were not consistent (18). The small number of NZ Maori over 80 year olds has limited the ability to reliably report on the aortic diameter in this group Survival data for Māori patients added from different locations was not available; therefore testing the influence of aortic diameters on survival in the Māori population could not be performed.

3.11 Conclusions

In a region where information on the normal aortic diameter is absent, the diameter of aortas, predictors of larger diameters and AAA presence were determined in a cohort of individuals undergoing CTC in New Zealand. Māori appear to have aortic diameters at least equivalent to NZ Europeans and this should be considered when defining aneurysms. A history of IHD was a predictor of larger aortas, and COPD and IHD were significant predictors of AAA development in females but not in males. Aortic diameter appeared to be an independent but modest predictor of overall survival in females. In males a bimodal association may exist, whereby both relatively small and large aortic size predict poor survival compared to intermediate sized aorta.

3.12 Future Work

Given the limitations discussed in this work, studies reporting on Māori will require a multicentre approach to yield large numbers within a reasonable study period. If an aortic screening program is introduced, obtaining aortic measurements and initiating cardiovascular risk assessments are warranted to reduce overall mortality in those with larger aortas.

Chapter 4: Determinants of Late Survival Following AAA Repair: A Systematic Review & Meta-Analysis

4.1 Overview

After an abdominal aortic aneurysm (AAA) is diagnosed and the diameter reaches a threshold for repair, a risk and benefit analysis is required to determine whether the risk of surgery outweighs the risk of AAA rupture along with the patients' life expectancy.

Predicting late survival prior to elective AAA repair remains the Achilles heel in AAA management. Risk calculators to predict 30-day mortality are well established with some 15 different preoperative models having been developed to predict mortality. Some of the parameters of these models rely entirely on preoperative factors whereas others rely on intra-operative parameters and include both open and endovascular repair. However, predictive models to aid in decision making for long-term prognosis are not widely available or used.

In order to provide information for such predictive modelling, reliable estimates for determinants that influence survival are required. This information can either be obtained directly from acquired survival data or from pooling relevant data from the published literature.

This chapter reports the results of a systematic review and a meta-analysis that provide quantitative and qualitative information on factors that may influence survival following AAA repair. Knowledge of such factors and their impact can be used in predictive model development to assist clinicians in decision-making surrounding AAA management.

4.2 Contribution

This chapter has led to three publications in peer-reviewed journals and I was the principal investigator in all the studies with the responsibilities of data searching, extraction, analysing and writing the manuscripts. Jonathan

Williman and Phil Hider provided specific assistance with the meta-regression and subgroup analysis.

4.3 Publications

Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Systematic Review and Meta-analysis of Factors Influencing Survival Following Abdominal Aortic Aneurysm Repair. European Journal of Vascular and Endovascular Surgery. 2016; 51(2):203-15

Khashram M, Hider PN, Williman JA, Jones GT, Roake JA. Does the diameter of abdominal aortic aneurysm influence late survival following abdominal aortic aneurysm repair? A systematic review and meta-analysis. Vascular. 2016; 24(6):658-67

Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Management of modifiable vascular risk factors improves late survival following abdominal aortic aneurysm repair: A systematic review and meta-analysis. Annals of Vascular Surgery. 2016; doi: 10.1016/j.avsg.2016.07.066

4.4 Background

Weighing the risks of AAA rupture against the risks of operative mortality remains one of the most challenging decisions in AAA management. In the clinical setting, this judgment is usually part of a shared medical decision process between clinicians and patients. Ideally, this process would take into account co-morbidities and estimates of life expectancy with or without repair. Unfortunately, predictive models to identify high-risk patients and aid this process are not available (172).

Results from a large Medicare database and a meta-analysis of randomized controlled trials have shown that there is no difference in overall long-term patient survival between endovascular aneurysm repair (EVAR) or open aneurysm repair (OAR) (59, 64). Therefore, existing patient co-morbidities and cardiovascular risk factors appear to have the strongest impact on overall late mortality following AAA repair.

Prognostic demographical and clinical variables associated with poor late survival following AAA repair have been well described but are often reported as single outcomes in multiple studies and are susceptible to selection and publication bias. These prognostic factors have included patient demographics, associated comorbidities and AAA anatomical factors.

4.5 Objectives

Given the importance of clinical decision-making in the management of AAA, the aim of this systematic review and meta-analysis was to report and quantify the impact of prognostic factors associated with long-term survival after AAA repair from the best available information in the literature.

4.6 Methods

A systematic review of published articles was conducted according to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines (173) and the Meta-analysis and systematic reviews Of Observational Studies in Epidemiology (MOOSE) (174).

In the **PICOT** (175, 176) format, this topic was defined as:

- **Population:** patients undergoing elective AAA repair, (via either OAR or EVAR);
- **Intervention and comparison:** presence/absence or magnitude of modifiable clinical preoperative risk factors;
- **Outcome:** all-cause mortality;
- **Time frame:** greater than or equal to one year.

4.6.1 Search strategy

Two researchers (MK & JR) independently conducted the study selection, data extraction and assessment of methodological quality. When disagreement arose, the reviewers met to resolve any issues. Medline, EMBASE and the Cochrane Library Database were searched via the OVID SP database. With the assistance of a clinical librarian, “exploded” medical subject headings (MeSH) terms for Medline and Cochrane and EMTREE

terms for EMBASE were used to broaden the keyword search for "abdominal aortic aneurysm", "risk factors", "long term survival" and "survival rate" along with their synonyms. The search history is included in appendix 8.2.

The search did not have any date restriction, and no limitations on publication language or study type were applied. The first search was conducted in May 2014, and it was updated in April 2015. A manual search of additional articles was conducted using references from relevant articles and review papers. The journals of *Annals of Vascular Surgery*, *European Journal of Endovascular and Vascular Surgery*, *Journal of Endovascular Therapy*, *Journal of Vascular Surgery*, *Vascular Medicine* and *Vascular* were searched for any relevant articles published "online first". Abstracts of conference proceedings were searched for full-text publication. Eligible titles or abstracts were imported into Endnote X7 (Thomson Reuters) library and full-text articles were obtained.

4.6.2 Inclusion and exclusion selection criteria

Two independent reviewers adhered to the following inclusion criteria: any studies reporting survival data and information about factors that may influence survival following elective AAA repair (OAR or EVAR), with at least one year follow-up with the primary endpoint of outcome being all-cause mortality; studies with greater than 100 patients; studies with symptomatic or rupture AAA in the analysis were included if the total number of symptomatic/rupture AAA was less than 20% of study participants; studies containing up to a small proportion of patients (<40%) undergoing complex open (suprarenal clamping/visceral debranching) or fenestrated EVAR; studies that included AAA repair as well as other vascular operations were included if the analysis was done separately for each type of surgery. However, the other vascular operations were not included. The exclusion criteria were studies that only included small AAA (<5cm), non-elective repairs, octogenarians, studies reporting intra or postoperative factors rather than preoperative factors, and non-patient-related factors such as hospital/surgeon volume status.

4.6.3 Study selection

When studies from large registries or known databases were included, the most recent study or the paper which contained the largest number of patients and relevant data was used. Data from national databases were also checked to ensure data from individuals were not duplicated in other published series. If two articles presented data from the same database but different variables were reported, then both studies were included for the two variables. Study authors were contacted when clarification was required.

4.6.4 Data extraction and quality assessment

Data extracted from studies meeting the inclusion criteria were entered into a Microsoft Excel spreadsheet (Microsoft Corporation, Richmond, VA). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the quality of evidence and strength of each factor identified; this was conducted using GradePro (www.gradepro.org). The Newcastle-Ottawa Scale (NOS) was also used to assess study quality, as it was anticipated that the majority would be observational studies (177). This scale employs a 9-point (star) system that assesses three domains: patient selection, comparability of the study groups, and the ascertainment of study outcome. Studies with a score of 9 stars indicate a low risk of bias, whereas 7 to 8 stars indicate medium bias risk, and a score of $\leq$ 6 stars indicates a high chance of bias.

4.6.5 Statistical analysis

A meta-analysis of time-to-event data was performed. Reported hazard ratios (HR) and confidence intervals (CI) from multivariable Cox proportional hazard models were extracted from individual studies. Pooled estimates with 95% CIs were calculated using a random effects model, due to expected heterogeneity among the studies. Heterogeneity was expressed with the I2 statistic, and degrees of heterogeneity were defined as greater than 25%, 50%, and 75% respectively (178). When CIs were not reported,

estimates were calculated using reported ratios and p-values (179). Sub-group analyses were performed according to *a priori* groupings related to: study design, duration of follow-up, type of repair (EVAR vs OAR), location and number of participants (<1000 *vs.* >1000). Meta-regression was performed in R using the metaphor package, with heterogeneity estimated using the DerSimonian-Laird method with inverse variance weights for meta-analysis containing 10 or more studies (180, 181). Statistical significance was set at a p-value <0.05. The meta-analysis was performed using Review Manager (RevMan) Version 5.2. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2012.

4.7 Results

A total of 304 articles were assessed in full and 59 studies met the inclusion criteria and were included in the analysis (Figure 4.1). Seven studies were included in the systematic review but were excluded from the meta-analysis as their data were descriptive without any reported hazard risk ratios (182-185), ambiguous without any variables defined (186) or included factors not relevant to this review (187, 188). In all, 21 authors were contacted and 11 provided information regarding the data or the study.

The individual study design, location and setting of the studies, number of participants and follow-up duration are presented in Table 4.1. Of the 59 studies, 29 were based in Northern America, 24 in Europe, 4 in Asia, one in Australia and one in South America. Fifty-seven studies were observational and two were *post hoc* analyses from prospective controlled trials. There were 54 studies that included elective procedures and the remaining five studies included both elective and emergency procedures. The majority of the studies were of high quality with an average NOS (standard deviation) score of 7.9 (1.1).

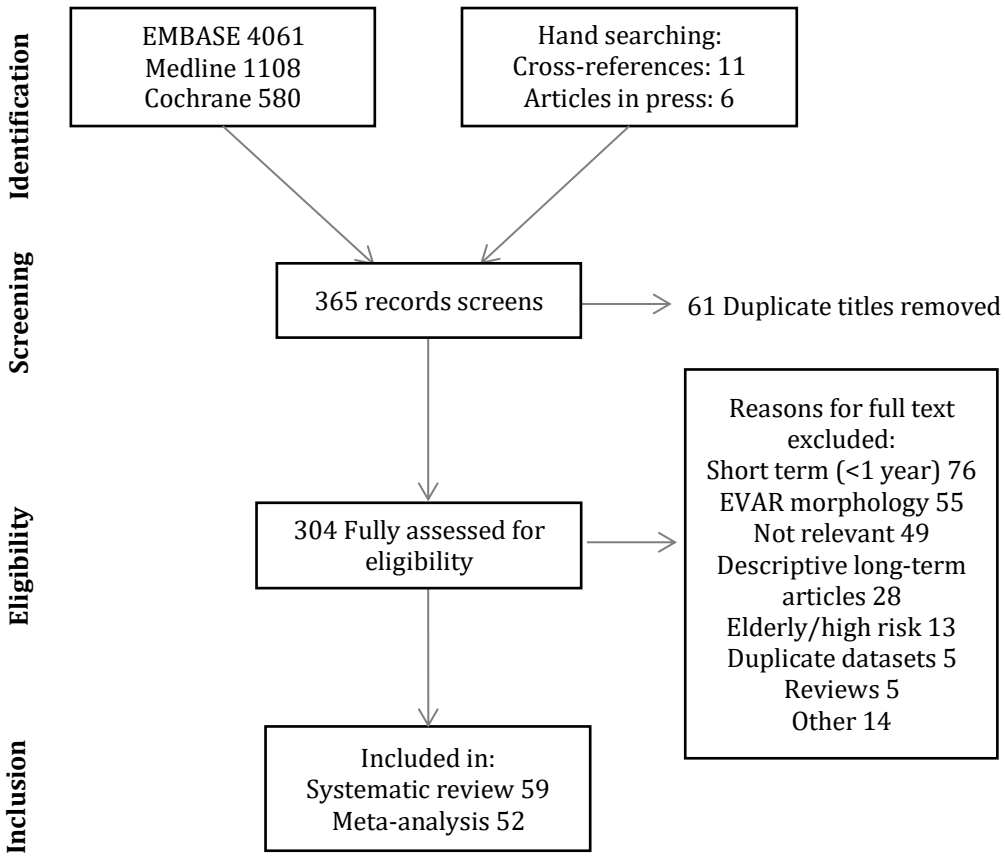


Figure 4.1: Literature PRISMA search flow diagram

Table 4.1 Summary of the studies included in the systematic review

Author	Country	Type of study	N	Treatment	Setting	Study Period	follow up	NOS
Batt	France	Observational	176	OAR	Elective	1987-1991	71	9
Beck	USA	VSGNE	639	EVAR	Elective	2003-2007	12	7
Berge	Sweden	Observational	1041	EVAR & OAR	Elective & Acute	1983-2002	NR	9
Biancari	Finland	Observational	433	OAR	Elective	1979-2002	54 [a]	8
Bonardelli	Italy	Observational	1111	OAR	Elective	1992-2004	43.7	8
Brady	UK	Observational	1139	NR	Elective	1991-1995	43.2	9
Brewster	USA	Observational	873	EVAR	Elective	1995-2005	27	6
Carlisle	UK	Observational	130	OAR	Elective	1999-2006	35 [a]	7
Conrad	USA	Observational	540	OAR	Elective	1994-1998	87	9
De Bruin	Netherlands & BE	RCT *post hoc* DREAM	351	EVAR & OAR	Elective	7 years	76.8 [a]	9
De Martino	USA	VSGNE	2367	EVAR & OAR	Elective	2003-2011	29	9
De Virgilio	USA	Observational	468	EVAR	Elective	1996-2005	78 [a]	6
Diehm	USA/ Switzerland	Observational	711	EVAR	Elective	1994-2006	48	7
Diehm	USA/ Switzerland	Observational	731	EVAR	Elective	1994-2007	48	7
Espinosa	Brazil	Observational	337	EVAR	Elective	1997-2007	58.7	7
Feinglass	USA	VA centres	280	OAR	Elective	1985-1987	NR	7
Galinaes	USA	Medicare & Medicaid	19323	EVAR & OAR	Elective	2007-2008	12	7
Gloviczki	USA	Observational	934	EVAR	Elective & Acute	1997-2011	45.6	8
Grant	UK	VGNW	4070	EVAR & OAR	Elective	2000-2013	NR	9
Grant	UK	Observational	506	EVAR & OAR	Elective	2007-2012	26[a]	8
Grootenboer	Europe	Eurostar registry	9227	EVAR	Elective	1996-2006	12.6 [a]	8

Author	Country	Type of study	N	Treatment	Setting	Study Period	follow up	NOS
Hertzer	USA	Observational	855	OAR	Elective	1976-2003	NR	9
Hertzer	USA	Observational	1135	OAR	Elective	1989-1998	44	9
Huang	USA	Observational	1116	EVAR & OAR	Elective	2000-2011	91.2[a]	9
Jaakkola	Finland	Observational	135	OAR	Elective	1976-1985	72	9
Johnstone	Canada	Observational	680	OAR	Elective	1986	NR	8
Kabbani	USA	Observational	245	OAR	Elective	1986-2013	54[a]	9
Keith	USA	Observational	740	EVAR	Elective	2000-2011	40	8
Kertai	Netherlands	Observational	510	Open	Elective	1991-2001	56.4 [a]	9
Khashram	Australia	Observational	1340	EVAR & OAR	Elective	1990-2013	69.6	9
Komori	Japan	Observational	332	OAR	Elective	1979-1995	NR	9
Koskas	France	Observational	794	OAR	Elective	1989	60	9
Lee	USA	Observational	440	EVAR & OAR	Elective	1996-2004	83.4 [a]	9
Lim	Korea	Observational	247	EVAR	Elective	2006-2013	33.9	7
Leurs	Europe	Eurostar registry	5,892	EVAR	Elective	NR	17	7
Lomazzi	Italy	Observational	235	EVAR	Elective	2000-2008	26.3	7
Mastracci	USA	Observational	412	EVAR	Elective	1998-2005	48	8
Matsumura	USA	*post hoc trial*	334	EVAR & OAR	Elective	NR	NR	6
McFalls	USA	VA centres	1598	EVAR & OAR	Elective	1999-2003	NR	8
Menard	USA	Observational	572	OAR	Elective	1990-2000	47.3	9
Moro	Japan	Observational	125	OAR	Elective & Acute	????-1986	NR	6
Parmar	USA	Observational	2063	EVAR & OAR	Elective	1985-2010	31	9
Piffaretti	Italy	Observational	276	EVAR & OAR	Elective & Acute	2000-2005	70 [a]	8
Rettke	USA	Observational	348	OAR	Elective	1979-1981	55.2 [a]	7

Author	Country	Type of study	N	Treatment	Setting	Study Period	follow up	NOS
Roger	USA	Observational	131	OAR	Elective	1971-1987	NR	9
Saratzis	Greece	Observational	224	EVAR	Elective	2008-2011	NR	7
Saratzis	Greece	Observational	383	EVAR	Elective	2008-2011	34	7
Schlosser	Netherlands	Observational	3457	EVAR & OAR	Elective	1997-2001	60	9
Starr	USA	Observational	582	OAR	Elective	1983-1988	131	8
Stone	USA	VSGNE	3455	EVAR & OAR	Elective	2003-2011	NR	9
Teufelsbauer	Austria	Observational	454	EVAR & OAR	Elective	1995-2000	30	7
Tsilimparis	Germany	Observational	119	EVAR	Elective	4 years	34	6
Welten	Netherlands	Observational	1324	OAR	Elective	1995-2006	72	9
Winkel	Netherlands	Observational	220	EVAR	Elective	2003-2008	34.8	7
Yasuhara	Japan	Observational	338	OAR	Elective	1980-1997	30	7
Yuo)	USA	Observational	1557	EVAR & OAR	Elective	2005-2008	NR	6
Zairns	USA	LIFELINE Registry	2664	EVAR	Elective	5 year	34	7
Zairns	USA	LIFELINE Registry	923	EVAR	Elective	1998-1999	60	8
Zeebregts	Netherlands	Observational	286	EVAR & OAR	Elective	1993-2003	42.7	6

Follow-up was reported as a mean unless otherwise stated. NR: not reported; VSGNE: Vascular Surgery Group of New England; VA: Veteran Affairs; VGNW: Vascular Governance North West: BE: Belgium

4.7.1 Demographical factors

4.7.1.1 Age

Age was the most common covariate identified and was reported as a continuous variable in 21 eligible studies (189-209) and as a categorical variable in 11 other studies (78, 210-219). Two studies were excluded since one did not define how age was categorised (220) and the other used patients aged over 80 years old as the reference category and meaningful HRs were not obtainable (221). The pooled HR from the 21 studies was 1.05 (95%CI: 1.04:1.06), I^2=81% related to each one-year increase in age. When the studies were stratified into groups of less than or greater than 1000 participants, heterogeneity was confined to the group of studies with > 1000 participants (Figure 4.2). When participants were categorised into age groups of 65-75 (n=8) and >75 (n=5) years old vs. the reference category (<65years), the estimated pooled HRs were 1.77 (95%CI: 1.36-2.30), I^2=77% and 2.32 (95%CI: 1.93-2.80), I^2=37% respectively.

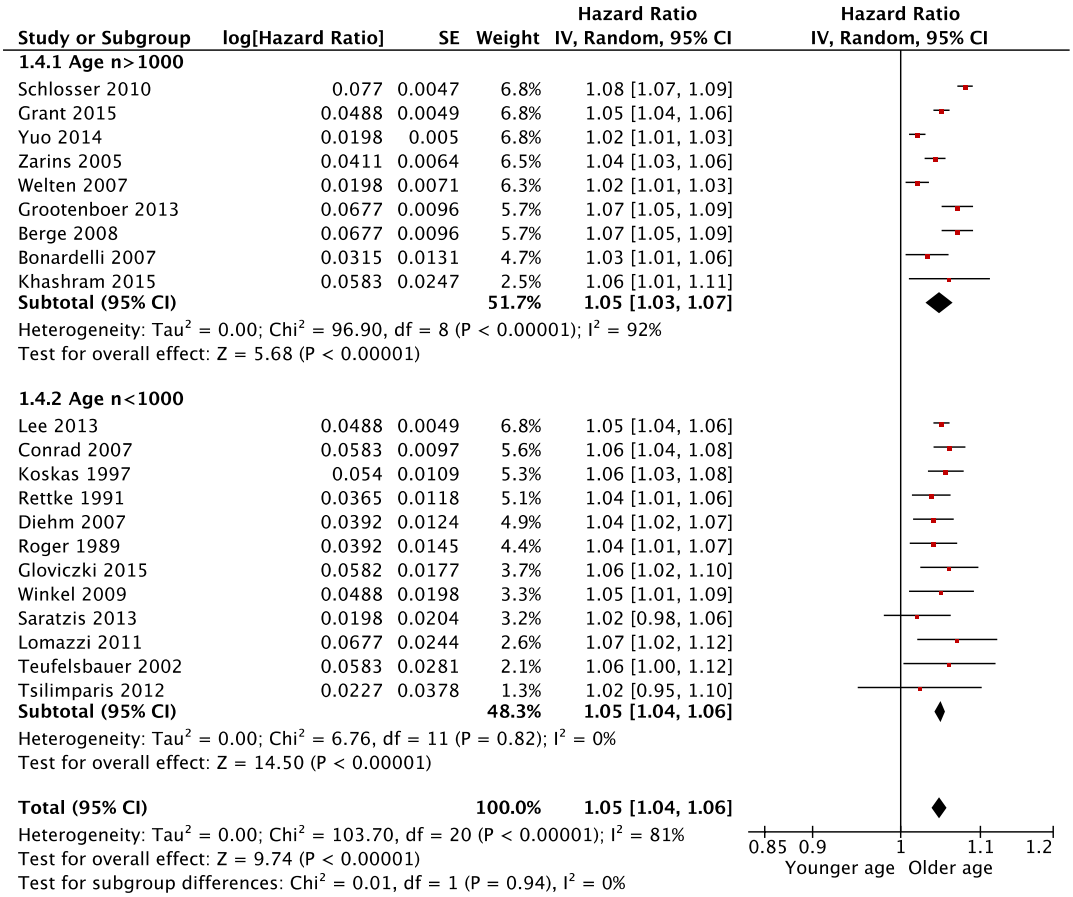


Figure 4.2 Forest plot of age (continuous/year) with sub analysis of number of patients included

4.7.1.2 Gender

Sex was the second most reported covariate and all reported hazard ratios were adjusted for age differences. Sixteen studies reported on the influence of gender on late survival (190-193, 195, 196, 199, 201, 202, 207, 209, 211, 213, 221-223). Females had a worse overall survival than males with a HR 1.16 (95%CI: 1.07-1.27), I^2=45% as represented in Figure 4.3.

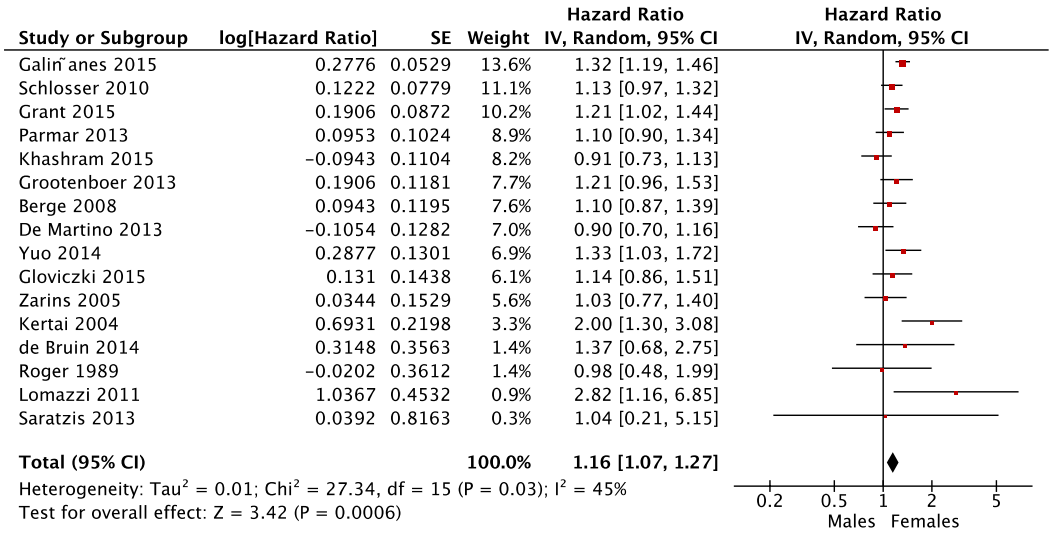


Figure 4.3 Forest plot of the effect of gender on survival

4.7.2 Clinical assessments/investigations

4.7.2.1 American Society of Anaesthesiologists (ASA) classification

The ASA physical status classification system of a 5-score categorical variable was kept in an ordinal (continuous) form in three studies (189, 196, 224) and categorised as greater than ASA 3 or 4 vs. less than 3 in one study (190). Pooled HRs related to each successive increase in ASA score and high ASA (3 and 4) were 1.30 (95%CI: 1.16-1.47), I^2=0% and 1.63 (95%CI: 1.42-1.87) respectively.

4.7.2.2 Hypertension

Of the nine (190-192, 201, 202, 207, 211, 221, 222) studies reporting on the influence of hypertension on survival, only two attempted to define hypertension or comment on treatment (221, 222). The pooled HR of the nine studies was 0.90 (95%CI 0.79-1.03), I^2=60%. When a history of hypertension was confined to the presence of left ventricular hypertrophy (LVH) on ECG, the effect on survival was harmful and heterogeneity was eliminated HR 2.25 (95%CI: 1.66-3.04), I^2=0% (78, 200, 212).

4.7.2.3 Body Mass Index

Anthropometric measurements were reported as body mass index (BMI) in three studies (190, 224, 225). However, there was inconsistency in the assessments and a lack of definitions for BMI categories. The Eurostar (190) and the investigational device exemption trial (224) reported BMI as "obesity", whereas Matsumara *et al.* reported body measurements as "smaller BMI". The combined HR for these two studies was 0.86 (95% CI: 0.76-0.99), revealing a protective effect with obesity. However, Matsumura *et al.* (225) reported that a smaller BMI was associated with improved survival: HR 0.29 (95%CI: 0.12-0.69). Given the differences and lack of definitions for BMI, the pooled estimates of all three studies could not be performed.

4.7.2.4 Haemoglobin

Three studies included information on preoperative haemoglobin concentration, and levels were analysed as a continuous variable (208, 226, 227). A higher baseline haemoglobin level was a protective factor, with a HR of 0.84 (95%CI: 0.74-0.96), I^2=47%.

4.7.3 Comorbidities & risk factors

4.7.3.1 Cardiac disease

Ischaemic heart disease

IHD was inconsistently defined among the included studies. Definitions included: a history of angina or myocardial infarction (MI), the presence of coronary disease on angiogram, and signs from ECG findings or cardiac stress test results. Eighteen studies reported the influence of IHD (however defined) on late survival with a pooled of HR 1.29 (95%CI: 1.18-1.48), I^2=46% (78, 189-194, 197, 204, 206, 207, 209, 211, 217, 218, 222, 228, 229). Seven studies reported specifically on the influence of a previous history of MI (78, 194, 197, 200, 202, 222, 223). When the analysis was confined to the presence of IHD based on a history of MI or ECG findings, heterogeneity

disappeared (I^2= 0%) but the pooled HR remained broadly consistent at 1.52 (95%CI: 1.32-1.73).

Cardiac failure

The impact of cardiac failure or congestive heart failure was also variably defined in the studies and was based on a mixture of clinical, radiological and echocardiographic criteria. The impact of heart failure, however defined, was reported in 14 studies (193, 194, 196, 207, 213, 215, 216, 218, 219, 222, 230-233). The pooled HR was 1.91 (95%CI: 1.58-2.30), I^2=70%. Subgroup analysis into type of repair reduced heterogeneity in OAR with an I^2=22%, but heterogeneity for EVAR and both types of repair remained high I^2=77%.

Cardiac revascularization

One study reported the survival advantage of planned coronary revascularization prior to AAA repair with a HR of 0.76 (95%CI: 0.59-0.98) (214) and two studies specified the risk associated with uncorrected IHD with a HR of 2.59 (95%CI: 1.14-5.88) (201, 229).

4.7.3.2 Respiratory disease

There were 18 studies reporting the influence of COPD on long term mortality following AAA repair (189-191, 196, 203, 205, 207, 211-214, 217, 218, 220, 225, 228, 230, 232). The pooled HR was 1.53 (95%CI: 1.37-1.70), I^2=70% (Figure 4.4). Three studies reported on COPD patients requiring supplementary oxygen therapy with a HR of 3.05 (95%CI: 1.93-4.80), I^2=63% (198, 216, 218). A subgroup analysis was undertaken to determine if the average duration of follow-up could explain the high heterogeneity. Studies with longer than 4-year follow-up resulted in I^2=0% compared to shorter follow-up studies with heterogeneity of I^2=82%.

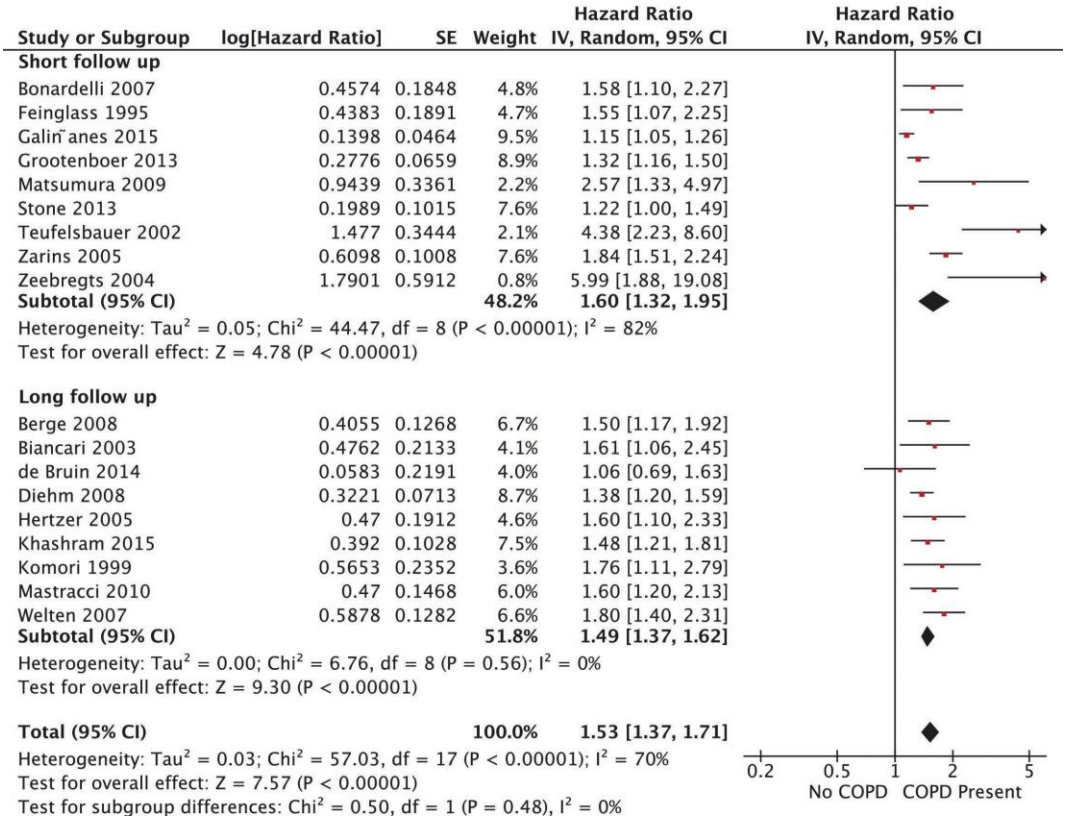


Figure 4.4 Forest plot of COPD and sub-group analysis of follow-up duration

4.7.3.3 Renal disease

There was inconsistency among the studies in the methods used to report renal impairment and differences in the units of measurement. Some of the differences were overcome by converting creatinine units in mg/dl into µmol/L. Creatinine values were either reported as categorical data or kept in a continuous form. Three separate analyses were performed: (1) a categorical group was defined based on creatinine levels between 150 to 200 µmol/L, (2) creatinine clearance or estimated glomerular filtration rate (eGFR) data were used for another analysis and (3) studies reporting on patients receiving haemodialysis or patients with end stage renal disease (ESRD) (creatinine >350µmol/L) were assessed. The results from the first analysis which included 16 studies (189-191, 194, 196, 201, 203, 207-211, 214, 218, 222, 234) indicated that the presence of renal impairment was associated with increased mortality risk HR of 1.54 (95%CI: 1.43-1.67), I^2=11%. Four studies reporting on eGFR or creatinine clearance had a HR of 0.98 (95% CI: 0.96-0.99), I^2=88%, for each increase in measurement unit

(ml/min) (202, 204, 205, 228). Five studies included patients with severe disease on dialysis or with ESRD and had a resulting HR of 3.15 (95%CI: 2.45-4.04) I^2=0% (198, 205, 216, 219, 233).

4.7.3.4 Cerebrovascular disease

Cerebrovascular disease when defined was reported as a history of a previous stroke or transient ischaemic attack. Two studies reported the influence of carotid disease but these were not included in this group as carotid disease is not primarily associated with all strokes and carotid disease was poorly defined (190, 211). Nine studies (191, 193, 198, 201, 202, 205, 212, 217, 234) reported the influence of cerebrovascular disease on late survival resulting in a pooled HR of 1.57 (95%CI: 1.40-1.77) I^2 =0%. The presence of carotid disease had a HR of 1.27 (95%CI: 0.93-1.73).

4.7.3.5 Peripheral artery disease (PAD)

Three studies reported the influence of PAD on the overall survival following AAA repair (196, 202, 224) with a pooled HR of 1.36 (95%CI: 1.18-1.58), I^2 =0%. One additional study included ankle brachial pressure indices (ABPI) with lower ABPI values predicting worse survival (225). However, given differences in the definitions, the results could not be pooled.

4.7.3.6 Diabetes

Fourteen studies (190-193, 201-203, 207-209, 211, 213, 217, 222) reported on the influence of diabetes in relation to survival. The type of diabetes, the treatment and the presence of any complication was only defined in one study (222). One study included “diabetes with complications” but this was not described (213). The pooled HR was 1.34 (95%CI: 1.20-1.49), I^2 =26%.

4.7.3.7 Smoking history

Seven studies (190, 198, 201, 204, 211, 217, 221) used various definitions for smoking, which ranged from current smokers to history of smoking/nicotine use to never smoked. Two studies specified “current smokers/smokers” rather than a history of smoking (204, 221). The pooled

HR for any history of smoking and current use was 1.27 (95%CI: 1.07-1.51), I^2 =45%.

4.7.3.8 Cancer history

A total of six studies reported on the impact of a history of a cancer diagnosis (201, 215, 226, 235), intraoperative tumour finding (197) or current cancer treatment (216) on the late survival following AAA repair. The pooled HR for any definition was 2.89 (95%CI: 1.29-6.47), I^2=76%. The heterogeneity remained high despite sub analysis according to the different definitions used.

4.7.4 Medication use

4.7.4.1 Lipid lowering agent use:

There were a total of 11 studies reporting the influence of statin/lipid-lowering use on survival (198, 202, 205, 206, 209, 211, 213, 218, 221, 228, 236). There was some variation in the definition of use; nine studies reported "statin use", one study examined "medication for hypercholesterolemia" (198), and another included all types of "lipid modifying drug therapy" (221). Statin/lipid-lowering use had a protective role on overall survival, with a pooled HR of 0.72 (95%CI: 0.67-0.78), I^2=35% (Figure 4.5). When analysis was confined to the nine studies reporting "statin use" the heterogeneity was reduced: HR 0.76 (95%CI: 0.71-0.81), I^2=6%.

In those studies, the proportion of patients using statins varied from 12.4% to 69.9%. In 2000, approximately 38% (95%CI: 28-48) of participants in AAA studies used statins. Since 2000, the proportion of participants who used statins increased at a rate of about 2.7% each year (95%CI: 0.7-4.8, p = 0.016) (Figure 4.6).

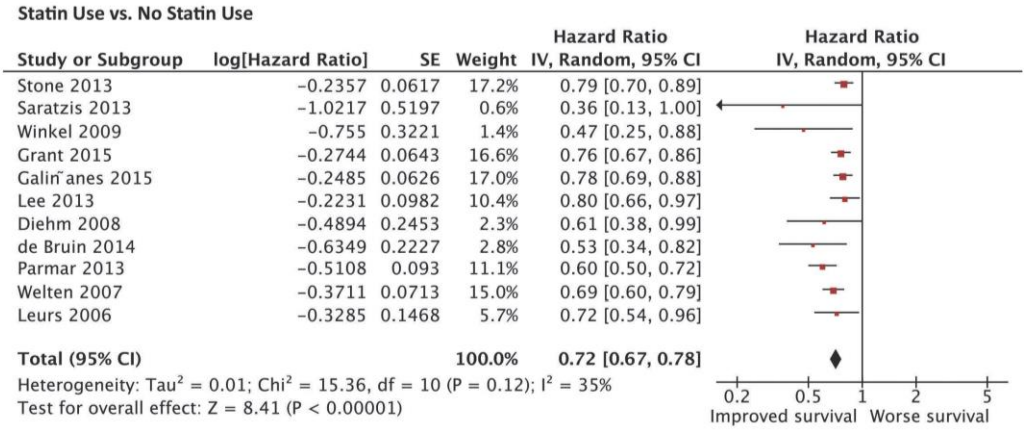


Figure 4.5 Forest plot of statin use according to proportion of patients using statin in each study

Top to bottom= highest to lowest percentage

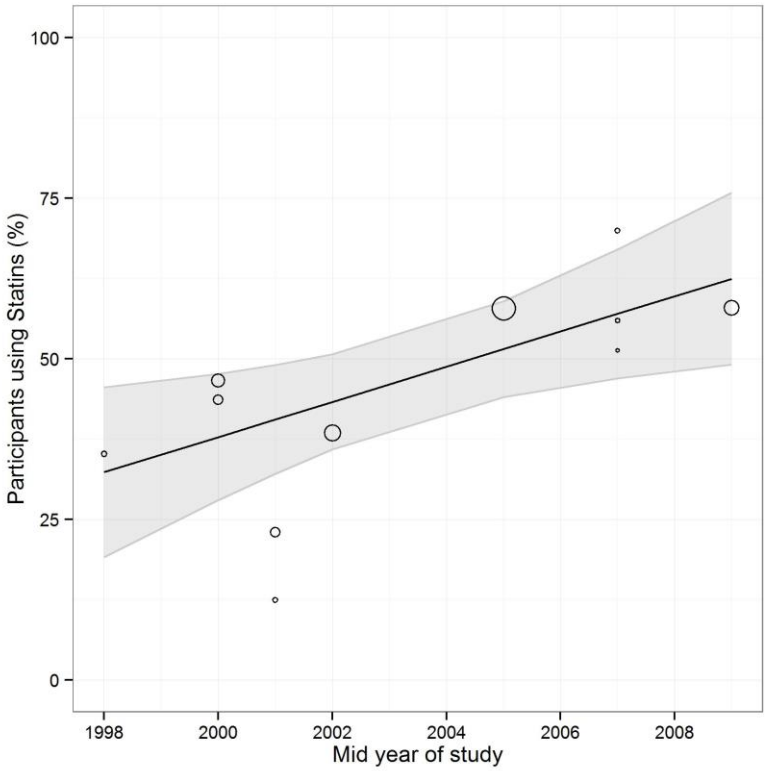


Figure 4.6 A weighted linear regression of study mid-year and proportion of patients using statin

Size of circle proportional to study size, shading represents 95% confidence intervals

4.7.4.2 Aspirin and anticoagulant use:

Six studies reported the effect of antiplatelet or anticoagulation use after AAA repair (198, 209, 211, 218, 222, 230). Definition of use varied by study; three studies (218, 222, 230) specified antiplatelet use as "aspirin," and the

other three defined it as “antiplatelet,” (209) “antiplatelet/anticoagulant”, (211) or “Coumadin” use (198). Antiplatelet use in four of these studies was associated with an overall protective effect, with an HR of 0.81 (95%CI: 0.73-0.89), I^2=9% when compared to non-aspirin/antiplatelet users. In one study, antiplatelet/anticoagulation use was combined and 76.6% of the patients were receiving either one or both drugs (211). This study was therefore not included in the analysis as the patients were inseparable. Anticoagulation (Coumadin) use was associated with reduced survival compared to non-anticoagulation users, with a HR of 1.41 (95%CI: 1.07-1.85) in one study (198).

4.7.4.3 Beta Blockers

Two studies reported the effects of preoperative beta-blocker use (211, 222) compared to patients not receiving beta-blockers. Information on specific beta-blocker agents or doses were not specified. The pooled HR was 0.75 (95%CI: 0.61-0.93) indicating a protective role following AAA repair.

4.7.5 AAA diameter

There were 16 studies comprising of 19,722 patients that reported data on AAA diameter. All of the studies adjusted for age while several also adjusted for comorbid conditions. Larger AAA diameter measured prior to AAA repair was associated with lower reported survival compared with smaller aneurysms. A 1cm increase in AAA diameter was associated with a pooled HR of 1.13 (95%CI: 1.10-1.18), I^2=48% (Figure 2). Excluding four studies with either categorical (204, 237, 238) or logarithmic (239) AAA diameter did not influence the overall risk- HR 1.13 (95%CI: 1.09-1.18), I^2=50% for each increase in 1cm of AAA diameter.

Thirteen studies were included in a subgroup analysis according to AAA repair type (OAR or EVAR), each contributing an equal weight (50%) into the sub-analysis. EVAR was associated with a significantly higher mortality risk compared with OAR for each 1cm increase in AAA diameter. Pooled HR for EVAR and OAR was 1.20 (95%CI: 1.15-1.25), I^2=0% and 1.08 (95%CI: 1.03-1.12), I^2=12% respectively (Figure 4.7). This subgroup analysis

excluded two studies that included both EVAR and OAR in the same analysis (235, 237), one study that categorized AAA diameter (204) and one that did not report how the AAA was repaired (239).

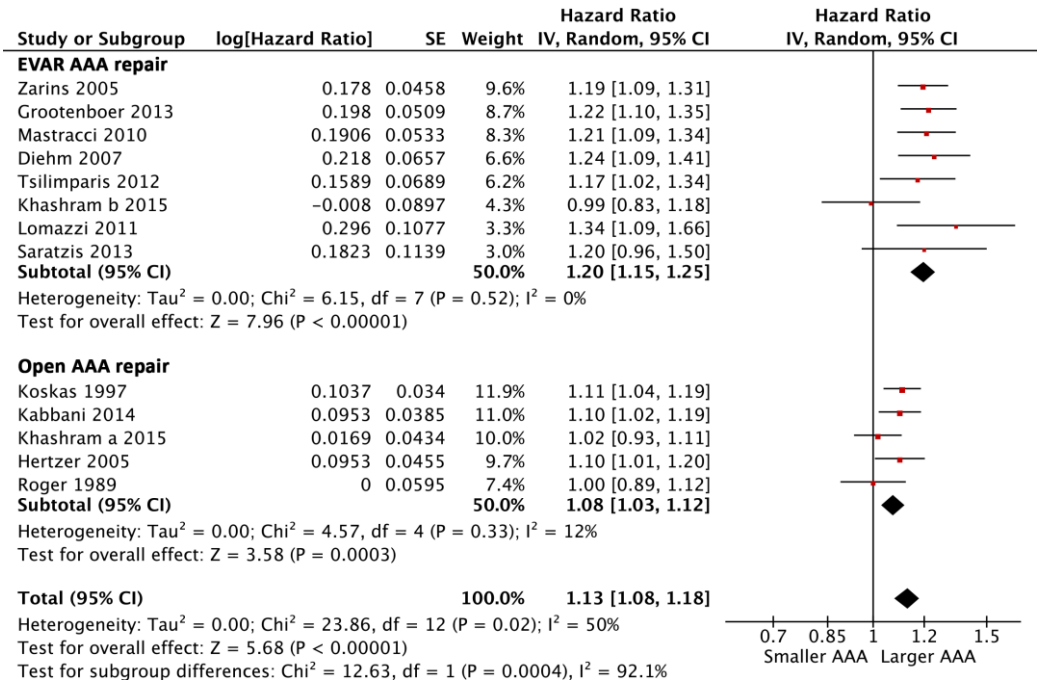


Figure 4.7 Subgroup analysis of AAA diameter according to type of repair

Per 1cm increase, EVAR: endovascular aneurysm repair, OAR: open aneurysm repair

Meta-regression was undertaken to determine if the between-study heterogeneity could be accounted for by the mid-year of study or duration of follow-up. Sixteen studies contributed to mid-year of the study and 15 studies contributed to the duration of follow-up. There was an association for a decrease in log(HR) by duration of follow up (β = 0.998, 95%CI: 0.996-1.000, I^2 = 24%, p < 0.013) (Figure 4.8). There was no evidence of a change in log(HR) by mid-year study (β = 1.004, 95%CI: 0.999-1.010, I^2 = 47%, p = 0.13).

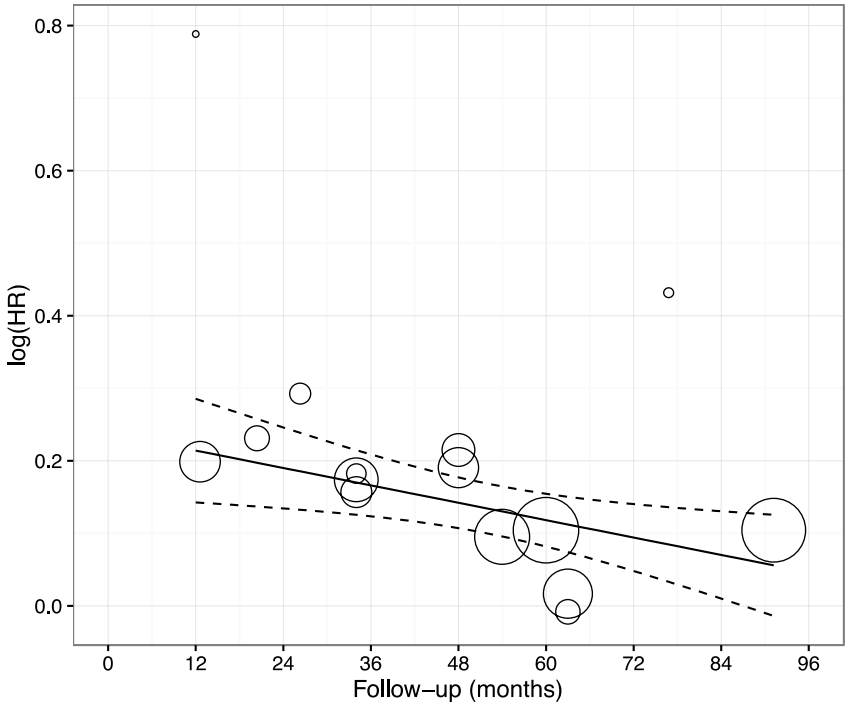


Figure 4.8 Log(HR) of AAA size vs. study follow-up duration

The solid line represents the regression line and the dotted lines correspond to the 95% confidence intervals. Each circle represents a different study and the size of the circle is proportional to the weight of study (inverse variance = 1/standard error^2 of the HR)

4.8 Discussion

In this comprehensive review, the pooled best-available prognostic data from studies reporting on late AAA-repair survival during the past 25 years were analysed and presented, including 81,928 individuals. The results from this review highlight several important issues in relation to long-term survival following AAA repair. The impact of some factors has been inconsistent in isolated studies such as gender and AAA diameter. This review also highlights that ESRD on dialysis and COPD on supplementary oxygen are associated with a three-fold increase in mortality.

There is some debate about whether gender influences survival following AAA repair. Data from the EUROSTAR and Lifeline registries and the Mayo Clinic revealed no difference in late survival between genders (190, 195, 207). In the general population, women have been shown to have a higher life expectancy than males. However, following AAA repair, this difference

appears to be negated and females had a significantly higher risk of death compared to males (HR 1.16 (95%CI: 1.07-1.27)) after adjusting for age.

Recent evidence from the United States Renal Data System suggests that late survival after AAA repair among patients with ESRD receiving dialysis may be poor, with an estimated 3-year survival of 23.1% compared to 41.9% survival of patients with ESRD without an AAA (192). This conclusion is consistent with the results from this review that also report that late mortality is high among these patients (HR 3.15 (95%CI: 2.45-4.04)) and brings into question the long-term benefits of elective AAA repair for this group, suggesting that careful selection should be considered on a case-by-case basis.

The results from this study underline the importance of making efforts to improve patient cardiovascular risk factors prior to AAA repair to increase survival. Despite improvements in medical therapy and operative repair technology, a systematic review reported that estimated 5-year survival following elective AAA repair (OAR and EVAR) remained at about 69% (95%CI: 67-71) for over 40 years (75). Further improvements in survival may require better utilization of medical therapy, and future studies need to follow established guidelines to improve reporting of specific medications, doses, and durations of therapy and assess whether medical therapy has been optimized.

4.8.1 AAA diameter

Based on the results from this meta-analysis there appears to be two factors that could explain why larger AAAs may have worse survival.

First, this association was found in both types of repairs therefore a biological cause seems plausible; larger AAA diameters might exhibit more inflammatory mediators, or larger-size AAA might be associated with more advanced cardiovascular disease (204, 240, 241). Five studies provided subgroup comparisons between small and large AAA. The results from three large studies (185, 224, 241) suggested that patients with larger AAA were older and had a greater burden of cardiovascular disease than patients with

small AAA. In the two other smaller studies (204, 242), there was no difference in morbidities between the groups. However, patient co-morbidities were adjusted for within the survival models and the influence of AAA size remained an independent predictor of late survival.

Secondly, the effect estimate of AAA size of EVAR treatment was significantly higher in this analysis compared to the OAR group. However, this does not adequately explain why the association was greater in EVAR than OAR. Results from the Lifeline and EUROSTAR registries have also shown that an increase in AAA diameter was independently associated with a higher AAA-related mortality, higher rupture post repair, re-intervention and surgical conversion to OAR. (207, 224, 241) One might speculate that each re-intervention might have an additive mortality risk.

Roger *et al*. were the first to include AAA size in a multivariate model but AAA diameter was not a significant mortality predictor in their study (201). Almost a decade later, Koskas and Kfieifer were the first to show that preoperative AAA size was an independent predictor of poor late-survival. Interestingly, this finding appeared to generate little discussion, including within the reporting paper. It was not until subsequent EVAR data began to emerge, highlighting morphological aortic neck and iliac artery differences between small and large AAA, that interest in this area began to increase (224, 241).

4.8.2 Strengths and weaknesses

As with most systematic reviews, this analysis is not immune to selection, publication and reporting bias. A key limitation of this study was that each of the factors have been analysed in isolation from any others, whereas in practice patients have more than one demographic and co-morbid factors to be considered in any decision about their care. It is possible that the effects of the various factors may be additive or multiplicative on the risk of late survival. Alternatively, the risks associated with some co-morbidities may even be subsumed into the risks associated with another comorbidity.

Publication bias is a concern with any systematic review and studies from centres with good or excellent results are more likely to publish their data than units with poor outcomes. However it is notable that the data included in this review included reports from national registries, *post hoc* RCT data along with the data provided by smaller groups of surgeons based at specialist institutions. The GRADE score was low for the majority of outcomes and this was predominantly due to the high bias and types of study included.

In this review the search and patient selection was broadened to quantify risks from the literature that would enable us to present generalizable hazard ratios for each factor analysed. In so doing, it was noted that there was a lack of consistency in risk factor definitions, a tendency towards categorising continuous variables or reporting categorical data as a continuous variable such as the ASA grade. These factors may reduce statistical power of subsequent meta-analysis (243). To improve future studies there is a need for standardisation in the reporting of variables that might influence survival following AAA repair.

4.9 Conclusions

In conclusion, using the best available estimates of risk from the literature, important preoperative risk factors were identified and effect estimates for factors influencing late-survival among patients undergoing elective AAA repair were calculated. COPD requiring supplementary oxygen and ESRD had the highest impact on survival, which raises questions with regards to the benefits of elective AAA repair in their presence. The inclusion of these reported factors in the clinical decision-making process, therefore, seems warranted when considering the most appropriate surgical management option for individualizing patient care. These data are particularly useful in preoperative assessment and model development to aid clinical decision-making.

4.10 Further Work

This review suggests that decision-making regarding AAA treatment and long-term survival needs to consider patient-related factors including age and gender along with a range of important clinical comorbidities. Further work is needed to determine the relative importance of each and how the risks from different combinations of the comorbidities may interact. Attention needs to be given to ensure these factors are consistently measured and reported in future studies so that updated and improved estimates can be readily obtained in future assessments and the obtained estimates could then be validated against AAA datasets. The factors and associated risks identified in this systematic review can be used to develop a predictive model to aid management of AAA repair.

Chapter 5: Trends and Outcomes of Abdominal Aortic Aneurysm Repair in New Zealand

5.1 Overview

Abdominal Aortic Aneurysm (AAA) repair is a well-established and effective prophylactic treatment against death caused by AAA rupture. Data from randomised trials summarized in a meta-analysis indicate lower perioperative mortality with EVAR compared to open aneurysm repair (OAR) (59). At two years and beyond, patient survival is very similar in both repair methods and patient pre-existing comorbidities are the predominant factors influencing overall survival, as presented in the previous chapter.

Since the late 1990s there have been significant changes in the detection and management of AAA. The incidence and mortality of AAA have fallen as observed in studies from New Zealand (NZ) and elsewhere. However, this finding has not been consistent internationally. Understanding the reasons for these changes is invaluable when attempting to document the national burden of AAA disease.

The overall theme of this thesis was to describe the contemporary presentation, management and outcomes of AAA disease in NZ, and to use patient outcome data to develop a predictive model that takes into account NZ-specific data. This chapter describes the process of acquiring and cleaning national AAA data and the validation process to provide accurate outcome data which can be used in the development of the predictive model (Chapter 6).

5.2 Contribution

I was responsible for analysing and presenting the data in the format shown in this chapter. The data presented required obtaining, matching and cleaning of large administrative and clinical databases to provide the best available information on AAA disease in NZ.

5.3 Publication

Khashram M, Thomson IA, Jones GT, Roake JA. Abdominal Aortic Aneurysm Repair in New Zealand: A Validation of the Australasian Vascular Audit. ANZ J Surg 2016. doi: 10.1111/ans.13702

5.4 Background

Clinical governance and accountability require that operative outcome-data are routinely collected by national health bodies. The majority of surgical units are also required to collect their own data for reporting, audit and research purposes. Surgeons and health-policy decision-makers rely on end outcomes such as 30-day or 1-year mortality for reporting operative outcomes. However, these relatively simple measures can differ depending on the data source. For example, in AAA repair, variation has been documented in 30-day mortality figures for elective repairs depending on the source of data: prospective population-based data reported 8.2% mortality compared to 3.8% from prospective hospital-based (244). This wide range of mortality may have implications on the quality of care provided to patients, establishing national standards and in auditing purposes.

In healthcare, there are broadly two types of data sources: administrative and clinical. The accuracy and reliability of each is an important issue and surgeons need to understand differences between them. The main purpose for collecting each dataset differs and therefore the variables recorded and the quality and accuracy of the data are likely to differ (245).

Models to predict perioperative mortality are usually derived from large clinical datasets and validated with administrative datasets or vice versa. Several AAA-specific validated and reasonably accurate 30-day morbidity and mortality predictive-models have been developed to aid in medical decision-making (246, 247). However, these models are not routinely used in the clinical setting (248). Most of the models rely on preoperative clinical factors to predict short-term mortality. However, some well-validated

models such as the Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) (249), the Vascular Biochemical and Haematological Outcome (VBHOM) (250) and AAA SCORE rely on intra-operative data (246, 248) such as blood loss and operative time. In 2014, an additional model -British Aneurysm Repair (BAR)- was developed for both EVAR and OAR using 11 preoperative variables (251). This model was tested against two other models and the BAR model has improved predictability and discrimination (252).

5.5 Objectives

The aims of this chapter were: first, to document the national trends of AAA disease and presentation during the 2000-2014 period; second, to validate the quality and accuracy of the datasets used; third, to report the 30 day, 1 year and 5 year outcomes of all AAA repairs; and finally, to determine prognostic predictors of short- and long-term survival following AAA repair in relation to the NZ context.

5.6 Methods

5.6.1 Ethics

The Health and Disability Ethics Committee approved this observational study and the obtaining of data from the Ministry of Health National Minimum Data Set (NMDS) for matching purposes. Written individual patient consent was not possible due to the nature of the study design.

5.6.2 Data sources used

As this was a NZ-based project, the best available data were sought to feed into predictive model building. In NZ, each patient has a unique seven-digit code comprised of three letters followed by four numbers (ABC1234), known as the National Health Index (NHI), which allows linkage to demographical data such as ethnicity and deprivation anywhere in the country.

To obtain national trends, outcomes and prognostic factors, the datasets discussed below were interrogated.

5.6.2.1 Ministry of Health - National Minimum Data Set

A data request to the Ministry of Health- Analytical Services was made for all International Classification of Diseases (ICD)-10 AAA diagnostic codes and procedures from 1st Jan 2010 to 31st December 2014 (Appendix 8.3.1). Patient's demographics, up to 20 diagnoses and up to 20 procedures were provided for each patient encounter.

Initially, a request for all patients with *a primary diagnosis* of I71.3 (abdominal aortic aneurysm, ruptured) and I71.4 (abdominal aortic aneurysm, without mention of rupture) was made, but it was noted that there were substantial missing cases. Therefore, an additional request was made for all patients who had an AAA diagnosis *in their first 20 diagnoses* (I71.3 and I71.4), and these were included to ensure a complete capture of all AAA cases recorded.

The operative codes for AAA-related procedures were reviewed and selected by two investigators independently to ensure that this method would capture all the patients. Aortic procedures for bypass operations were not included as these are more likely to be for arterial occlusive disease rather than aneurysmal disease.

Several validation and data checks were then performed. Operative codes for rupture procedures were checked to ensure that diagnosis of rupture AAA was recorded (I71.3). Two investigators cleaned and checked the data independently and the final datasets were checked for consistency and completion.

A total of 23,501 health encounters (hospitalizations) were provided from the 1st of July 2000 to the 31st of December 2014, of which 14,343 were unique individuals.

These data were then grouped into three broad categories to allow analysis:

1) Those diagnosed with an AAA and have not undergone an AAA repair N=6,775 (examples: small AAA or large AAA turned down for elective surgery or repaired at private hospital);

2) Those diagnosed with an AAA and have undergone an AAA-related procedure N=6,494;

3) Those without an AAA diagnosis but with an AAA-related procedure N=1,065 (examples: aorto-iliac or iliac procedures).

Patient comorbidities were extracted from ICD codes for individual patients and were chosen *a priori* according to factors that have been shown to influence late survival after AAA repair (253). The most prevalent ICD codes in the dataset were grouped and used to define the following co-morbidities: ischaemic heart disease (IHD), smoking status (ex-smoker/current), respiratory disease, hypertension, cerebrovascular disease, atrial fibrillation and diabetes (Appendix 8.3.2).

5.6.2.2 Australian Vascular Audit

The Australasian Vascular Audit (AVA) is a bi-national web-based audit and is the official audit for the Australia & New Zealand Society of Vascular Surgery (254). It collects demographic data, risk factors, operative details and outcomes for all vascular inpatient events. Data entry was commenced in January 2010 with gradual uptake from the majority of vascular units at both private and public hospitals in NZ and has replaced several individual hospital databases and the Otago Clinical Audit from that date. Since 2012, it has been compulsory for vascular surgery trainees to use AVA for generating their operative logbook.

The Australian data in the AVA has been subjected to internal validation using 4% of the sample with a reported error rate of 2.6%. With regards to external validation, AVA in Australia captures 62% of AAA-related procedures (61). However, this form of validation in NZ has not been formally documented.

The AVA was filtered to capture those AAA procedures performed within New Zealand. Between 1st of January 2010 and 31st December 2014, all AAA procedures identified from the AVA were obtained. Duplicate patients and secondary procedures were removed and the primary AAA procedure was considered the index case. The database was checked for procedures performed for graft infections, mycotic aneurysms, isolated iliac aneurysms, EVAR conversions to open surgery and all re-interventions, and these were excluded from the analysis and matching. Of the NHI identified, all except one was matched with the NMDS database and three additional fields were returned and added into the AVA dataset: ethnicity, deprivation from the 2013 census data and date of death for patients that died and were registered in NZ.

The AVA collects data on pre-intra operative data and inpatient postoperative morbidity and complications. The variables used in this study include: age, sex, history of IHD, diabetes, hypertension, renal impairment, smoking history, type of repair and maximum AAA diameter.

5.6.2.3 National Mortality Collection

All deaths registered in NZ are recorded on the National Mortality collection dataset and this database was interrogated to retrieve all deaths with a primary diagnosis of aortic diseases (I71.0 to I71.9) from December 1987 to December 2013. This dataset included demographic information but did not include existing co-morbidities. This permitted defining aneurysm-related mortality for those patients who had an AAA repair and died because of an AAA-specific cause. In addition, two further groups were created for patients who died with a ruptured AAA in the community or those presented to the emergency department and died prior to hospital admission.

These datasets were then “cleaned”, combined and duplicates removed. A diagrammatic scheme of the data synthesis is shown in Figure 5.1.

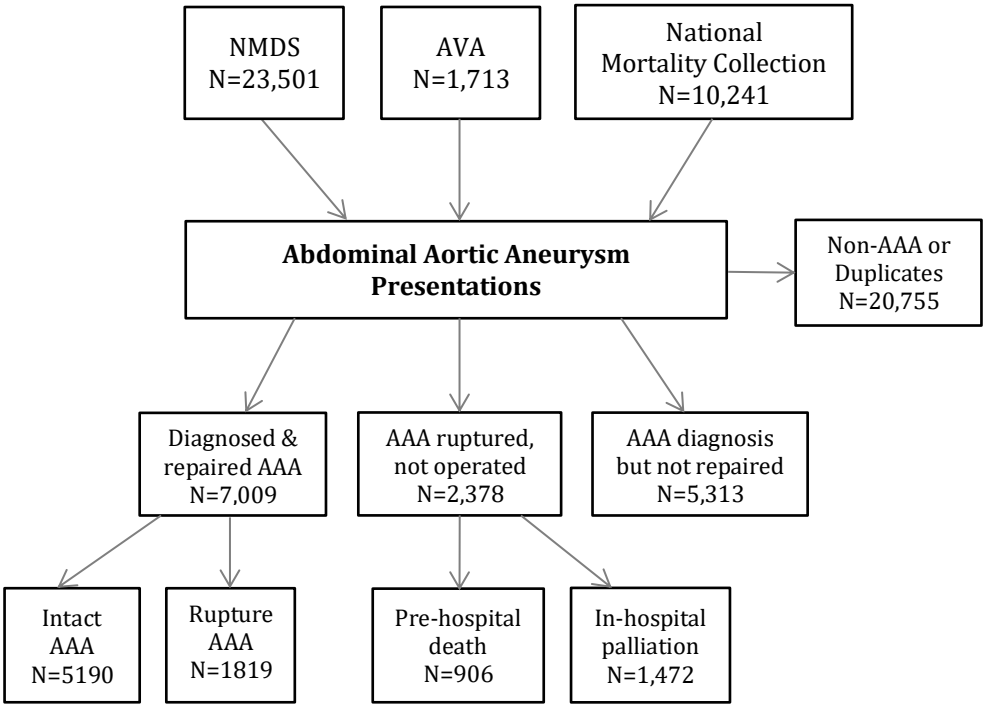


Figure 5.1 Diagram showing data synthesis from the three datasets

5.6.3 Definitions

5.6.3.1 Mortality

Early mortality was presented as inpatient (in-hospital) deaths and deaths occurring within 30 days. Inpatient mortality as recorded in the AVA was defined as a death occurring while under the vascular team or occurring in the same hospital admission.

For patients who were discharged but died within 30 days, the entries were checked and confirmed against the NMDS. For patients re-admitted within 30 days and died, this was included as a 30-day mortality and not as an inpatient death. The turn-down rate of patients not offered aneurysm repair was calculated by dividing the number of patients who presented to hospital with a ruptured aneurysm and did not undergo surgery by the total number of patients diagnosed with a ruptured AAA.

5.6.3.2 Co-morbidities

Risk factors were defined as outlined in the AVA manual; briefly: renal impairment as creatinine ≥150mmol/L; IHD based on history, revascularization or stress tests/ECG; hypertension if on anti-hypertension medications or if systolic >140mm Hg systolic and diastolic >90mm Hg; current smokers if consumption of cigarettes occurred within 2 weeks of operative procedure.

Hospital volume was grouped into two categories: individual hospitals performing greater than 10% of total (national) AAA repair and individual hospitals performing less than 10%. Procedures in private hospitals were included in the high-volume group because the majority of the procedures were performed by vascular surgeons affiliated with high-volume institutions. Procedures performed in a private institution but subsequently requiring a transfer to a public hospital were included in the private hospital group. Mode of admission (arranged or unplanned), length of hospital stay and number of AAA-related hospitalizations were recorded. Early mortality was defined as a postoperative death occurring within 30 days of surgery date.

5.6.3.3 Ethnicity

New Zealand national ethnicity standards dictate the use of prioritization of ethnicities. This means that if a patient identifies with more than one ethnicity, specific protocols are put in place to determine which ethnic group a patient will be counted within for the purposes of statistical analysis. This is designed to ensure indigenous communities are counted and prioritized. It also works to ensure other ethnic minorities are enabled with the largest possible inclusion of membership to enable appropriate statistical analysis to be undertaken. New Zealand national ethnicity standards encourage all primary, secondary and tertiary health institutions to have patients complete a form in which they can self-identify with the ethnic group or groups that they believe best describes their ethnic affiliations. There were

32 patients that had more than one ethnicity, which were manually prioritized.

Four ethnic categories were created: NZ European, NZ Māori, Pacific and Asian/Other. The NZ European included: NZ European, other European and European not further defined. The Pacific group consisted of: Pacific Island not further defined, Samoan, Cook Island Māori, Tongan, Niuean, Fijian and other Pacific Island. The Asian/other group comprised: Asian not further defined, Southeast Asian, Chinese, Indian, other Asian, Middle Eastern, African and other.

5.6.3.4 Deprivation

The New Zealand Index of Deprivation (NZiDep) is a measure obtained from census data and is linked to geographical location rather than individuals (255). The NZiDep was calculated based on nine domains: access to transport, access to communication, living space, income, recipient of benefit, single-parent family, home ownership, qualifications and employment) and was collected in the NZ 2006 and NZ 2013 census. Each patient in the study was assigned an NZiDep score based on their domiciliary address. A deprivation 1 indicates least deprived (high SES) and 10 indicate most deprived (low SES). Deprivation categories were grouped into quintiles.

5.6.4 Statistical analysis

Data validation, cleaning and initial coding was carried out on Microsoft Excel (Microsoft Office 2011). Aberrant and incorrect values were checked, corrected or removed where applicable. Continuous variables were reported as median (range) or interquartile range (IQR) where appropriate or as means and standard deviation (SD) depending on the distribution of the data. Categorical variables were reported as counts (percentages).

5.6.4.1 Incidence calculation

Age, sex and ethnic (when applicable) specific rates per 100,000 population per year were calculated from the NZ population at each respective year. The

World Health Organization standard population was used to age-standardize the rates. All cases identified were assumed to be new cases and each case was identified once only. Those less than or equal to 44 years of age were excluded from the majority incidence calculation as the number of patients <44 years old who had an AAA was very small and this skewed the incidence rates.

5.6.4.2 AVA and NMDS validation

The following information was used for data validation: patient demographics (age and sex), date of admission, length of hospital stay, mode of presentation (acute/arranged) and risk factors: IHD, diabetes, smoking history and hypertension. For admission dates and date of birth differences> +/-1 day, a manual check across the datasets was performed to ensure that procedures matched. Discrepancies among binary outcomes were expressed as odds ratios (OR) and 95% confidence intervals (CI). For the purpose of dataset validation, it was assumed that demographic data and survival status were correctly coded in NMDS, and clinical risk factors and operative details were correctly recorded in the AVA.

5.6.4.3 Predictors of death at defined points in time

Clinically-known variables that may have an impact on 30-day and one-year death were entered into a logistic regression model and analysed at a univariate level. Clinically-important and significant predictors were then added into a multivariate logistic regression model and the impact of predictors was expressed as OR and 95% CI.

5.6.4.4 Time-to-Event analysis (survival)

Dichotomous univariate outcomes were analysed with the log rank test and Kaplan-Meier methodology. Continuous and multivariable data were expressed as hazard ratios (HR). Clinically-meaningful and statistically-significant covariates were entered into a multivariate Cox proportional hazard model. Patients dying within 30 days were excluded from this analysis as including them violated the rules of the Cox model. Censoring for

survival analysis was set at the 17th of December 2015; this allowed nearly one year of minimum follow-up. A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 23 for Mac (SPSS Inc., Chicago, IL) and R statistical software (180) version 3.2.3.

5.7 Results

5.7.1 Trends of AAA repair & presentations

Between the 1st of July 2000 and 31st of December 2014, some 14,700 patients were diagnosed with an AAA or registered as having died of an AAA-related death in NZ. The median (IQR) age was 71 (77-83) years and 10,183 (69.3%) were males. Of these patients, 10,503 (71.4%) had an intact AAA and 4,197 (28.6%) had a ruptured AAA. Of those with a diagnosis of ruptured aneurysm, 1,819 (43.3%) had a repair, 1,473 (35.1%) where palliated/treated conservatively in hospital and 906 (21.6%) died prior to hospitalization. The turndown rate for patients with a ruptured AAA reaching hospital was therefore 44.7%.

The average annual number of AAA repairs remained fairly constant during the studied period. There were approximately 350 cases/year of intact repairs and 125 cases/year of ruptured repairs. The most noticeable decline was observed in the number of AAA diagnosed but not repaired between 2007 and 2009 (Figure 5.2).

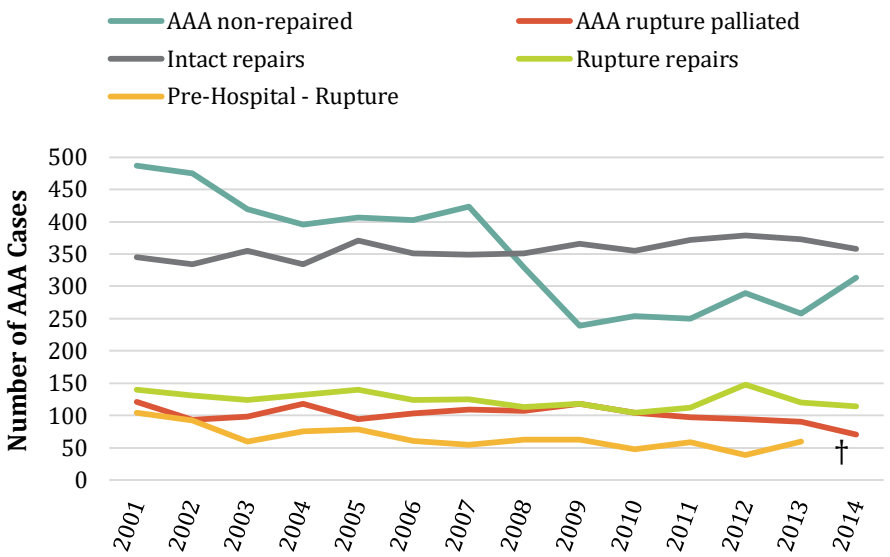


Figure 5.2 Crude counts of AAA cases grouped according to presentation

† For the pre-hospital rupture group data was only available up to December 2013

Crude counts were then age-standardized to represent incidence per 100,000 persons. A pronounced decline in the total of AAA presentations was observed in men from 2001 to 2010 and to a lesser extent in females (Figure 5.3).

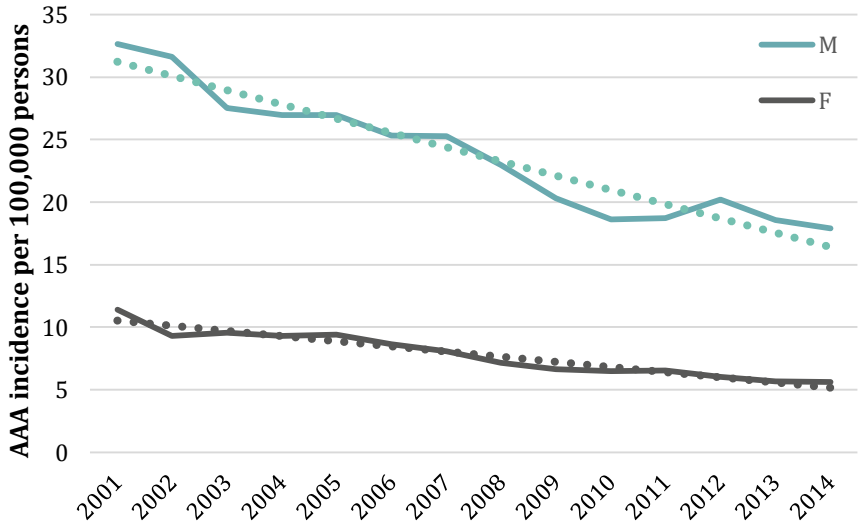


Figure 5.3 Age-standardized AAA presentations in New Zealand by sex, 2001-2014

Including the less than 45 years old group, broken lines represent linear trends

The largest decline in aneurysm incidence was observed in those where AAA was diagnosed but no documented AAA repair was recorded. This group was then excluded, as it did not represent a clinically meaningful AAA presentation-type since patients did not undergo repair or die from the condition and very little was known about them. Therefore, it was deemed to have little contribution to the national burden for the purposes of the analysis in this chapter. After exclusion, the decline was still observed but to a lesser extent (Figure 5.4).

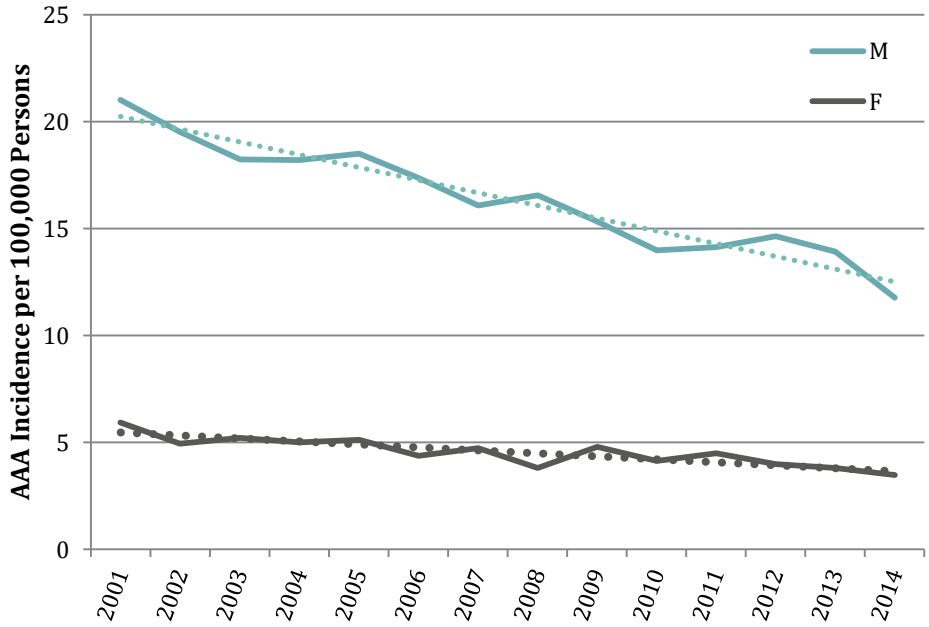


Figure 5.4 AAA age-standardized incidence after excluding those diagnosed with AAA but not repaired

Includes <45 years old

When the data was separated by presentation, the largest decline in incidence was observed in those in which AAA was diagnosed but no repair was recorded (Figure 5.5).

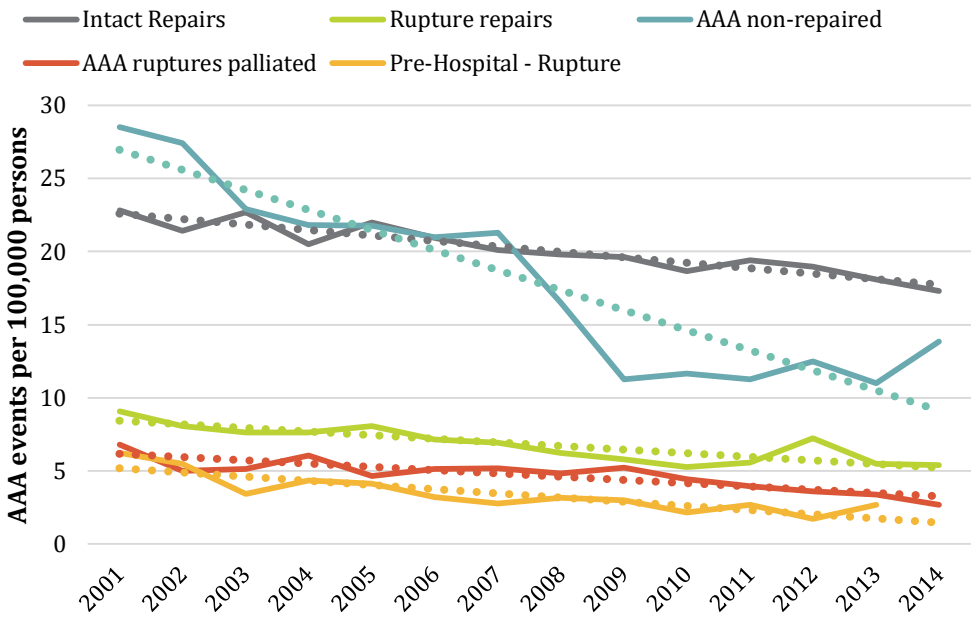


Figure 5.5 Age standardized presentations of AAA from 2001 to 2014 in males and females

Dotted lines represent linear trends

5.7.2 AAA presentations according to sex

There were some differences in AAA presentations between sexes (Figure 5.6). Females were more likely to die from a ruptured AAA than males (21% versus 14%) and were 3.5 years older. On the other hand, males were more likely to undergo an AAA repair (54% versus 34%) at a very similar average age (males= 73.1 versus females=74.1 years).

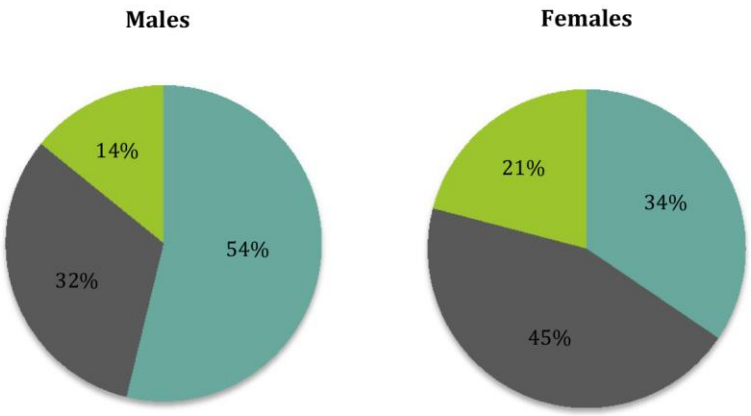


Figure 5.6 Proportion of AAA presentation among males and females

Males n=10,183, females n=4,517. Blue indicates AAA repairs, grey indicates those patients that did not undergo repair, and green indicates patients who ruptured their AAA prior to hospitalization

5.7.2.1 Methods of AAA repair

EVAR has gradually replaced OAR for the majority of patients requiring repair for an intact AAA. There was a marked rise in the use of EVAR in all age groups and this effect was most profound in those older than 75 years of age during the study period (Figure 5.7).

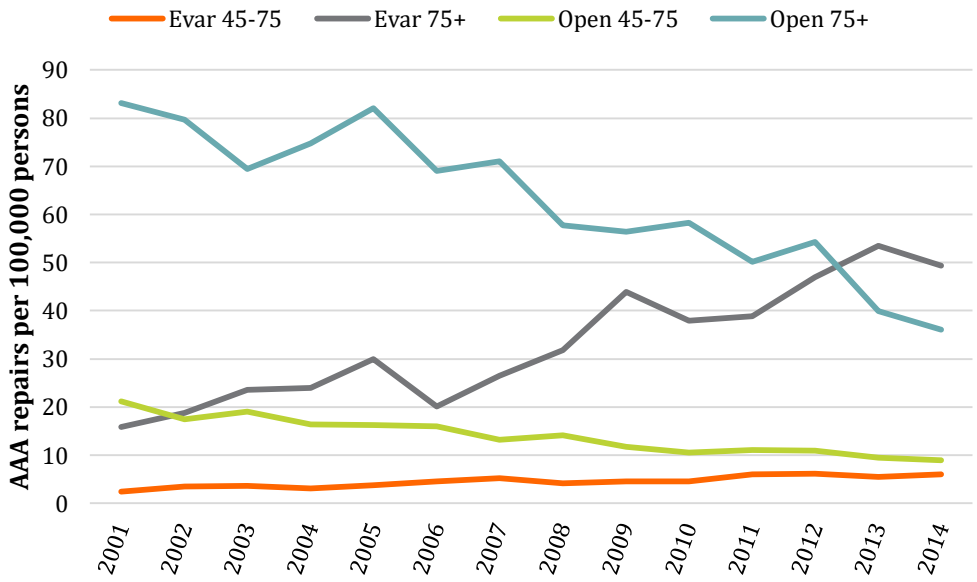


Figure 5.7 Trends of all AAA repairs dichotomized into type of repair and age groups

5.7.3 Trends of operative mortality

As shown in Figure 5.8, an approximately 50 percent decline in the 30-day mortality for patients undergoing intact AAA repair was observed over the last decade. This appeared to coincide with the rise of EVAR usage from 17% in 2001 to 55% in 2014.

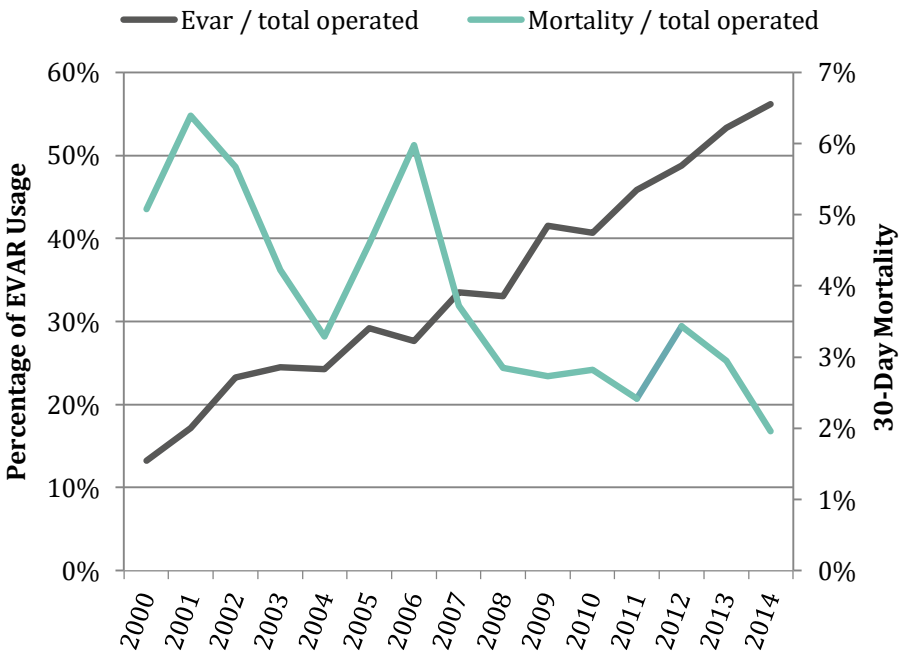


Figure 5.8 Dual-axis line graph representing intact AAA mortality and proportion of EVAR usage

5.7.4 Validation of AVA data

Since the datasets used have not been subjected to any formal validation previously, it was of importance to understand the reliability and accuracy of such databases. Of the 1713 patients included from AVA, there were 1608 (93.9%) patients found in the NMDS administrative dataset and this comprised the group used for validation.

There were some demographic data errors identified in the AVA. 39 patients (2.4%) had an incorrect date of birth (error of greater than +/-2 days) recorded and 14 patients (0.9%) had incorrect gender identification. Admission date and length of stay details (error of greater than +/-2 days) were incorrect in 33 (2.1%) and 113 (7.0%) patients respectively.

The NMDS, however, correctly identified 98.1% of the patients as receiving an EVAR and 94.2% as an elective (arranged) admission. Of the comorbidities crosschecked, there was major underreporting in the presence of IHD and hypertension in the NMDS compared to the AVA. The proportion of patients with a smoking history was similar between the two datasets but there was a 32.8% lack of concordance between them (OR 1.56 (95% CI: 1.34-1.83), P <0.001). The presence of diabetes was more consistently recorded in both databases as presented in Table 5.1.

Table 5.1 Validation of 1604 verified patients between the NMDS and the AVA

	NMDS (%)	AVA (%)	Discrepancy (%)	OR (95%CI)	P Value
Males	1278 (79.7)	1284 (80.0)	14 patients	0.98 (0.82-1.16)	0.79
Age, mean (SD)	74.3 (7.8)	74.2 (8.2)	39 patients†	-	0.72§
Date of Admission	-	-	33 patients‡	-	-
IHD	161 (10.0)	774 (48.3)	687 (42.9)	0.12 (0.10-0.14)	<0.001
Diabetes	198 (12.3)	187 (11.7)	148 (9.2)	1.07 (0.86-1.32)	0.55
Hypertension	563 (35.1)	1236 (77.1)	829 (51.7)	0.16 (0.14-0.19)	<0.001
Smoking history	1241 (77.4)	1100 (68.6)	514 (32.8)	1.56 (1.34-1.83)	<0.001
Admission type (elective/non-acute)	1117 (69.6)	1124 (70.1)	93 (5.8)	0.98 (0.84-1.14)	0.79
EVAR	745 (46.4)	737 (45.9)	30 (1.9)	1.02 (0.89-1.17)	0.77

OR: odds ratio, NMDS: National Minimum Data Set, AVA: Australasian Vascular Audit.

† (> +/-2 days), Range difference: (-5,330 – 31,047) days, ‡ (> +/-2 days), Range difference: (-173 – 590) days, § t-test, || Odds ratio of data recorded by NMDS compared with AVA data

5.7.5 AVA data

The NHI for each entry was entered manually into a free-text space. Thirteen patients had incomplete NHIs and a further 30 patients had an incorrect NHIs. Hence, the NHIs were grouped into their respective locations and surgeons from each unit were contacted and the correct data was requested. All the incorrect/missing NHIs were obtained from the treating hospitals and corrected for the analysis except for one patient whose correct NHI was

not obtainable and hence was excluded from any analysis (the patient was a 60-year-old man with a 5 cm AAA who had undergone an elective open repair at a private hospital).

There were two patients with negative survival times, and both were due to human errors in entering the fields (one was delayed entry and the subsequent date was added as the default date and the second was due to an operation finishing on the next day- the operation date was entered on the second day).

5.7.5.1 Overall AVA summary

Between 1st January 2010 and 31st December 2014, there were 1,804 aortic-aneurysm-related procedures recorded and after applying the exclusion criteria, 1,717 procedures on 1,713 patients were included. The median, minimum and maximum age was 75, 35 and 93 years old respectively. The population consisted of 1369 (79.9%) males and 344 (20.1%) females.

The overall proportion of patients undergoing OAR and EVAR was 938/1,713 (54.6%) and 775/1,713 (45.2%) respectively. Stratifying the population into the indication for AAA repair changed the proportion of OAR to 543/ 1,220 (44.5%) for elective, 135/207 (65.2%) for symptomatic and 260/286 (90.9%) for ruptured AAA.

The inpatient (in-hospital) mortality recorded for elective, symptomatic and rupture AAA repair was 1.8, 4.3 and 34.3% respectively. The corresponding values for 30-day mortality matched to the national death records were 2.0, 5.3 and 34.3% (Table 5.2) indicating that the majority of early deaths occurred while in hospital.

Table 5.2 Operative Mortality stratified into type of repair and presentation from the AVA and NMDS returns

	Elective	Symptomatic	Ruptured
OAR	19/543 (3.5)	10/135 (7.4)	92/257 (35.8)
EVAR	6/677 (0.9)	1/72 (1.4)	6/29 (20.7)
IP deaths from AVA (verified from NMDS)	21/1220 (1.7)	9/207 (4.3)	97/286 (33.9)
IP deaths recorded on AVA	20/1220 (1.6)	9/207 (4.3)	92/286 (32.2)
Total (AVA 30 day from NMDS)	25/1220 (2.0)	11/207 (5.3)	98/286 (34.3)
Total 30 days NMDS (n=2078)	42/1697 (2.5)	N/A	120/381 (31.5)

Percentages presented in parenthesis, deaths as defined by AVA (discharged from AVA), N/A: not available

IP: Inpatient, AVA: Australasian vascular audit, NMDS: National Minimum Data SetThere were 97 patients who underwent repair at a private hospital: 57 open AAA repair and 40 EVAR. There were no 30-day mortality in this group and the majority of indications were asymptomatic AAA (93 patients), and in 4 patients were due to pain.

5.7.5.2 Predictors of 30-day mortality

A predictive model for early mortality was built using the population of patients undergoing intact AAA repair. Both elective (asymptomatic) and acute (symptomatic but non-rupture) AAA were included for this analysis. These were combined for the following reasons: the ICD coding for procedures only codes non-rupture (intact) and rupture diagnoses; the 30-day mortality of the combined group was considered low; the addition of symptomatic AAA was not a predictor of 30-day mortality in the multivariate analysis; and combining the groups would increase the power of the model.

Table 5.3: Univariate analysis of perioperative factors associated with 30-day mortality after intact AAA repair

	Category	No. of Patients	30-day mortality n (%)	Odds Ratio (95% CI)	P value
Age	<75	676	18 (2.7)	Reference	0.749
	≥75	751	18 (2.4)	0.90 (0.46-1.74)	
Sex	Males	1143	24 (2.1)	Reference	0.045
	Females	284	12 (4.2)	2.06 (1.02-4.17)	
Hospital type	Public	1330	36 (2.7)	-	-
	Private	97	0		
Ethnicity †	NZ European	1251	29 (2.3)	Reference	
	NZ Māori	98	6 (6.1)	2.75 (1.11-6.79)	0.028
	Pacific	32	1	-	-
	Asian/other	21	0	-	-
NZiDep 2013 ‡	1-2	182	3 (1.6)	Reference	
	3-4	239	4 (1.7)	1.02 (0.22-4.60)	0.984
	5-6	343	8 (2.3)	1.42 (0.37-5.44)	0.604
	7-8	363	8 (2.2)	1.35 (0.35-5.13)	0.665
	9-10	293	12 (4.1)	2.55 (0.71-9.2)	0.152
IHD	Yes	702	24 (3.4)	Reference	0.038
	No	725	12 (1.7)	2.1 (1.04-4.23)	
Renal impairment	Yes	132	8 (6.1)	Reference	0.009
	No	1295	28 (2.2)	2.9 (1.30-6.54)	
Smoking history	None	445	15 (3.4)	Reference	
	Ex-smoker	793	17 (2.1)	0.63 (0.31-1.27)	0.195
	Current	189	4 (2.1)	0.62 (0.20-1.89)	0.401
Diabetes	Yes	173	3 (1.7)	Reference	0.48
	No	1254	33 (2.6)	0.65 (0.20-2.16)	
Hypertension	Yes	1131	32	Reference	0.156
	No	297	4	2.14 (0.75-6.09)	
ASA	1 & 2	540	8 (1.5)	Reference	0.056
	3 & 4	887	28 (3.6)	2.17 (0.98-4.79)	
AAA size	<6cm	722	11 (1.5)	Reference	0.018
	>6cm	705	25 (3.5)	2.38 (1.16-4.87)	
Repair Type	EVAR	749	7 (0.9)	Reference	<0.001
	OAR	678	29 (4.3)	4.73 (2.06-10.89)	
Indication	Elective	1220	25 (2)	Reference	0.008
	Symptomatic	207	11 (5.3)	2.68 (1.30-5.54)	

Number of patients n=1427. †25 missing ‡ 7 missing, - no analysis performed due to no or low events

Univariate analysis suggested a trend towards higher 30-day mortality in female patients, NZ Māori, patients with a history of IHD or renal impairment, patients who had an AAA diameter greater than 6cm, had undergone OAR or presented with a symptomatic aneurysm (Table 5.3). On multivariate analysis, only females, patients with renal impairment or IHD, larger AAA diameter and patients undergoing OAR remained significant predictors in the model (Table 5.4).

Table 5.4 Multivariate analysis of factors associated with 30-day mortality

	Odds ratio (95% CI)	P Value
Age (continuous, per year)	1.01 (0.96-1.06)	0.66
Female sex	2.12 (1.02-4.40)	0.040
Renal impairment	2.85 (1.24-6.57)	0.014
IHD	1.63 (1.08-4.52)	0.029
AAA diameter (per 1cm increase)	1.27 (1.011-1.59)	0.04
Open aneurysm repair	4.55 (1.92-10.74)	0.001

IHD: ischaemic heart disease

5.7.5.3 One year predictors of death

There were 103 (7.2%) deaths within one year from the date of surgery. The variables that showed a trend towards a higher one year mortality were: IHD, renal impairment, ASA grade $\geq$3, larger AAA size and symptomatic presentations. The association of gender, Māori ethnicity and type of repair with 30-day mortality did not remain significantly associated with one-year death rates (Table 5.5).

Table 5.5 Univariate analysis of perioperative factors associated with one-year mortality after intact AAA repair

	Category	Odds ratio (95% CI)	P value
Age (years)	<75	Reference	0.2
	≥75	1.3 (0.87-1.95)	
Sex	Males	Reference	0.250
	Females	1.32 (0.82-2.11)	
Hospital type	Public	Reference	0.04
	Private	0.13 (0.02-0.91)	
Ethnicity †	NZ European	Reference	-
	NZ Māori	1.71 (0.88-3.33)	0.112
	Pacific	1.40 (0.42-4.70)	0.583
	Other	0.69 (0.09-5.11)	0.706
NZiDep 2013 ‡	1-5	Reference	0.29
	6-10	1.26 (0.83-1.91)	
IHD	No	Reference	0.013
	Yes	1.69 (1.118-2.54)	
Renal impairment	Yes	Reference	0.001
	No	2.43 (1.42-4.14)	
Smoking history	None	Reference	-
	Ex-smoker	0.68 (0.44-1.04)	0.074
	Current	0.61 (0.31-1.21)	0.158
Diabetes	Yes	Reference	0.63
	No	0.852 (0.45-1.63)	
Hypertension	Yes	Reference	0.54
	No	1.17 (0.70-1.97)	
ASA	1 & 2	Reference	0.013
	3 & 4	1.78 (1.13-2.80)	
AAA diameter	<6cm	Reference	<0.005
	>6cm	1.83 (1.206-2.763)	
Repair type	OAR	Reference	0.822
	EVAR	0.96 (0.64-1.43)	
Indication	Elective	Reference	0.021
	Symptomatic	1.34 (1.05-1.71)	

Number of patients n=1427. †25 missing, ‡ 4 missing, ASA: American Society of Anaesthesiology

Predictors that remained significant in a multivariate model after adjusting for age and sex were: renal impairment, the presence of IHD and a large AAA diameter, as shown in Table 5.6.

Table 5.6: Multivariate predictors of one-year mortality

	Odds ratio (95% CI)	P Value
Age (continuous, per year)	1.02 (0.99-1.05)	0.16
Female sex	1.45 (0.88-2.34)	0.13
Renal impairment	2.28 (1.32-3.93)	0.003
IHD	1.64 (1.08-2.49)	0.021
AAA diameter (per 1cm increase)	1.26 (1.08-1.47)	0.004

Number of patients n=1427. IHD: ischaemic heart disease

5.7.5.4 Mid-term survival prognostic factors

After excluding 30-day postoperative deaths (36 patients), there were 224 (16.1%) deaths during the follow-up period. The median (range) follow-up was 35.3 (1.4-70.1) months in 1,392 patients.

Covariates that remained significant in the multivariate model and were associated with a lower overall mid-term survival included: age, the presence of renal impairment, ASA 3 or 4 and receiving an EVAR (Table 5.7).

Table 5.7 Univariate and multivariate risk factors asscoiated with mid-term survival aftr intact AAA repair

	Category	Hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Age	Continuous per year	1.05 (1.03-1.07)	0.001	1.04 (1.02-1.06)	0.001
Gender	Female	Reference	0.96	0.99 (0.71-1.39)	0.97
	Male	1.01 (0.72-1.41)			
Hospital type	Public	Reference	0.049	0.65 (0.35-1.20)	0.17
	Private	0.54 (0.30-1.00)			
Ethnicity	NZ European	Reference	-	-	-
	NZ Māori	1.28 (0.80-2.05)	0.306		
	Pacific	1.26 (0.52-3.07)	0.605		
	Other	1.00 (0.31-3.02)	0.953		
NZiDep 2013	1-2	Reference	0	-	-
	3-4	1.15 (0.68-1.96)	0.60		
	5-6	1.24 (0.76-2.04)	0.38		
	7-8	1.40 (0.87-2.26)	0.16		
	9-10	1.41 (0.86-2.30)	0.17		
IHD	No	Reference	0.024	1.08 (0.82-1.43)	0.58
	Yes	1.36 (1.04-1.76)			
Renal impairment	No	Reference	0.001	1.73 (1.22-1.5)	0.002
	Yes	2.05 (1.45-2.91)			
Smoking history	No	Reference	0.67	-	-
	Yes	1.07 (0.80-1.42)			
Diabetes	No	Reference	0.79	-	-
	Yes	1.06 (0.71-1.58)			
Hypertension	No	Reference	0.16	1.04 (0.73-1.48)	0.82
	Yes	1.27 (0.90-1.79)			
ASA	1 & 2	Reference	0.001	1.78 (1.30-2.45)	0.001
	3 & 4	2.1 (1.55-2.83)			
AAA diameter	Continuous per cm	1.04 (0.93-1.18)	0.48	-	-
Repair type	OAR	Reference	0.001	1.78 (1.25-2.20)	0.001
	EVAR	1.90 (1.44-2.51)			
Indication for repair	Elective	Reference	0.95	-	-
	Symptomatic	1.01 (0.84-1.21)			

HR: Hazard ratio

5.7.5.5 Outcomes from the NMDS

NMDS was filtered to report on the long-term outcomes of infrarenal AAA repair (those who had an AAA diagnosis and an AAA-related procedure). The demographic and clinical profile of the patients presenting with intact and rupture aneurysm is shown in Table 5.8.

There were 32,699 patient-years follow-up and the median survival for all-cause mortality after 30 days of surgery was 5.2 years. There were 2,521 (44.7%) deaths during this follow-up period. The 1, 5 and 10-year survival for those who survived 30 days was 94.9, 72.5 and 42.6% respectively.

The HRs for all included covariates are presented in Table 5.9. On univariate analysis, increasing patient age, female sex, higher hospital volumes, deprivation greater than or equal to 7, IHD, atrial fibrillation, PAD, respiratory and cerebrovascular disease showed a trend to decreasing survival. Asian people had in improved survival compared to NZ Europeans.

Multivariate analysis on Cox proportional hazard model showed that an increase in age, and a history of smoking, IHD, chronic respiratory disease and cerebrovascular disease were predictors of reduced survival. In addition, those undergoing EVAR and repairs performed in high-volume centres were also predictors of mortality. After adjustment for confounders and excluding in-hospital mortality, NZ Māori had a 48 percent higher all-cause mortality compared to all other ethnic groups (Figure 5.9). Living in areas of high social deprivation greater than or equal to 7 was also an independent predictor of worse survival when compared to living in deprivation deciles 1 or 2.

Table 5.8 Demographics of patients undergoing infrarenal AAA repair from the National Minimum Data Set between July 2000 and December 2014

	Category	Intact aneurysms (n=5071)	Ruptured aneurysm (n=1347)
Age	<75	2549 (50.3)	663 (49.2)
	≥75	2522 (49.7)	684 (50.8)
Sex	Females	4000 (78.9)	1058 (78.5)
	Males	1071 (21.1)	289 (21.5)
Hospital type	Private	135 (2.7)	-
	Public	4936 (97.3)	1347 (100)
Hospital volume	Low	1755 (34.6)	526 (39.0)
	High	3316 (65.4)	821 (61.0)
Ethnicity †	NZ European	4518 (91.5)	1136 (87.5)
	NZ Māori	306 (6.2)	114 (8.8)
	Pacific Island	65 (1.3)	30 (2.3)
	Asian/Other	49 (1.0)	18 (1.4)
NZiDep 2006 ‡	1-2	700 (13.9)	155 (11.6)
	3-4	838 (16.6)	224 (16.8)
	5-6	1132 (22.4)	282 (21.1)
	7-8	1331 (26.3)	352 (26.4)
	9-10	1053 (20.8)	321 (24.1)
IHD	No	1094 (78.4)	1039 (77.1)
	Yes	3977 (21.6)	308 (22.9)
Smoking history	No	1224 (24.1)	655 (48.6)
	Yes	3847 (75.9)	692 (51.4)
Hypertension	No	2840 (56.0)	688 (51.1)
	Yes	2231 (44.0)	659 (48.9)
Diabetes	No	4513 (89.0)	1217 (90.3)
	Yes	558 (11.0)	130 (9.7)
Atrial fibrillation	No	4195 (84.0)	1032 (76.6)
	Yes	800 (16.0)	316 (23.6)
Peripheral artery disease	No	4547 (87.9)	1231 (91.8)
	Yes	603 (12.1)	116 (8.2)
Chronic respiratory disease	No	4547 (91.0)	1182 (87.8)
	Yes	449 (9.0)	165 (12.2)
Cerebrovascular disease	No	4794 (96.0	1272 (94.4)
	Yes	202 (4.0)	75 (5.6)
Repair period	2000-2007	2537 (50.7)	782 (58.1)
	2008-2014	2498 (49.3)	391 (41.9)
Type of repair	EVAR	1780 (35.1)	58 (4.3)
	OAR	3291 (64.9)	1289 (95.7)

† 30 missing, ‡ 182 missing

Table 5.9 Factors of post 30-day all-cause mortality from NMDS following AAA repair

	Category	HR (95%CI)	P Value	HR (95%CI)†	P Value
Age	per year	1.06 (1.06-1.07)	0.001	1.07 (1.06-1.08)	0.001
Sex	Males	Reference	0.003	Reference	0.625
	Females	1.15 (1.05-1.26)		1.03 (0.93-1.13)	
Hospital volume	Low	Reference	0.002	Reference	0.009
	High	1.14 (1.05-1.24)		1.12 (1.03-1.22)	
Hospital type	Public	Reference	0.396	Reference	0.445
	Private	0.87 (0.62-1.21)		1.16 (0.79-1.70)	
Ethnicity	NZ European	Reference	-	Reference	-
	Māori	1.21 (1.03-1.41)	0.017	1.48 (1.25-1.74)	0.001
	Pacific	0.81 (0.56-1.16)	0.248	0.96 (0.66-1.14)	0.807
	Asian	0.75 (0.57-0.99)	0.044	0.87 (0.66-1.14)	0.311
NZiDep 2013	1-2	Reference	-	Reference	-
	3-4	0.99 (0.85-1.15)	0.889	0.98 (0.84-1.14)	0.788
	5-6	1.10 (0.96-1.26)	0.185	1.08 (0.94-1.25)	0.260
	7-8	1.23 (1.08-1.41)	0.002	1.22 (1.07-1.39)	0.004
	9-10	1.19 (1.04-1.37)	0.12	1.18 (1.03-1.36)	0.020
IHD	No	Reference	0.001	Reference	0.001
	Yes	1.32 (1.21-1.44)		1.22 (1.12-1.33)	
Smoking history	None	Reference	-	Reference	-
	Ex-smoker	0.99 (0.91-1.09)	0.858	1.05 (0.96-1.15)	0.297
	Current	0.96 (0.86-1.07)	0.418	1.33 (1.18-1.49)	0.001
Hypertension	No	Reference	0.104	Reference	0.983
	Yes	1.07 (0.98-1.15)		0.98 (0.91-1.07)	
Diabetes	No	Reference	0.142	Reference	0.140
	Yes	1.10 (0.97-1.25)		1.10 (0.97-1.25)	
Atrial fibrillation	No	Reference	0.001	Reference	0.001
	Yes	1.43 (1.30-1.58)		1.20 (1.09-1.33)	
Peripheral artery disease	No	Reference	0.006	Reference	0.313
	Yes	1.17 (1.05-1.32)		1.06 (0.95-1.19)	
Chronic respiratory disease	No	Reference	0.001	Reference	0.001
	Yes	1.66 (1.49-1.85)		1.61 (1.44-1.80)	
Cerebrovascular disease	No	Reference	0.001	Reference	0.001
	Yes	1.97 (1.68-2.30)		2.02 (1.72-2.38)	
Repair period	2000-2007	Reference	0.345	Reference	0.469
	2008-2014	0.95 (0.87-1.05)		0.96 (0.87-1.07)	
Type of repair	OAR	Reference	<0.001	Reference	<0.001
	EVAR	1.33 (1.21-1.45)		1.19 (1.08-1.31)	

N=5,368 excluding patients who died within 30 days and those with unknown ethnicity

† Adjusted (multivariate) analysis

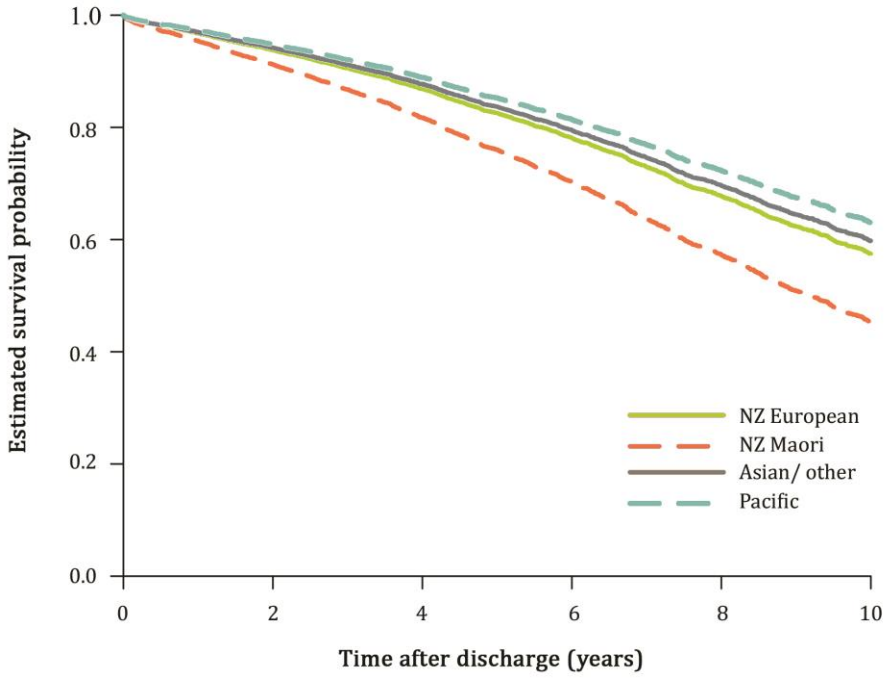


Figure 5.9 Difference in predicted survival post-discharge by ethnic groups

Lines represent predicted probability of survival for a 75- year old man, non-smoker with no comorbidities after hospital discharge from an elective open aneurysm repair

5.8 Discussion

In this chapter, the trends in AAA presentations, repairs and outcomes were presented using the best information available from NZ by interrogating both the national (administrative) and the vascular surgery (clinical) datasets. This enabled accurate and reliable calculation of short and long-term outcomes, description of AAA incidence and presentations during a 14.5-year period, and highlighting some sources of errors between these datasets.

The salient findings observed in this study were: first, the outcomes of intact AAA repair have improved during the last decade; second, the overall counts of AAA repairs have remained fairly steady but the age-standardized incidence has declined; third, the incidence of ruptured aneurysms and the proportion of patient's turndown for surgery has only decreased slightly. In describing these findings, the disparity of sex on aneurysm presentations and outcomes has also become more apparent.

5.8.1 NZ aortic aneurysm outcome data

Every year on average in New Zealand, approximately 220 people are recorded as dying of AAA, of which 75% are the result of a ruptured AAA without undergoing any form of repair, and the remaining are a consequence of undergoing AAA procedures predominantly for ruptured aneurysms. The proportion of patients dying with a ruptured aneurysm before reaching hospital (21.6%) appears 30 to 50% lower than what was previously reported (6, 256). This underreporting therefore might equate to an additional 15 to 20 deaths missed every year.

Data on aortic aneurysms from NZ has been limited to a few studies. Nair *et al.* used the NMDS to report on AAA outcomes in 2002-2006 (121). The 30-day mortality rate reported for intact AAA was 6.7%. This figure was higher than the 4.8% figure obtained in this study for the same study period. This difference might be attributed to the data-mining and cleaning process used to correctly identify those who had rupture or intact AAA code based on presentation type and operative coding. However, the operative mortality for ruptured aneurysms was very similar at around 35%. It also appears that operative mortality has decreased from 46% as reported by a study from Auckland in the mid-1990s (118).

Previous studies identified a higher 30-day mortality in NZ Māori compared to NZ Europeans (119, 121). In this study, this was only statistically significant in univariate analysis, with the difference diminishing after adjusting for possible confounders. Māori, however, had worse long-term overall survival compared to NZ Europeans. Moreover, Māori women had significantly higher AAA-related mortality compared to other women and these figures were comparable with NZ European males. This rate has not changed between 1996 and 2007 (11.7 per 100 000 and 9.2 per 100 000 population respectively) compared to all other groups (120). The reasons for this apparent disparity are unknown, but may well be because of the known high smoking rates of Māori women (257).

The high mortality associated with ruptured AAA and the unchanged ruptured AAA incidence underline the importance of detecting and managing aneurysms before they rupture.

5.8.2 Incidence of aortic aneurysm

Sandiford and colleagues reported that the incidence and mortality of AAA hospitalizations between 1995 and 2008 in NZ have declined (13). This study overlaps the data presented in this chapter. The AAA incidence during the overlapping years was very similar between both studies and the incidence of aneurysms appears to have plateaued from 2008 onwards.

In contrast to Sandiford's report, AAA presentations in this study were separated in order to provide some explanation for this decrease in age-standardized incidence. In doing so, one of the major contributors to this decline appeared to be those patients who had an AAA diagnosis but did not have a repair. Multiple methods to try to understand what this group consisted of were made and the reasons for this sharp decline from 2007 to 2009. A random sample of patients from Christchurch Hospital was taken and checked against the electronic medical charts. This revealed that the majority of those patients had small AAAs, and other minor reasons for the decline were: patients with AAA who had their repair in private hospitals, patients with threshold AAA who were turned down for elective repair and miscoding of the I71.4.

These data were then separated by district health boards (DHB), which showed that the number of AAA patients in some locations did not correspond to the expected volume of patients with AAA clinically managed by the population served. The coding team at Christchurch hospital was then contacted and the explanation was that, prior to this period, patients who had a diagnosis of AAA but presented to hospital with any other condition were coded as having an aneurysm, whereas after 2007, the Ministry of Health discouraged this practice and AAA was only coded if it was the principal reason for hospitalization.

5.8.3 Changes to AAA management and outcomes

The first EVAR for treating AAA in NZ was performed in 1997 at Waikato Hospital and since then it has complemented conventional OAR and has slowly replaced open surgery across the country. NZ remains conservative with the use of EVAR, which is similar to some European countries and parts of the UK but unlike the majority of Australia and the USA centres (62, 258). This can be partly explained by access to universal national healthcare and vascular surgeons offering both types of procedures.

The decline in 30-day mortality following intact AAA repair has been observed elsewhere and has been predominantly related to the rise in EVAR usage (65, 259), but advancement in medical and surgical care with specialization in vascular surgery and some centralization might have also contributed to the lower operative mortality.

Although the mortality from AAA has been shown to have declined in the last two decades in several countries (14, 15, 19), this has not been consistent in all regions of the world (17). Analysis from the Global Burden of Disease Study suggests that the mortality from AAA has actually increased by 45% from 1990 to 2010 (25).

In this study, when possible, aneurysm incidence and presentation was separated by sex to document differences. Although the overall incidence of AAA is decreasing in males, the incidence of AAA appears to decreasing a slower rate in females, with almost 30% of females presenting with ruptured aneurysms. More efforts to reduce this apparent disparity is required.

5.8.4 Predictors of 30-day mortality

There are well-documented predictors of 30-day mortality after AAA repair that have been incorporated into most predictive logistic models (246). The predictors of thirty-day mortality in this study (age, AAA diameter and renal impairment) were consistent with contemporary data from Australia and Europe (258).

The 30-day mortality after AAA repair has consistently been higher in females compared to males for both OAR and EVAR. A meta-analysis reported that the pooled OR for women after elective OAR and EVAR was 1.28 (95%CI: 1.09-1.49) and 2.41 (95%CI: 1.14-5.15) respectively (105). Interestingly, in the AAA SCORE model, gender was not shown to be a predictor in the model-validating process and hence was not included (248). In this study, despite the relatively small number of patients included, females had a higher operative mortality than men, OR 2.13 (95%CI: 1.03-4.54).

5.8.5 Long-term outcomes & prognostic factors

A meta-analysis that included published studies from the majority of continents reported that the 5-year survival after AAA repair was 69% (75). In the NZ data reported here, the observed actuarial 5-year survival was 72% and therefore consistent with others findings.

Some of the predictors of late survival were consistent with the factors reported in chapter 4, including age, IHD, current smoking, respiratory disease and cerebrovascular disease (Table 5.10). However, female sex and PAD were not predictors of mortality but they did show a weak association in univariate analysis. This might be due to the smaller number of patients included in this study compared to the meta-analysis and the method used for case definition. For example, the use of ICD coding to detect PAD has been shown to be an insensitive method to capture the prevalence of the disease in the general population (260).

Although hospital volume was not included in the data extraction in the previous chapter, it was noted that patients who had their AAA repaired in high-volume institutions had a lower overall survival. This may be due to referral of high-risk patients from small-volume hospitals and perhaps a tendency by smaller units to turn down higher-risk patients for procedures particularly ruptured AAA (261).

Table 5.10 Comparison between the impact of prognostic factors in this study and the meta-analysis from Chapter 4

	HR 95%CI	
	Current study	**Meta-analysis**
Age	1.06 (1.05-1.07)	1.05 (1.04-1.06)
Females	1.05 (0.95-1.15)	1.15 (1.07-1.27)
Smoking history	1.16 (1.06-1.27)	1.27 (1.07-1.51)
IHD	1.22 (1.11-1.34)	1.29 (1.18-1.48)
Respiratory disease	1.61 (1.44-1.80)	1.53 (1.37-1.70)
Diabetes	1.13 (1.00-1.29)	1.34 (1.20-1.49)
Hypertension	0.96 (0.87-1.04)	0.90 (0.79-1.03)
Cerebrovascular Disease	1.94 (1.66-2.27)	1.57 (1.40-1.77)
PAD	1.10 (0.98-1.24)	1.36 (1.18-1.58)

IHD: ischaemic heart disease, PAD: peripheral artery disease, HR: hazard ratio, CI: confidence interval

Social deprivation has been associated with worse outcomes and survival following cardiac surgery (262) but its impact on AAA is unknown. This relationship has not been well investigated in countries with universal health care. The generally worse outcomes observed with uninsured patients and ethnic minorities has been reported in the Unites States (263, 264) and does not appear to have changed during the last decade (213). In NZ and most European countries, national healthcare access is free. Despite this, we identified vulnerable groups that had higher mortality after AAA repair.

5.8.6 Data validation and accuracy

There were missing patients from each dataset, however the mortality rates were similar. Regulatory bodies are very likely to use the most accessible data rather than the "best" available data when policy decisions are made, therefore understanding the limitations of each dataset is important.

This type of validation study has been reported elsewhere in different geographical settings. Several similar studies linking administrative and clinical databases have been conducted in the UK and conflicting results have

been reported. Holt *et al*. compared 1102 elective AAA patients from the English Hospital Episode Statistics with clinical case records and 86% of the cases were confirmed as an elective AAA repair (265). Johal *et al.* reported that of patients undergoing AAA replacement, the diagnosis of AAA was consistent in greater than 90% (266). However, a study from Scotland highlighted that such discrepancies between clinical and national data can lead to significant under-reporting of mortality in national figures (267). In our study, the results were similar, but including both datasets allowed more accurate documentation of outcome data.

The mortality rates for AAA repairs from each dataset were very similar and the results compare favourably with reported contemporary international elective AAA repair figures (258). However, differences between the two datasets might be attributed to the unclassified diagnosis of "symptomatic" but non-ruptured AAA, which occurred in about 12% of AAA presentations. The majority of private AAA procedures performed were not found on the NMDS. Therefore, the total number of repairs performed in the private sector is unknown. Excluding private AAA repairs from national figures could also partially account for the 0.5% higher mortality reported in the NMDS.

5.8.7 Strengths and limitations

Each dataset has inherent strengths and weaknesses that are worth mentioning. Unlike most data from large population database or registries where data-pooling and analysis is automatically performed, in this study, there were multiple levels of data-cleaning and matching to ensure that any errors and biases were reduced. To date, this is the first study of this nature to report such data from NZ. The number of patients included is relatively large and the outcomes presented reflect current local AAA practice.

There are potential limitations that are inherent to administrative national datasets and the design of studies of this type. First, the deprivation index is not linked to individuals but to geographical neighbourhoods, hence cannot be directly related to unique patients. Second, there were several other

important predictors of long-term survival that could not be included because of lack of recording, such as medications (aspirin, statins), renal impairment and AAA diameter. Third, the influence of other lifestyle and behavioural factors such as physical exercise, psychological stress and diet are not well-reported in AAA literature. Furthermore, the mortality collection records that were used included only those deaths that occurred within New Zealand; any deaths occurring outside New Zealand would not be captured and this would likely have resulted in some degree of under-reporting.

For the period of July 2000 to Dec 2009, the previous national audit of vascular surgery (Otago Surgical Audit) could not be retrieved as the software was outdated. Therefore, data matching could not be performed for that phase and potentially some patients might have been missed. If the numbers of AAA performed in private were constant during the past 15 years, then an approximately 160 patients might have been missed.

5.9 Conclusions

This study highlights the contemporary incidence, presentation and outcomes of patients with AAA in NZ by using the best information available. There were major changes to AAA management during this period with important implications for early outcomes.

While the overall age-standardized incidence of AAA is slowly decreasing, the number of recorded ruptures occurring prior to hospitalization has not changed. The reduction of AAA mortality has been predominantly related to the increase in EVAR usage.

Along with the known predictors of overall survival, Māori ethnicity and patients living in high deprivation areas are associated with higher mortality after repair. Efforts should target this higher-risk group to improve outcomes and reduce disparity.

All AAA datasets used (clinical and administrative) were incomplete, but this analysis has allowed us to understand the differences and to combine the

databases, therefore providing the best estimates to date, ensuring a better representation of absolute national work load, enabling accurate survival status and increasing the utility of such datasets to reflect real world clinical outcomes.

5.10 Future Work

This data synthesis has highlighted several novel findings within the NZ population that are worthy of further exploratory work, in particular the disparity in outcomes among different ethnic groups and social deprivation. In addition, exploring the reasons for lower survival seen in patients who underwent repair in high-volume centres and understanding the referral pattern of patients among services is important for provincial vascular surgery service-planning. The contemporary short- and long-term outcome data and factors influencing survival can be used in predictive modelling and in any national policy-making surrounding AAA management.

Chapter 6: Development and Validation of a Predictive Model to Aid in Management of Intact AAA

6.1 Overview

Randomised controlled trials are the 'gold standard' to test the effects of different treatments on participants. As discussed earlier, some aspects of AAA management have been subjected to good-quality trials during the last three decades. However, applying such evidence to individual patient care can be complex, as several factors need to be taken into consideration. As mentioned in chapters 4 and 5, there are ample models that predict short-term preoperative mortality, but the literature lacks well-developed long-term decision models.

The main determinants of an individuals' life expectancy are baseline demographics and comorbidities. Patients with an untreated AAA have an additional factor of ongoing rupture risk. Predictive models require such inputs to inform the results of undergoing or not undergoing an AAA treatment.

In this chapter, the outcome and prognostic data synthesized from the previous chapters compounded by evidence established from the literature will be compiled and used to develop and validate a predictive model to aid personalized decision-making for AAA management.

6.2 Contribution

Data obtained in the past chapters come together to provide information to design a decision-aid predictive tool to assist in the management of AAA. Some of the parameters used in this model were obtained from chapters 4 and 5. Mr Giorgi Kvizhinadze helped develop the simulation software of the predictive model. I have tested and validated the model using several datasets that required data collection and cleaning.

6.3 Significance

Tools to assist clinical decision-making for patients with AAA are limited in the literature and have predominantly been developed to predict the short-term outcomes of aneurysm intervention. It has also been highlighted as a research area of need (246, 268, 269). The simulation model developed in this chapter shows very promising results with good predictability and discrimination. Further external validation from other datasets will be required to test the model's generalisability in different clinical settings. This work has not been presented at a conference, but the manuscript is being prepared for submission to a peer-reviewed journal.

6.4 Background

The ongoing risk of AAA-related death, uncertainty of aneurysm expansion and rupture, and the background mortality risk from other causes make AAA-management pathways ideal for predictive modelling.

The clinical decision-process usually involves consideration of both patient and AAA factors. The patients' clinical profile which determines their likelihood of survival with or without repair is usually predominantly determined by their demographic and clinical comorbidities. The aneurysm diameter is the most important determinant of rupture probability and therefore forms a crucial element in the probability matrix (1). Additional considerations include anatomical complexity characteristics of the aneurysm and the proposed procedure. A decision on the best management options usually involves a discussion between surgeons, the patient and their families and is most often based on gut feeling (268) and clinical experience rather than validated predictive tools designed to assist decision-making.

However, as described earlier, integrating all possible scenarios can be complex for each patient encountered in a clinical environment. There are four general modes of death for a patient with an aortic aneurysm: mortality post scheduled repair, aneurysm rupture prior to repair, death from a non-

AAA related (i.e. cardiac or oncological) cause and death as a consequence of long-term AAA-treatment-related complications, such as late graft rupture or graft infection. Therefore, weighing the risks and benefits of treatment in any individual can be a complex process.

Questions that require clinical decision-making include whether or not to offer AAA treatment based on an individual's life expectancy, which treatment modality to offer (open aneurysm repair vs. EVAR) and at what AAA diameter should a patient be offered treatment. For patients in the extreme profile ranges (very low risk or high risk) the clinical decision-making is usually straight forward with experience, but for those intermediate-risk patients, the decision is not always so (270). Although there are good evidence-based treatment strategies for some aspects of AAA care such as type of repair and size of AAA (51, 59), management of patients outside the studied population cannot always be generalised to those in extreme age groups or those with no or extensive co-morbidities.

Tools to inform clinicians of the predicted outcomes to aid in decision-making are becoming increasingly important as a part of individualizing patient care. However, unlike cardiac surgery where predictive scores such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) has been widely and routinely used clinically (271), prediction tools for AAA repair have not been commonly adopted in clinical vascular surgery practice (252).

Possible reasons that surgeons or interventionists might be reluctant to use such predictive models for decision-making surrounding AAA management include: a decline in perioperative aneurysm mortality in the recent era, particularly with the use of EVAR (65); the advancement of this technology (EVAR) which enabled procedures to be performed with percutaneous femoral access (272), as a day case and often a under local anaesthetic (273, 274), indicating that morbidity is also reduced; and furthermore, there might be financial rewards in some countries with over-treating patients with smaller AAA particularly using EVAR (275). These compounded factors

have made inpatient or 30-day mortality an uncommon event, thus limiting the requirement of early predictive models.

Patients with an AAA have a lower expected survival compared to an age-sex matched population (276). In addition, contemporary data suggests that the 5-year overall survival after an aneurysm repair is 70% (75). A model that can predict this long-term survival might therefore be a more beneficial tool for clinicians and patients particularly when considering management of elderly patients with relatively small aneurysms, as prevalence data included in Chapter 2 shows that this is potentially a very large group.

6.4.1 Model definition and reasons for its use

Models can be defined as mathematical tools that allow complex systems to be simplified to represent essential components of reality (277, 278). In this chapter, such models are used to predict health outcomes and therefore are considered as prognostic research models (279). This method of research involves reporting the relationship between baseline health profiles and future end outcomes, such as the comorbidities of a patient undergoing AAA repair at baseline and the outcome of interest of either morbidity or death over a specified time. On the other hand, simulation refers to the process of imitating an actual system by an interactive representation in a model format (278). These terms are often used interchangeably and therefore it is worth defining them in the context they are used in.

The use of decision-making models has increasingly become an important component of clinical research. The number of decision-analysis publications in the literature has exponentially risen during 2004 to 2014 (280). They are particularly useful in situations of uncertainty and high complexity especially when randomized controlled trial data are lacking and it is important to individualize care.

In healthcare, there are many unknowns with regards to predicting clinical outcomes, and direct experimentation is not always possible. Clinical trials can be very costly and often require a long time to complete (281). Moreover, implications of economic analyses and cost effectiveness in an era of ongoing

financial constraints can be simulated to assist decision-makers and stakeholders. In response to growing knowledge of diseases, national or societal guidelines and protocols have been developed to assist in clinical decision-making. However, such documents are not always individualised to unique patients and therefore generalizability cannot be applied to all. In such instances health models and simulations might be a more appropriate strategy.

Another advantage in using models is that the selection or personal bias in choices can be reduced and better streamlined. Rather than being based on gut feeling or instincts formed by clinical experience (282), properly designed analytical models can consider all clinically relevant inputs prior to contemplating a treatment decision.

However, health models also have limitations. These are confronted when uncertainties are encountered and assumptions have to be made since creating reality is impossible (283). Another limitation of models is that they can be complex and require reasonable understanding to interpret the behaviour and the background structure, which requires transparent model-development-process reporting from developers. Guidelines for good practices have been proposed to help uniform model development and standardize reporting, (284).

6.4.2 Types of models & simulations

There are several methods of modelling that are commonly used in healthcare (278), whose application may vary depending on the intended use of the model. There are generally two types of patient-modelling approaches used: population-based models (also referred to as cohort modelling) and models of individuals within a population (also known as patient-level simulation or individual-simulation) (285).

The most common use for modelling is to compare different strategies of care in terms of health economics and cost-effectiveness analysis. The common types of predictive and prognostic models used in healthcare are briefly discussed below.

6.4.2.1 Survival calculators

Prognostic calculators that are sometimes represented as nomograms are a well-established form of prediction-models used commonly in oncological conditions (286) to estimate survival. They provide a simple graphical probability of clinical events based on a formula (287). They can lack the complexity of the models where interaction and changing background mortality can occur.

6.4.2.2 Decision trees

These represent the simplest model design and remain the basic framework for the majority of decision analyses and thus the most widely used (278). The structure involves branches that are mutually exclusive with associated probabilities. The limitations of this approach are the inability of events to interact and that the analyses are based on fixed time-frames (288), therefore any changes that occur in the system or in time would require a separate run of the model.

6.4.2.3 Discrete event simulation

Discrete event simulation (DES) was described in the 1950s in the operational field (289) and is now used in a wide range of industries. This modelling approach focuses on the individuals' defined characteristics, their associated events over time and the consequences of those events at a patient-level. This micro simulation and flexibility of DES allows the model to take into account the patients' clinical profiles and therefore take heterogeneity into consideration. The process randomly samples time-to-event distributions making it ideal for time-to-event analysis. Another important feature of DES is that it allows individuals to queue for events and involves competition for resources (288). The strength of DES is that it is a very flexible model and allows interaction within the system (278).

6.4.2.4 Markov models

Markov models were first introduced by a Russian mathematician in 1906 (290) and are probability-based models that allow transitions between

states to occur during a defined time period (time-horizon). These transitions occur at random, follow a stochastic process and are independent of other transitions (291). The number of patients remaining in each cycle is determined by probability transitions. Historically, Markov models are the most commonly used models in economic analyses (292). They are useful to simulate ongoing risks in a particular situation.

6.4.3 Comparison of model types

With widespread development and use of decision-analysis tools, selecting the most appropriate approach is a vital initial step. The choice between a cohort-simulation and an individual-simulation approach is the first step. When simulating a certain target patient-group, individuals do not usually have the same proportion of comorbidities. A cohort-simulation approach such as a Markov model assumes that the proportion of comorbidities is averaged in the population, whereas a patient-level simulation takes into account each individual's risk profile (285). In reality, an individual with more comorbidity is more likely to reach the end outcome than someone without comorbidity.

The academic community has been more familiar and has had more experience with the Markov family of approaches and therefore they were more commonly used (285). Emerging evidence, however, suggests that DES models might be a more useful approach in areas where Markov models have shortcomings. DES allows patients to interact and compete, the timing of each event can be an independent rather than a "fixed" length cycle like Markov models, and each interaction can create a change in the model state (293).

In DES, the explicit element is the patient rather than the "state" or outcome as seen in Markov models (294). Another limitation of Markov models when compared to DES is that it has fixed equal states and it fits all the cohort in a series of states. This might lead to inaccuracies if some patients in the cohort have not completed the state (285).

DES has consistently been shown in cost effectiveness and clinical outcomes studies to be superior to Markov modeming in predicting long-term survival (288, 295). Furthermore, a comparative analysis of Markov and DES models which included 22 studies concluded that when the patient's history is an important prognostic factor, a DES model is the preferred approach (290).

Therefore, the DES was chosen over a Markov model because the time-to-event can occur at random rather than in a fixed cycle as in Markov models, and the concept of competing risks for events is critical in AAA clinical management (296).

6.4.4 Existing models in predicting long-term AAA survival

The use of models and simulations in the AAA literature has often been reserved for economic analyses to determine cost effectiveness of AAA screening and costs associated with type of treatments (68, 98). While there are several perioperative scores to predict outcomes of AAA repair in the elective and the emergency setting, there is very limited data on models that can predict longer-term mortality and therefore might be more relevant to patients and physicians (268).

The first reported model to predict long-term outcomes used the Glasgow Aneurysm Score (GAS) in two different datasets to predict long-term survival following AAA repair. The GAS score is calculated using the following formula: age +7 points for myocardial infarction +10 points for cerebrovascular disease +14 points for renal disease (297). Using the EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair (EUROSTAR) registry, the GAS was able to distinguish the long-term survival of patients undergoing EVAR when stratified into GAS tertiles (298). Following this, the DREAM investigators used the GAS on their trial cohort for further validation, and the plotted receiver-operated-characteristic (ROC) curve for OAR and EVAR was 0.74 and 0.78 respectively, indicating reasonable reliability at predicting 2-year survival (299).

Mastracci *et al.* developed a nomogram to predict 2, 4 and 8-year survival after EVAR using predictors of survival for 412 patients (230). This model

was internally and externally validated using normal and high-risk cohorts and the c-statistic was 0.68 (95% CI: 0.65-0.71), demonstrating a fair predictability. However, there have been no further attempts at using this predictive tool or further validation.

Stuart and colleagues developed a DES to aid decision-making in aneurysm repair (269) using parameters from the British Aneurysm Repair (BAR) score to predict in-hospital mortality (251) and RESCAN data to estimate AAA growth and rupture rates (32, 300). The outputs of the model include survival probabilities and life expectancy. However, this model has not been tested or validated to date and was developed on a complex statistical software package, therefore its use has not been translated into the clinical environment.

Carlisle developed a survival-predicting calculator that estimates trajectories of survival with and without aneurysm repair taking into account the patient's clinical profile and cardiopulmonary exercise (CPX) testing variables (301). The concept of this model was well-documented and has been validated externally on 1096 patients (302). The calculator is also simple to use and is available freely online. The limitations of such a model, however, are the complexity of variables required, such as CPX and anthropometric measurements. In addition, the growth and rupture risk of AAA were based on linear calculations from the RESCAN data which were not adjusted to gender differences.

As the experience with EVAR increased, certain arterial anatomical features have been attributed to early failure and endoleak development (303-305). An interactive decision tool was developed by Barnes and colleagues to predict the short- and long-term outcomes after EVAR (306). This model uses patients' age, sex, American Society of Anaesthesiologists (ASA) grade, AAA diameter and creatinine, along with three additional aortic morphology features- aortic angle, neck diameter and neck length, and 17 possible outputs are generated. This model has been validated by a centre in the UK (307) and another centre in Queensland, Australia (308) and was shown to be a good predictor of early mortality and endoleak complications. However,

when the model was tested in a clinical setting in the Netherlands, it did not appear to be adequately accurate (309). In addition, the fact that this model only addresses a proportion of patients that undergo aneurysm repair (EVAR) limits its use in the wider clinical setting.

The general limitations of all the above-mentioned prognostic models are the lack of robust validation against other datasets and that prognostic variables have been developed from specific patient populations (most models included EVAR patients only), and therefore their utilisation in the clinical setting has been restricted.

6.5 Objectives

The primary objective of this chapter was to develop an interactive model that can assist in clinical decision-making of AAA management for individual patients and externally validate it against existing databases of patients with small AAA and those who have had an aneurysm repair.

6.6 Methods

The clinical management and natural history of AAA were mapped at an individual patient level by two persons (MK and JR), then the probability estimates at each level were obtained from national and international data.

6.6.1 Input variables

A comprehensive search for the best available information from the literature revealed that the RESCAN data provided the largest and most accurate contemporary estimates of AAA growth and rupture (Table 6.1 and Table 6.2) and hence they were used to represent the natural history of AAA (32, 300).

Table 6.1 Annual growth rates of AAA per mm per year according to diameter

	Mean expansion rate (mm per year)	
AAA diameter (cm)	**Males**	**Female**
3	1.28	1.46
3.5	1.86	1.98
4	2.44	2.51
4.5	3.02	3.06
5	3.61	3.62
5.5	4.21	4.22
6	4.81	4.82

Table 6.2 AAA annual probability of rupture risk according to diameter and gender

AAA diameter (cm)	Males (%)	Females (%)
3	0.05	0.22
3.5	0.09	0.45
4	0.17	0.79
4.5	0.32	1.47
5	0.64	2.97
5.5	1.28	5.94
6	2.56	11.88
6.5	5.12	23.76
7	20	40
8	50	50

Table 6.1 and Table 6.2 were both adapted from Stuart *et al.* Calculating when elective abdominal aortic aneurysm repair improves survival for individual patients (209)

Data on >5cm AAA is extrapolated

6.6.1.1 Selection of comorbidities

The reported hazard ratio (HR) obtained in chapters 4 and 5 was used to predict additional (excess) mortality after AAA repair. The process of selecting comorbidities for model inclusion is highlighted below.

Age as a continuous variable (per year), gender and ethnicity (NZ Māori or non-NZ Māori) were used to adjust for background mortality in the general population which was derived from the NZ life tables, 2010-2012 (127). The natural history of AAA requires an aneurysm diameter to be included in order to predict future growth rates and rupture risk as it is an important prognostic factor and an independent predictor of survival in the long term (310).

The remaining comorbidities were selected if the HR had a significant impact on survival (harmful or protective), large number of participants contributed to the meta-analysis (more than 5,000 participants) or was present in a large proportion of the AAA repair cohort. The following comorbidities were included: ischaemic heart disease (IHD), myocardial infarction (MI), cardiac failure, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, diabetes and a history of smoking. Renal disease was kept categorical and defined as a creatinine plasma concentration greater than 150mmol/L. The uses of statin and antiplatelet therapy were the only protective factors and were also included in the model. Although relatively uncommon comorbidities, COPD on supplementary oxygen and end stage renal disease (ESRD) were included as their impact on mortality was associated with a HR greater than three. A summary of the variables included is shown in

Table 6.3.

Hypertension, Peripheral artery disease (PAD), the use of beta-blockers or anticoagulation, coronary revascularisation, cancer history, ASA grade, body mass index (BMI) and haemoglobin concentration were all excluded from the model due to having no or small hazard effects, small numbers of

participants contributing to the meta-analysis, or a large unexplained inconsistency (effect heterogeneity) making the results difficult to interpret.

Table 6.3 Summary of hazard ratios and estimated proportion of variables included in the model development

Factor	Number of patients	Number of studies	HR (95%CI)	Proportion (%) range
Demographic:				
Age (continuous)/year	31,100	21	1.05 (1.04-1.06)	72-76 years †
Gender (females, males as a reference)	49,653	16	1.15 (1.07-1.27)	22
NZ Māori	420	1	1.43 (1.21-1.69)	6.5
Comorbidity:				
IHD	31,441	18	1.29 (1.18-1.48)	50 (40-60)
MI	5,433	7	1.52 (1.32-1.73)	25-30
Cardiac failure	35,525	14	1.91 (1.58-2.30)	5
COPD	43,953	18	1.53 (1.37-1.70)	37.8
COPD on O_2 supplement	4,142	3	3.05 (1.93-4.80)	3.7
Creatinine (>150-200µmol/L)	26,974	16	1.54 (1.43-1.67)	16
Dialysis or ESRD	4,744	5	3.15 (2.45-4.04)	1
Cerebrovascular disease	7,726	9	1.57 (1.40-1.77)	7
Diabetes	44,211	14	1.34 (1.20-1.49)	13.8 (11-15)
AAA diameter (per cm)	19,722	16	1.14 (1.10-1.18)	51-64mm †
Statin use	38,252	11	0.75 (0.70-0.80)	46-70
Antiplatelet use	8,447	4	0.81 (0.73-0.89)	60
History of smoking (any)	12,663	7	1.27 (1.07-1.51)	77 (75-80)

† Median (range)

IHD: ischaemic heart disease, MI: myocardial infarction, COPD: chronic obstructive pulmonary disease, O_2: oxygen, ESRD: end stage renal disease, AAA: abdominal aortic aneurysm, HR: hazard ratio, CI: confidence intervals

6.6.1.2 Predicted survival

Patient survival post-AAA is well documented in the literature with an approximately 30% probability of dying within 5 years. Survival post ruptured AAA is different to survival post intact repair in the initial 30-day period, but when the early period is excluded, they are very similar. The average contemporary elective mortality of intact AAA was assumed to be

4%. The preoperative (pre-hospitalization & hospital non-operated) rupture mortality was 60% and the operative mortality risk for a ruptured AAA was 35%. The actual survival curves for rupture and intact repair are shown in Figure 6.1.

6.6.2 Model structure & development

An individual with an AAA diameter range of 3 to 10 cm is entered into the simulation model and three management options are considered: immediate elective repair, surveillance or conservative management. The first decision is made when setting an aneurysm threshold for AAA treatment (usually 5.5cm for males and 5cm for females), but the threshold for intervention can be altered depending on age, sex, and patient or surgeon preferences. If the aneurysm diameter is larger than the threshold then a surveillance survival is not calculated.

The surveillance survival is based on AAA expansion until threshold is reached, then the patient undergoes elective aneurysm repair. The conservative management arm is based on the aneurysm rupture risk depending on the selected baseline AAA diameter and no elective repair is permitted. For those with an AAA diameter less than the operative threshold, three survival probabilities are calculated: elective repair, AAA surveillance and conservative management (no repair or surveillance). If the AAA size is greater than the threshold set, then the surveillance survival probability is not calculated. The overview of the DES model structure is shown in Figure 6.2.

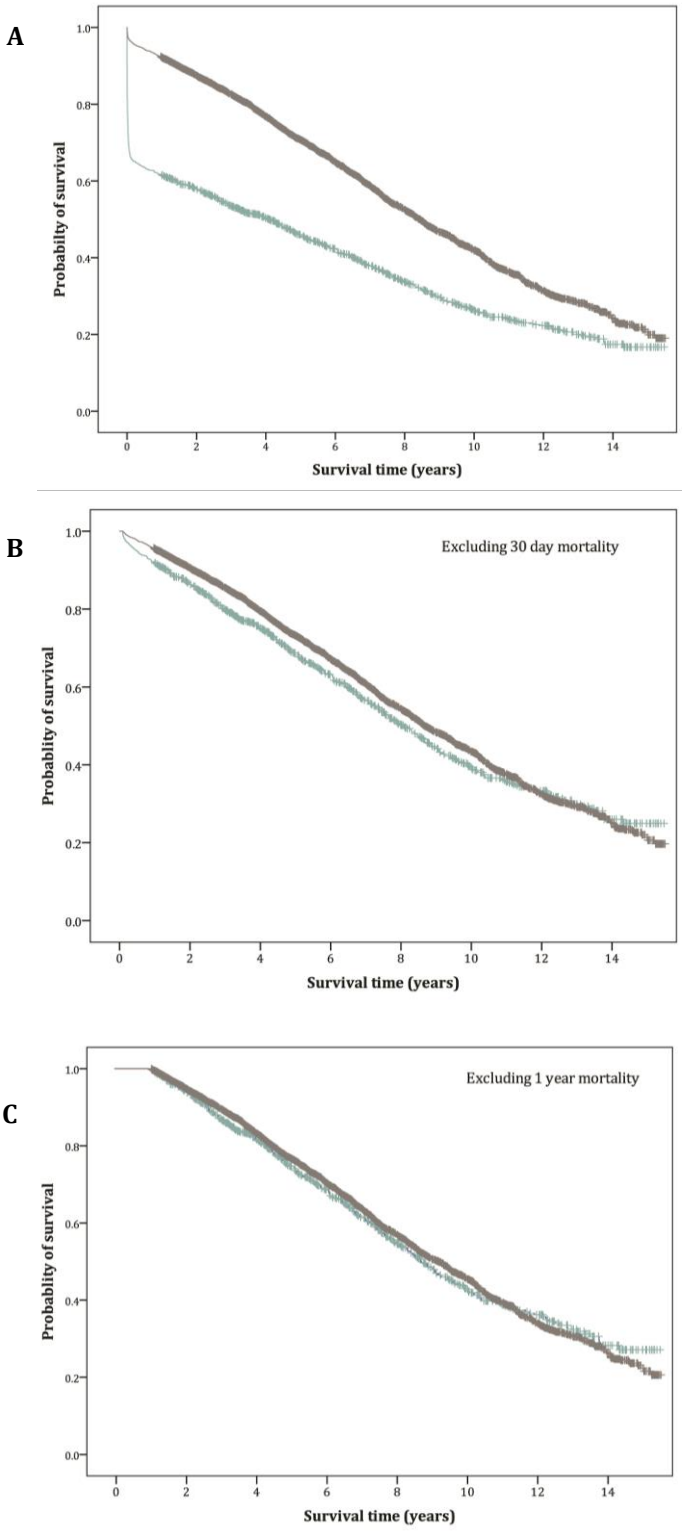


Figure 6.1 Kaplan-Meier survival of patients undergoing AAA repair from the National Minimum Data Set

A: All-cause mortality, B: Excluding 30-day mortality, C: Excluding 1 year mortality

Grey line is intact AAA and blue indicates rupture AAA. The numbers of intact and ruptured patients being: A: 5071 & 1347, B: 4898 & 902 and: C 4675 & 830, respectively

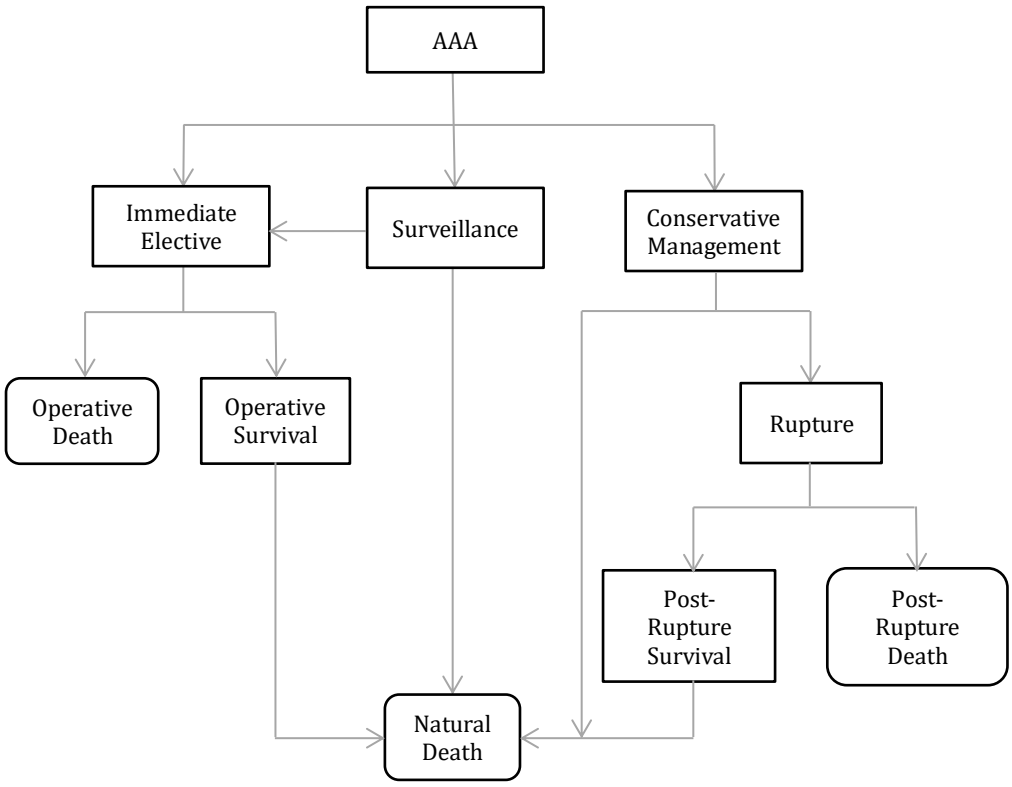


Figure 6.2 Model diagram used to produce the simulation of AAA management

6.6.2.1 Assumptions

Some assumptions had to be made to allow the model to behave as close to contemporary natural AAA history as possible and to reflect current clinical practice.

1) Once an AAA is detected and planned for scheduled repair, no preoperative rupture occurred.

2) If aneurysm surveillance is chosen, no aneurysm acute or rupture presentations occurred.

3) Conservative treatment assumes that the AAA can rupture based on estimated annual rupture risks and no elective surgery occurs.

4) There was no late overall survival difference following EVAR and OAR, in contrast to 30-day mortality where an odds ratio of 0.2 for EVAR compared to OAR was chosen.

5) The impact of patient risk-factors was the same on 30-day and long-term mortality.

6) The risk of late AAA-related mortality (re-rupture or graft-related complications) was in fact very small and hence was included in the overall background mortality.

7) Baseline comorbidities did not change over time.

8) There were some limits to the continuous variables: age 35 to 90 years old and AAA size 3 to 10cm.

6.6.2.2 Model behaviour

A DES was built to simulate the natural history of AAA where time to death from all causes competes with time to death from aneurysm rupture and post-operative mortality. Time to death from all causes was drawn from an all-cause cumulative mortality distribution function. Time to aneurysm rupture was modelled based on AAA growth and the annual probability of rupture, whereas time to post-operative mortality was drawn from the patient's specific profile cumulative mortality distribution function.

The model interface and platform was built on Microsoft Excel and is shown in Figure 6.3. For each patient, the life events were iterated 2,000 times using their baseline demographics, AAA diameter and comorbidities. The simulation for each patient entry takes 15-25 seconds to complete the calculation using a standard personal computer.

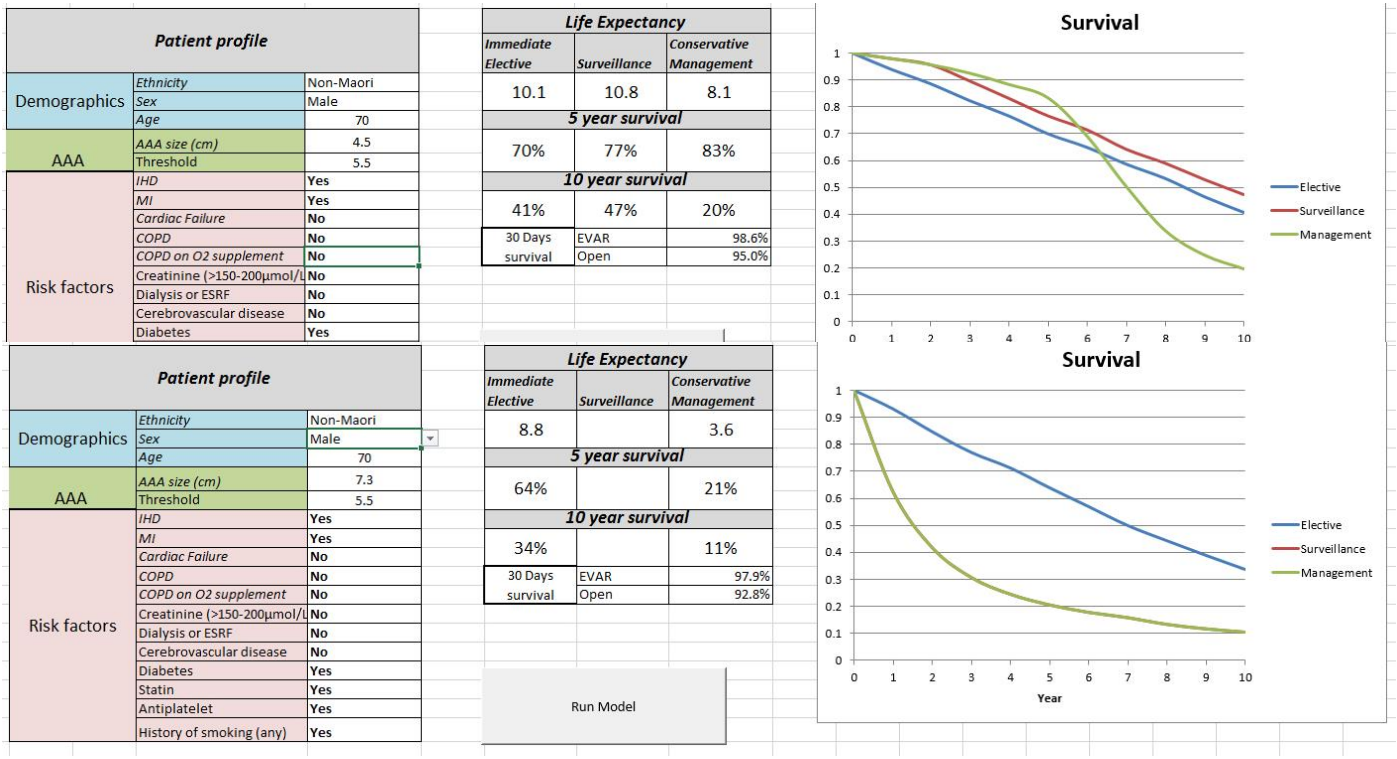


Figure 6.3 Discrete Event Simulation model interface showing the inputs and outputs for a hypothetical 70-year-old man

Top with a 4.5cm AAA and the patient's comorbidities include: IHD, MI, diabetes and history of smoking. He is taking antiplatelet and statin therapy. Bottom with a 7.3cm AAA and the patient's comorbidities include: IHD, MI, diabetes and history of smoking. He is taking antiplatelet and statin therapy. The x-axis is time in years and the y-axis is the probability of survival.

6.6.2.3 Model performance

Reports from the International Society for Pharmaeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) guided the reporting and validation (311) of the model development. The predictive performance of the model was tested and externally validated using a systematic approach proposed by Steyerberg and Vergouwe (312).

Calibration refers to the agreement between the observed (actual) endpoints and the model's prediction. It is presented as a calibration plot where the intercept alpha (A) relates to the calibration-in-the-large (ideally being 0) and the calibration slope beta (B) being 1. The line should be close to 45 degrees. Discrimination refers to the ability of the model to distinguish a patient who has reached the binary endpoint (dead) to a patient who has not (alive). This is usually quantified with the concordance (c) statistic, and for a binary outcome, c is identical to the area under the receiver operating characteristic (ROC) curve. A value of 0.5 suggests no discrimination, 0.5 to 0.69 indicates poor discrimination, 0.7 to 0.8 considered acceptable discrimination and a value of 1 indicates perfect discrimination (313). ROC values greater than 0.85 are uncommon in the AAA model literature (246, 252, 268).

6.7 Results

The DES model produced three outputs for each patient: 30-day mortality for EVAR and open, probability of survival between 0 and 10 years and predicted life expectancy for the elective, surveillance or conservative management treatment options. The model predicted a range of survival probabilities that increased during the follow-up period as shown in Figure 6.4.

The predicted 1-year and 5-year survival probability for the validation dataset (n=270) ranged from 77.5 to 95.7% and 6.5% to 87.3% respectively, indicating that the model had a wide range of probability and enabled stratifying patients into different risk groups.

Model predictions for less than 5 years will not be discussed further as the event rates were too low to provide any clinically or statistically meaningful information. Therefore, five-year survival will be used as a surrogate for long-term survival and will be the output of interest for the remainder of this chapter.

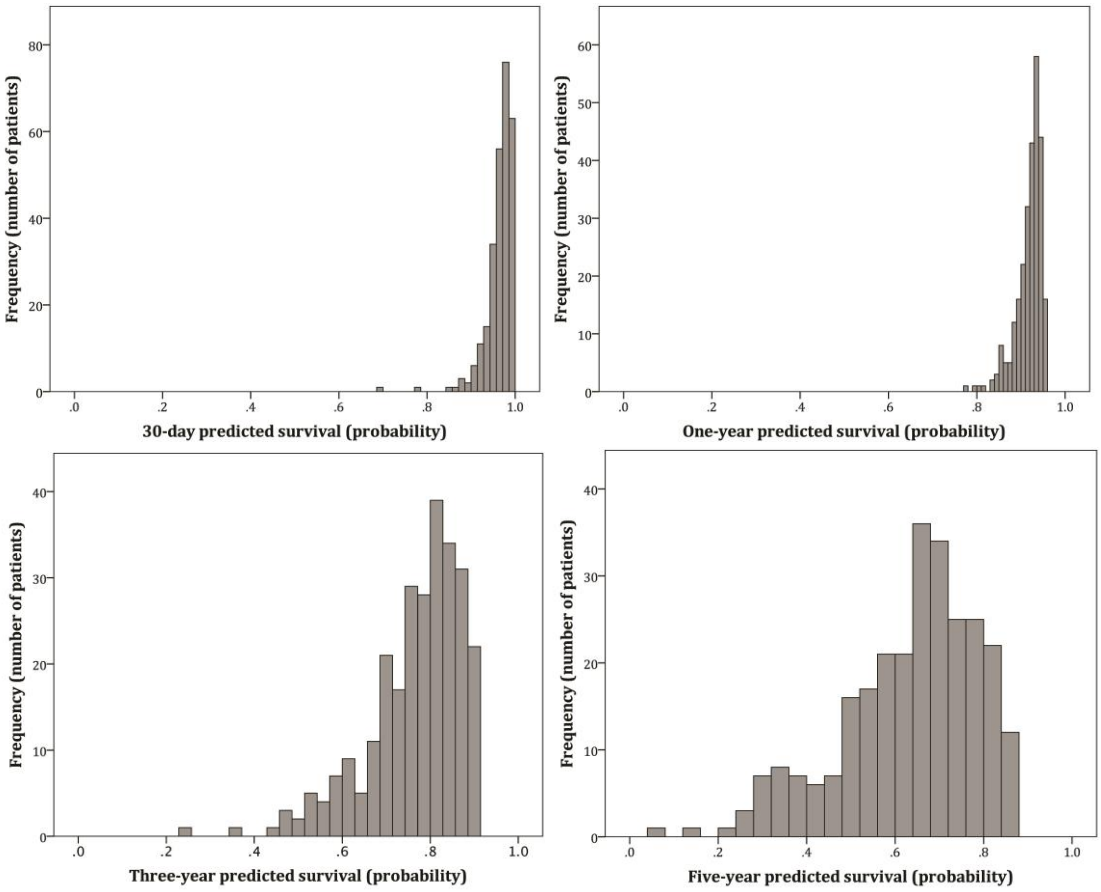


Figure 6.4 Range of predicted 30-day, 1, 3 and 5-year survival probability of 270 patients used for external validation

Note: same x-axis scale used

6.7.1 External validation

To test the model's performance several independent datasets discussed below were used.

6.7.1.1 Dataset 1: AAA performed in 2010

Consecutive patients who underwent an intact AAA repair during 2010 identified from the Australasian Vascular Audit and the National Minimum Data Set were extracted and risk profiles were collected. Those patients with a small AAA (<5cm) and those lost to follow-up were excluded. A total of 270 patients were included and there were 80 (70.4%) deaths in this cohort at 5 years follow-up. The average age was 74.9 years old, 210 (77.8%) were males and the remaining demographics are shown in Table 6.4.

Table 6.4 Demographics of consecutive patients who underwent intact AAA

Age/ years, average (SD)	74.9 (7.0)
> 80 years old, n (%)	77 (28.5)
Males, n (%)	210 (77.8)
NZ Māori, n (%)	22 (8.1)
AAA diameter/cm, median (IQR)	6.2 (5.3 - 6.5)
OAR, n (%)	146 (54.1)
IHD, n (%)	129 (47.8)
MI, n (%)	24 (8.9)
Cardiac failure, n (%)	14 (5.2)
COPD, n (%)	20 (7.4)
Renal impairment, n (%)	29 (10.7)
ESRD, n (%)	2 (0.7)
Diabetes, n (%)	28 (10.4)
Cerebrovascular disease, n (%)	7 (2.6)
Statin use, n (%)	176 (63.0)
Aspirin use, n (%)	200 (76.7)
Smoking history, n (%)	187 (69.3)

Number of patients =270. Values in parenthesis are percentages of binary variables unless otherwise stated. SD: standard deviation, IQR: interquartile range

The calibration intercept (A) was -0.36 (95%CI: -0.63 to -0.08) and the slope (B) was 1.17 (95%CI: 0.74-1.59) indicating that the model over-predicted mortality (Figure 6.5). The confidence intervals of A did not overlap 0, indicating that the model consistently predicted a worse outcome than actually observed. The confidence intervals for B included 1, suggesting that

there was no evidence that the model was better or worse at predicting an outcome for someone with a short versus long life expectancy. The model appears to under-predict survival in all risk groups (Table 6.5). The discrimination was acceptable with a c-statistic of 0.71 (95%CI: 0.64-0.78) (Figure 6.6).

Table 6.5 Observed and predicted survival for 270 patients who underwent intact AAA repair in 2010

Quintile (n=54/quintile)	Observed deaths (n)	Predicted Survival (%)	Observed Survival (%)	Observed: Expected
1st	31	38.94	42.49	1.09
2nd	18	56.93	66.67	1.17
3rd	13	66.17	75.92	1.15
4th	11	72.74	79.62	1.09
5th	7	81.39	87.03	1.07

1st represents lowest survival, 5th represents highest survival

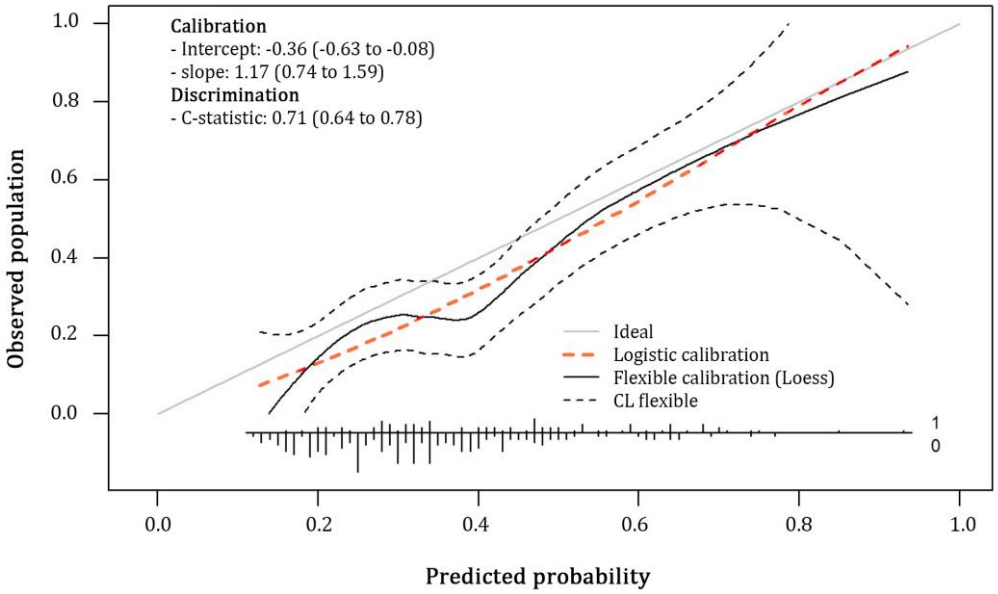


Figure 6.5 Probability of 5-year mortality represented as a calibration plot in a logistic regression model

0 indicates alive, 1 indicates dead

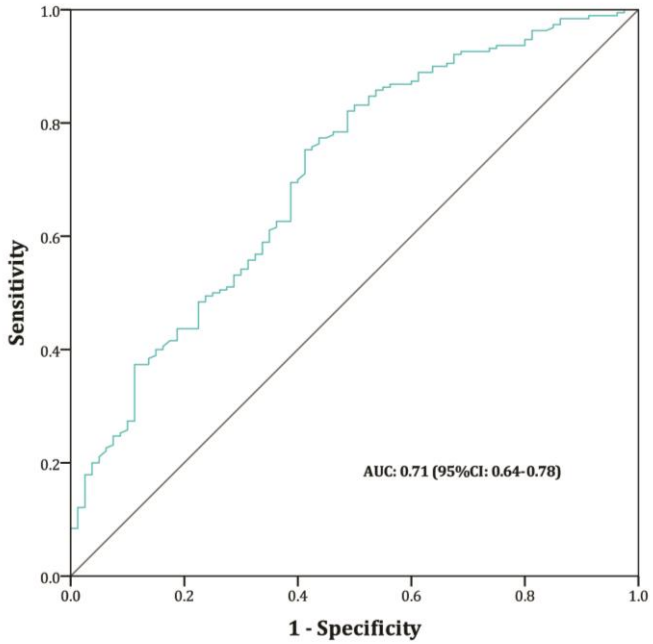


Figure 6.6 Receiver operating characteristic curve for the 5-year prediction of the model

The diagonal grey line represents the line of equality

6.7.1.2 Dataset 2: age & sex

To test the model's performance using only age and sex as predictive variables, a random sample comprising of 651 patients with an AAA repaired between 2008 and 2010 who had at least 5 years follow-up from the National Minimum Data Set were entered into the model. The mean (standard deviation) patient age was 73.4 (7.4) years and 499 (76.7%) were males. There were 187 (28.9%) people who were deceased at 5 years and the remaining were censored. The AAA diameter was set at 6cm (the average AAA diameter in NZ) and all other variables were entered as "not present". The calibration intercept and slope of the model were -0.21 (95%CI: -0.39 to -0.04) and 0.84 (0.57-1.0) respectively, suggesting over-predicting mortality. The c-statistic was 0.64 (95%CI: 0.60-0.69), indicating poor discrimination. Separating data into gender did not change the c-statistic for either males (0.66, 95%CI: 0.60-0.72) or females (0.59, 95%CI: 0.49-0.70).

6.7.1.3 Dataset 3: small AAA

Since the model was structured and developed to manage all patients with an intact AAA and not just patients with those undergoing repair, a dataset of small aneurysms on surveillance was interrogated. Between October 2010 and November 2011, there were 122 patients with an aneurysm diameter less than 5cm who had at least 5 year follow-up. Their baseline clinical profiles are shown in Table 6.6. There were 33 (27.0%) patients who died during follow-up and the predicted 5-year mortality was 24.4%. The calibration intercept (A) was 0.16 (95%CI: -0.27 to 0.60) and the slope (B) was 0.71 (95%CI: 0.25-1.17), indicating that the model under-predicted mortality. The c-statistic was 0.67 (95%CI: 0.57-0.78), indicating poor discrimination.

Table 6.6 Baseline demographics of 122 patients with small AAA (<5cm)

Age/ years, mean (SD)	74.1 (8.2)
Males, n (%)	84 (68.9)
NZ Māori, n (%)	5 (4.1)
AAA diameter in cm, mean (SD)	3.8 (0.6)
IHD, n (%)	23 (18.9)
MI, n (%)	28 (23.0)
Cardiac Failure, n (%)	12 (9.8)
COPD, n (%)	16 (13.1)
Renal impairment, n (%)	5 (4.1)
Cerebrovascular disease, n (%)	15 (12.3)
Diabetes, n (%)	23 (18.9)
Smoking history, n (%)	97 (79.5)
Antiplatelet use, n (%)	68 (55.7)
Statin use, n (%)	83 (68)

Values in parenthesis are percentages of binary variables unless otherwise stated

Note: continuous variables followed a parametric pattern; there were no patients who had COPD requiring supplementary oxygen or ESRD receiving dialysis

6.7.2 Tightness of the model runs

Both AAA repair and small AAA datasets were run three times to test the reproducibility of the model's predicted outcomes. Figure 6.7 below shows the standard deviation by the mean of each participants replicate predictions (expressed as percentage surviving). The red line and text in top left corner indicates the mean of the standard deviation. Standard deviations are smaller in early years where most participants are expected to survive, but even at five years the mean standard deviations do not exceed 1%.

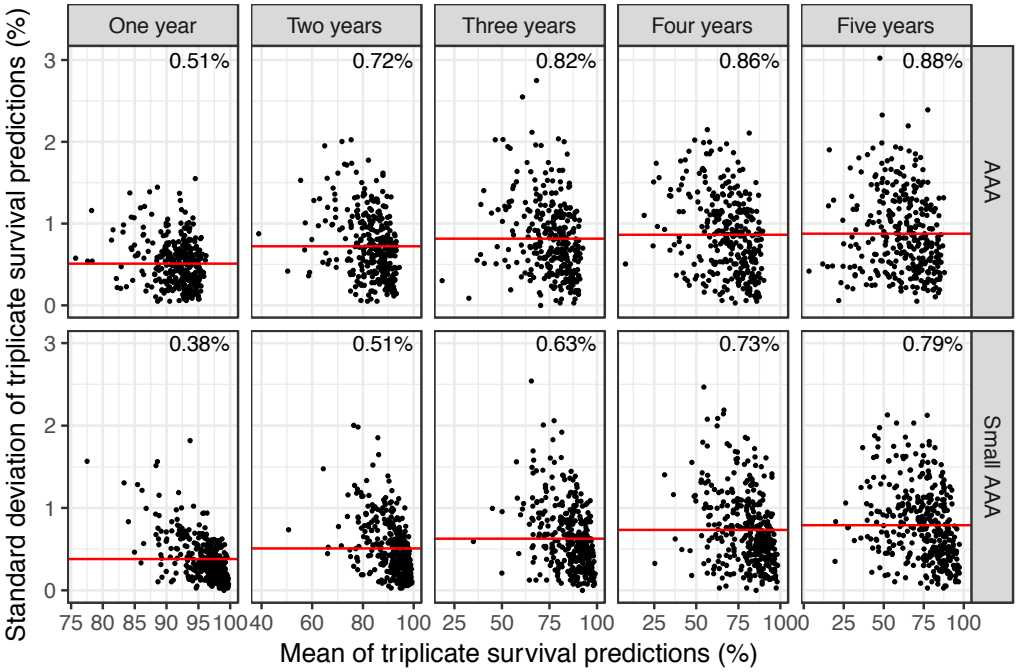


Figure 6.7 Triplicate runs of model representing the mean and standard deviation

6.7.3 Sensitivity analyses

Sensitivity analyses were undertaken to test the internal validity of the model using the effect of age, AAA diameter and number of comorbidities present on the model's outcomes.

6.7.3.1 Age

The predicted life expectancy for 40, 50, 60, 70, 80 and 90 year-old men with a 6cm AAA that had been repaired was 32.2, 24.9, 18.8, 11.6, 6.4 and 3.3 years respectively. The corresponding values for men with an unrepaired 6cm aneurysm were 10.8, 9.2, 7.5, 5.5, 3.9 and 2.6 years. The predicted 5-year survival probability for men who have had an aneurysm repair and those who have not had a repair is demonstrated in Figure 6.8.

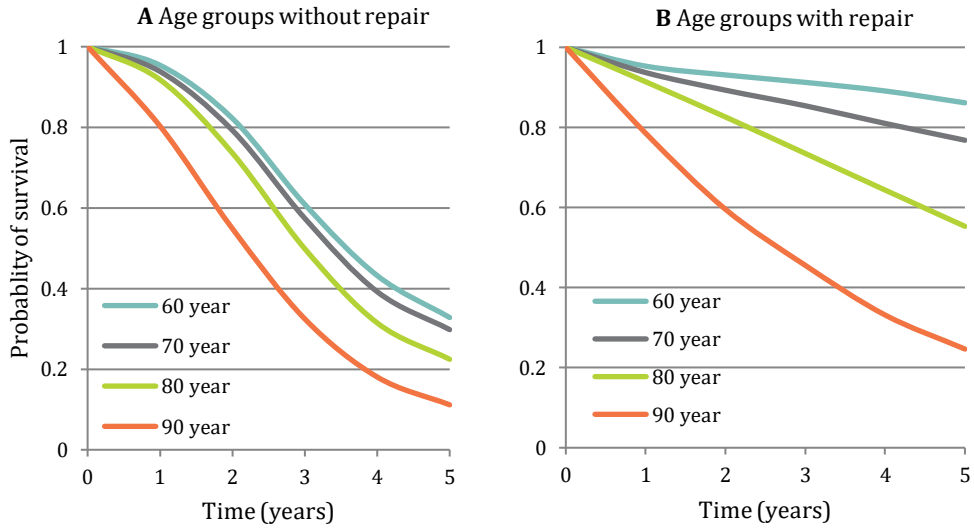


Figure 6.8 Sensitivity analysis for 5-year survival probabilities according to age group

(A) Patients without aneurysm repair and (B) patients with an aneurysm repair

6.7.3.2 AAA diameter

The predicted life expectancy for a hypothetical 70 year-old man without any comorbidities and an aneurysm repaired at a diameter of 3, 4, 5, 6, 7 or 8cm was 12.2, 12.1, 11.8, 11.5, 11.2 and 10.9 years respectively. The corresponding values for a man with an unrepaired aneurysm were 13.8, 12.9, 12.0, 5.6, 4.4 and 4.1 years. The survival probabilities of 4, 5.5 and 6cm aneurysm diameters undergoing a repair with the range of non-operated AAA diameters 4 to 8cm are shown in Figure 6.9.

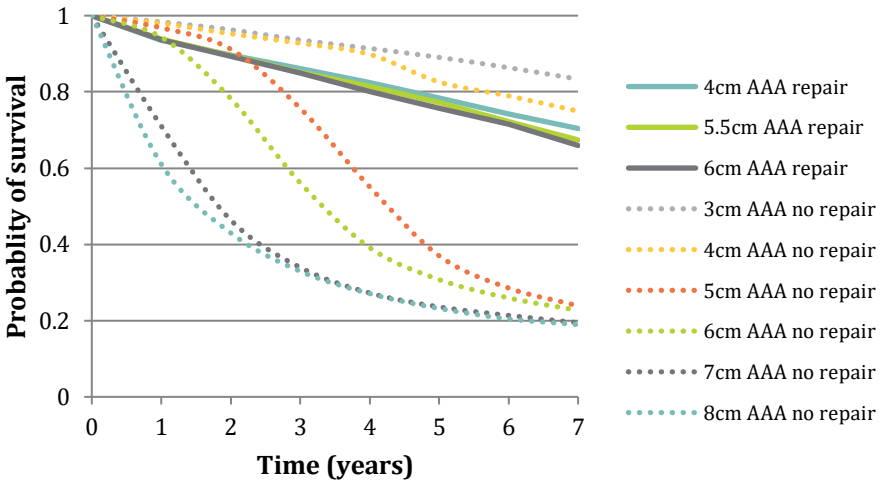


Figure 6.9 Sensitivity analysis of the impact of AAA diameter on the survival probability

Solid lines indicate a repaired AAA and dotted lines indicate non-operated aneurysms

6.7.3.3 Patient comorbidities

There were ten comorbidities included in this model that reduced survival. These were added onto the clinical profile of a hypothetical 70-year-old, non-Māori man with a 6 cm AAA by adding two comorbidities at a time from the most prevalent risk factors (IHD & smoking) to the least common (having COPD on oxygen therapy and being on renal dialysis). The predicted survivals for this patient having an aneurysm repair and not having an aneurysm repair are shown in Figure 6.10.

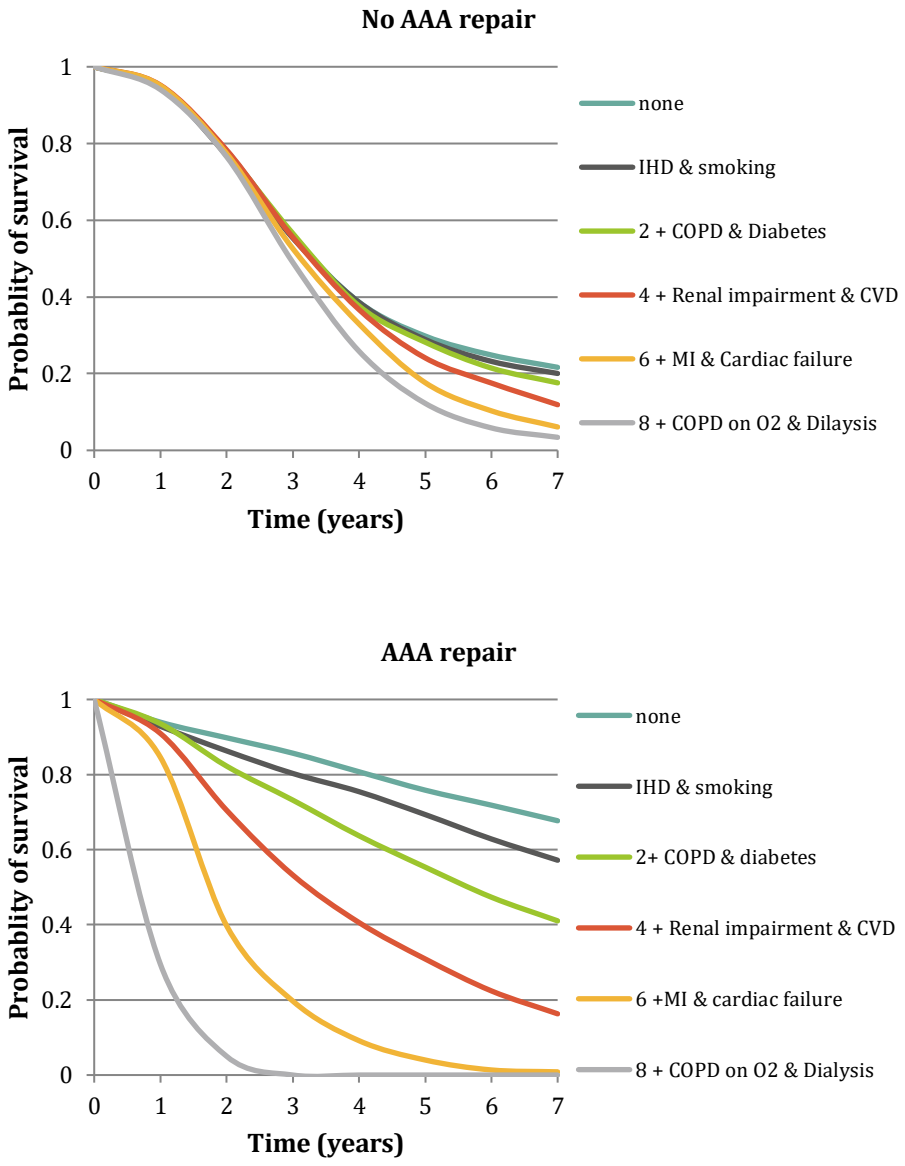


Figure 6.10 Predicted survival probability according to number of comorbidities present

The number in the legend corresponds to the number of comorbidities from the above curve, i.e. "2+ COPD & diabetes" means IHD + smoking + COPD + diabetes

6.7.3.4 Case scenario

A 72-year-old woman on antiplatelet therapy with a history of MI, ex-smoking, diabetes, COPD and a 4cm AAA. The predicted life expectancy and survival according to AAA diameter and treatment options is shown in Table 6.7. For this patient, the time taken for the 4cm AAA to reach 5cm is approximately 3.5 to 4 years, indicating that surveillance is the safest strategy. The point at which the probability of survival in surveillance is

equal to that in a repair at 4cm was estimated to be at 8 years. This point is potentially reduced to 5 years if the patient was using antiplatelet therapy and did not have a history of MI, smoking, COPD or diabetes.

Table 6.7 Decision repair output for a 72-year-old woman with a history of MI, ex-smoking, diabetes, COPD and on antiplatelet therapy

	AAA elective repair (cm)					Surveillance	Conservative
Outputs	4	5	5.5	6	6.5	at 4cm	at 6.5cm
Life expectancy (age)	80	79.5	79.2	78.8	78.6	81.8	75.3
Survival (%) at 1 year	94.3	92.9	93.1	94.1	92.2	97.8	68.8
3 year	77.0	73.7	72	72.9	69.2	91.5	33.1

6.8 Discussion

Clinical decision-making surrounding AAA management can be a challenging process. In this chapter, a DES model was developed and validated to assist in the clinical decision-making process surrounding AAA management. Using the best available information in the published literature, this decision tool included a comprehensive list of comorbidities that impact upon the survival of patients with AAA.

The model's structure and design reported in this current study is novel in this field and the predictability appears promising. The model appeared to perform better when it was validated by an external dataset comprising of 270 patients than with a model which only included age and gender data.

The EVAR-2 trial conducted in the early 2000s randomised high-risk patients who were unfit for open repair to undergo either EVAR or best medical management (conservative) (66). This study showed that there was no apparent difference in overall survival, but the aneurysm related mortality decreased in those treated with EVAR. While the definition of "high-risk" is inconsistent, other observational studies have also shown that in certain high-risk groups (COPD on oxygen, ESRD and congestive heart

failure), aneurysm repair was associated with poor outcomes (192, 216, 218). This questions aneurysm treatment in some individuals.

As seen in Figure 5.8, there has been a rise in the number of EVAR procedures performed in patients older than 75 years. With the improvement in life expectancy, it is likely that these rates will continue to rise. This simulation model can be used to prioritise patients who are more likely not to benefit from surgery, particularly in countries with universal health care access and constraints on health systems.

6.8.1 Strengths of the model

To avoid any bias towards right censoring using time-to-event analysis, all patients included in external validation within this study had a minimum of five years of follow-up. This, in turn, has reduced the number of patients available for external validation in both the repaired AAA and the small aneurysm datasets.

The co-morbidities added to this simulation model were derived from meta-analyses rather than a stepwise method derived from an internal validation set. It is, therefore, unlikely that this would lead to over-fitting of the model. This approach might lead to an increase in the applicability of this model in other AAA patient groups.

How does this model compare to other models?

Some authors tended to report the model's discrimination performance and the calibration was tested using the goodness of fit (247, 248, 252). However, this method of calibration might not provide the reader with information on the direction of the slope line and only provides a p-value for the differences between observed and predicted outcomes (312).

It is not uncommon for preoperative AAA-mortality models to achieve high model discrimination as demonstrated by the c-statistic values reported. This is very likely due to the relatively direct impacts of certain clinical risk-factors on early mortality and the influence of background mortality within

this short time period, a situation which is somewhat unusual in the boarder context of risk modelling.

The AAA calculator developed by Carlisle requires an extensive list of variables and some that are not routinely tested (301), therefore the clinical utility of this calculator is limited. In addition, although the calculator has been validated using some 1000 patients, only about 60% completed follow-up, which will likely lead to serious right censoring (302). The c-statistic for the AAA calculator at 5-years was 0.68 compared to 0.71 observed in this study.

6.8.2 Other benefits of the model

Although management of small AAA is well-established with non-operative treatment until the aneurysm diameter reaches threshold (51), some patients with a high-predicted life expectancy (those with few or no comorbidities) might benefit from treatment at lower AAA diameters than the 5.5cm set threshold. There is some interest in treating selected patients with good risk profiles who might benefit from AAA repair at lower thresholds than the 5.5cm defined threshold. A comparative survival analysis of a hypothetical patient with and without comorbidities and the projected survival if the aneurysm was repaired or managed conservatively is summarized in Figure 6.11.

In a 70 year-old-man with an aneurysm repaired at 4cm without comorbidities, there was a small (1%) difference in survival compared to a repair conducted at 5.5cm and therefore might be justified provided the baseline predicted life-expectancy is high. In contrast, in a similar aged man with co-morbidities, repair of a 4cm aneurysm was associated with a 6% difference in survival compared to a repair at 5.5cm confirming the associated harm with this strategy.

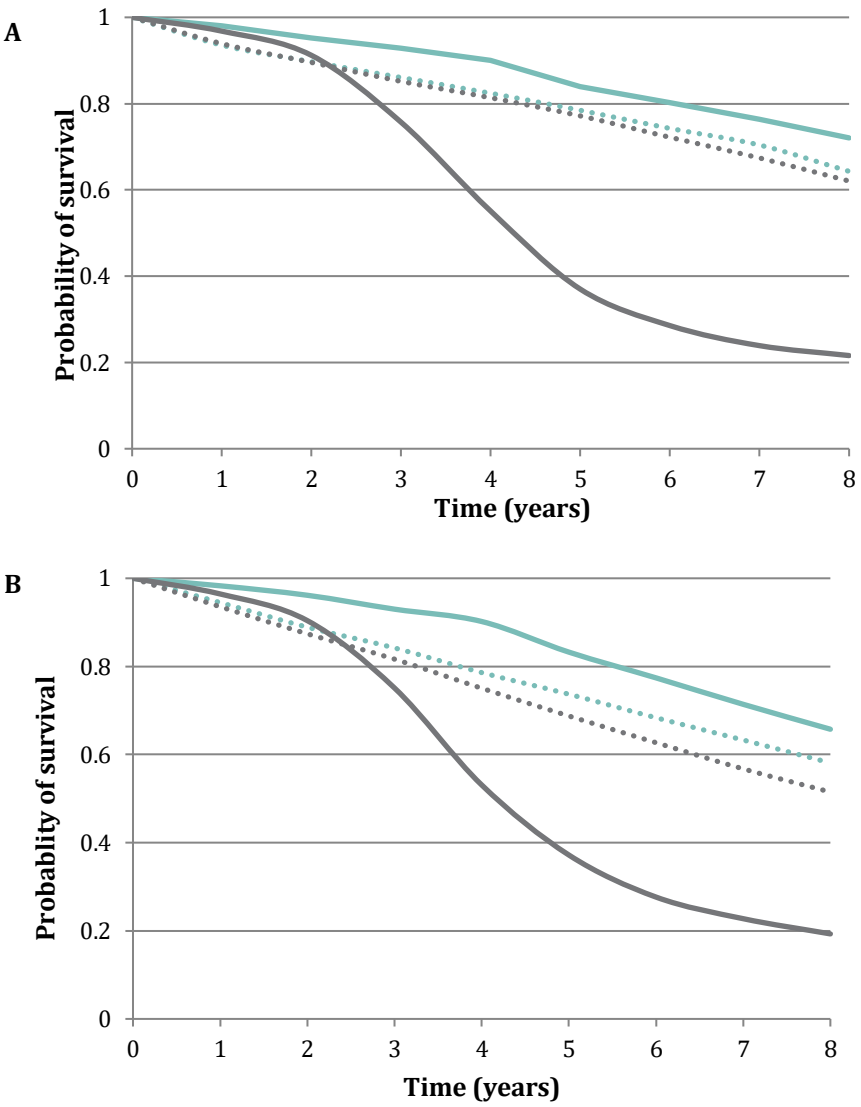


Figure 6.11 Survival probabilities of a 70 year old man with different comorbidities and AAA diameter undergoing a repair and no repair treatment options

A: patient has no comorbidities, B: patient has ischaemic heart disease, smoking history & diabetes.

Blue lines indicate 4cm AAA and grey indicate 5.5cm AAA, solid lines indicate a non-operative management and dotted lines indicate a repair option

The aim of this model was not to decide on whether patients should be treated with OAR or EVAR as this remains a shared clinical decision between the vascular surgeon and the patient. However, the model may give surgeons an indication on expected life years remaining and therefore a judgment for the choice of repair could be based on predicted life-expectancy. Patients

with long life-expectancy might be better candidates to undergo OAR to reduce long-term EVAR-related interventions and endograft ruptures (315).

Moreover, in some healthcare systems where there are financial constraints and limited access to resources, a decision-making tool that can prioritize and predict which patients are more likely to benefit from corrective aneurysm surgery using a well-developed approach is of significant value. Such tools are used clinically in prioritising ESRD patients on waiting lists for renal transplantation (314). This model can potentially be used to triage AAA patient on an elective waiting list according to the life years gained and predicted life expectancy from the procedure. This strategy might ensure that resources are used for those most likely to benefit from intervention.

Moreover, the model might be utilised in determining which patients with small AAA might benefit from surveillance. The status quo for most AAA surveillance programs is that patient will continue to be enrolled unless they wish not to attend further surveillance. It is expected that in this cohort some patients mainly due to comorbidities would not benefit from any AAA related procedures in the future and hence can be removed from surveillance by using such models.

6.9 Limitations

Like with any mathematical model, the inputs, design and behaviour determines the overall applicability of its use and performance. The specific limitations of this model are discussed below.

6.9.1 Model specific

An embedded limitation of DES models is that they try to facilitate a realistic environment and hence minor details that would not play an important role in reality would be accounted for in the model (294). This might explain the reason for the higher 5-year predicted mortality than the actual mortality, as surgeons would have excluded some patients based on their co-morbidities and this group would not have been included in this validation testing. In New Zealand, management of AAA sways towards the conservative side and

this is evident by the larger average diameters, the relatively high proportion of OAR used and the higher turn-down rates for ruptured AAA compared to other Western countries (275, 316).

6.9.2 Variables included

Despite the fact that cancer is one of the leading causes of death within the post-AAA repair population (197, 317), history of cancer was not included in this model as a variable. The reason for this was due to the lack of a clear definition of cancer observed within the systematic review, which led to a wide confidence interval and high heterogeneity (I^2>70%). This might have limited the long-term survival prediction of the model.

Other important patient factors such as patient frailty, functional status and ASA and hospital volume might appear to have an independent impact on survival but were not included in this model.

6.9.3 Input variables

Growth patterns and the risk of AAA rupture used in this model were based on the RESCAN data which in itself has some limitations, including heterogeneity in measurement methods and modalities used (300). In this model, variables were only sex-adjusted while other interactions such as slower growth-rates in diabetics and faster aneurysm expansion in current smokers or those with hypertension were not included as interactions (32).

There were no patients in the validation sets with COPD on supplementary oxygen and only two patients with ESRD requiring dialysis, therefore testing the usefulness of such variables is limited in this study. With an all-inclusive strategy of enrolling AAA patients, further validation of the utility of such parameters can be directly assessed.

6.9.4 Model validation

Another limitation in the validation of the DES AAA model was the relatively small number of patients available for external validation and this was evident by the wide confidence intervals in the discrimination and

calibration analyses observed in the small AAA under surveillance and those patients who had a repair in 2010.

The internal validation set used to provide the 30 day mortality, the range of overall 10 year survival and the limits for the low and high risk groups where derived from the national minimum data set which also included a proportion of patients from 2010 that underwent AAA repair and were included in the external validation. This however, is unlikely to lead to a major bias, as the outcome of elective AAA is similar among most published series. Ideally, a different dataset should have been used to provide such estimates but this was not available at the time the model was developed.

6.10 Conclusions

The AAA DES model developed in this chapter performed well in predicting 5-year survival for those participants who underwent repair, but less so for those enrolled in a small aneurysm surveillance programme. Overall, this approach to guiding AAA management is encouraging but requires further testing and validation with different patient groups in other clinical settings.

6.11 Future Work

This AAA clinical decision tool is still in its infancy and requires further prospective testing and refinement. However, it showed promising results with acceptable calibration and discrimination. The structure of the DES model can be updated or modified to reflect any changes to background mortality, hazard ratios of risk factors or the comorbidities included.

The ultimate testing of the model requires inclusion of all patients seen with an intact AAA, including those turned down or those that did not want follow-up or repair. Such a prospective study comparing actual survival and the model's predicted outcomes is of clear interest to physicians, patients and stakeholders.

Chapter 7: General Discussion

7.1 Overview

The impact of Abdominal Aortic Aneurysms (AAA) on the NZ health system remains a considerable health concern. This study estimated that there were 450 patients who underwent repair every year, and at least 220 patients who have had a death attributed to AAA. The mortality rate has not greatly changed from what was reported a decade ago (121) and is similar to the annual road death rate in NZ.

The overall prevalence of AAA was relatively high in a selective group undergoing CT colonography for gastrointestinal symptoms, and the numbers of aneurysms increased in both males and females with age. This supports that the burden of AAA that require management is still high and is likely to continue with the aging population and improved life expectancy.

In NZ, in the absence of a formal aortic screening programme, patients rely on incidental radiological imaging for AAA detection. It has been noted that there was a large proportion of patients with AAA who have not had their aneurysm measured, reported or diagnosed and therefore were not able to be managed. This has implications when a condition such as aneurysm can be monitored for growth and repaired when the threshold for treatment is reached.

Prognostic factors that influence patient survival after AAA repair have usually been reported from single or multi-centred studies. In this thesis, the systematic review allowed documentation of a number of factors and quantifying the impact of each variable on long-term survival after aneurysm repair. This information, compounded with data from the literature, has enabled the development of a predictive model that can be used in clinical decision-making surrounding AAA management

The authors of the PROGnosis RESearch Strategy (PROGRESS) propose four research themes for developing prognostic models (279):

1) Describing the nature and quality of current care.
2) Documenting specific factors associated with the disease prognosis.
3) Development and validation of prognostic models.
4) Using the model to aid in decision-making for individuals.

This framework was used throughout the thesis in understanding the prevalence of AAA and the impact of outcomes, then deriving specific prognostic factors that are associated with survival from the published literature, and finally developing and validating a predictive individualized model. The final stage requires further prospective work to test the model's ability to be used in the clinical setting.

The aims of this chapter were to consider and discuss the significance and implications of the thesis findings and consider the limitations and future directions for further research.

7.2 Major findings and Implications

This thesis has contributed to the AAA literature with five papers published and four additional manuscripts in preparation. I was the principal investigator in the majority of these studies.

Prior to this work, the natural history and clinical outcome data on AAA disease in NZ has been limited to less than ten published studies. The work from the thesis has contributed to the existing literature in the areas discussed below.

7.2.1 Abdominal aortic aneurysm prevalence and definition

Prior to 2010, there was very little knowledge on AAA prevalence in NZ. The information from this thesis has highlighted that the prevalence of AAA was high in a selected population undergoing CTC in the South Island of NZ. This relatively high aneurysm prevalence has also been reported by other authors in other selected populations in NZ (135, 136).

For practical purposes, the 3cm definition of AAA has provided consistency in measuring and diagnosing aneurysms (318). However, this current binary

definition of AAA seems limited for an aorta that dynamically changes diameter with age in both males and females. Therefore, it seems logical that this definition should be tailored to individuals when considering the definition of 'abnormal' aortic diameter.

Although the relationship between male aortic diameters, cardiovascular survival and overall mortality has been previously reported (170, 171, 319), the association in females has been less documented. In this thesis, I was able to demonstrate that larger aortic diameters in females appeared to be associated with a higher mortality, an association which remained valid when body size measurements were considered. This relationship appeared novel, and the association of aortic diameter and survival might be a further prognostic marker of overall survival that can be used in risk classification and requires further exploratory work.

7.2.2 Women & AAA disease

After years of focused strategies to reduce AAA-related mortality by detecting aneurysms in males, it appears that some attention has turned into research into women with AAA, as the prevalence in males has declined.

The work in this thesis has shown that women comprised of 30.7% of all patients defined as having an AAA in NZ from 2000 to 2014. This proportion differs from those who have had an aneurysm repair (21.1%), and of the 223 AAAs diagnosed in the CTC study, 57 (25.6%) patients were women.

In the CTC cohort, despite the selective nature for inclusion, women had a similar AAA prevalence to that reported in the literature (320), which was consistent with other targeted screening groups from NZ (135, 136).

Screening women without a history of smoking and younger than 75 years old is unlikely to yield sufficient AAA prevalence. In the CTC study, of the 57 women with AAA detected, a third did not have a history of smoking and all the patients were older than 75 years.

Therefore, a screening program that includes women with a history of smoking might be justifiable, as the prevalence in this group was similar to

prevalence rates of 65-year-old men reported by national screening programs from the UK and Sweden (115, 321).

7.2.3 Outcome of repair in women

Although AAA disease has been traditionally considered a male predominant condition (322), this thesis highlights some concerns with this.

From this work and others, it was noted that women were more likely to die from a ruptured AAA prior hospital admission and were less likely to undergo corrective AAA surgery for ruptured aneurysms (110, 323). In scheduled aneurysm repair, the reported 30-day mortality has consistently been higher in women compared to males for both OAR and EVAR and has also been supported by data from this thesis, with our New Zealand data suggesting an adjusted odds ratio of 2.12 (95% CI: 1.02-4.4) for female 30-day post-operative mortality compared to their male counterparts. A meta-analysis reported that the pooled odds ratio for women after elective OAR and EVAR was 1.28 (95%CI: 1.09-1.49) and 2.41 (95%CI: 1.14-5.15) respectively (105).

With regards to long-term survival, the results of the systematic review in chapter 4 have provided further important information that has previously been inconsistent. After adjusting for confounders, women had a 15% increase in mortality after AAA repair compared to men. This is despite the fact that women in the general population have a longer life-expectancy than men. This finding was also reported later from the UK national data, in which women had an 8% additional risk of death compared to men after adjusting for age (324).

Both the definition of aneurysm (threshold diameter) and better understanding of the natural history (particularly expansion rates) of aortas in women need future work to reduce the disparity in outcomes. This information should be considered with decision-making regarding AAA screening or repair of small aneurysms in women.

7.2.4 Māori and AAA disease

The New Zealand population composition consists of several ethnic groups, and understanding the burden of a disease might reduce ethnic health-related inequalities. This thesis has highlighted important findings regarding AAA disease in Māori that has not been previously reported.

First, using multiple data sources, reliable information on the normal aortic diameters of NZ Māori have been documented and compared to the NZ European population. This provided baseline aortic diameter data that can aid in decision-making with defining an AAA in Māori. It also highlights that the association of smaller aortic diameters observed in other ethnic groups, such as Asian, is not relevant.

Second, previous studies reported that the 30-day mortality following AAA repair in Māori was higher than NZ Europeans (119, 121). This study supports these findings, but this association was only observed at univariate analysis. When potential confounders were added into the logistic regression model, Māori did not appear to have a higher mortality risk. Furthermore, this study supports that Māori were more likely to present with ruptured AAA than present with an intact abdominal aneurysm (120), corresponding to a higher aneurysm-related mortality.

The average life expectancy of Māori and Pacific island people is lower than that of NZ Europeans (127). However, after AAA repair and excluding 30-day mortality, Māori had a 40% higher risk of death compared to NZ Europeans while the survival of Pacific Island people was very similar to that of NZ Europeans.

Another novel finding was observed in the over representation of females undergoing aneurysm repair (41%) compared to the ~20% female proportion that is consistently reported in the literature (105). This might be due to the known high smoking rates of Māori women (257) and the lower life expectancy of Māori men causing an under representation in those with an AAA (127).

These findings highlight the disparity in outcomes following AAA repair in Māori and should stimulate further work to understand association of AAA in different ethnic groups and therefore potentially reduce health inequalities.

7.2.5 Prognostic decision-making tools

The vascular surgery community might benefit from a decision-making model that can better inform surgeons and patients of the individualised risks of those undergoing aneurysm repair or surveillance as part of a shared decision-making process. Ideally, this practice should be tailored to the individual patient risk rather that based on results published from national reports or clinical trials. Surgeons can vary with their perception of risk-benefit analysis (325) and this may therefore result in discrepancies in treatment choices.

In this thesis, one of the primary aims was to develop and externally validate a clinical decision tool that could aid in the management of AAA. There are a few developed prognostic models that can predict long-term outcomes after AAA repair reported in the literature. Three models have been validated, with discrimination for 5-year survival resulting in c-statistics of 0.68-0.69 (230, 302, 306). Despite the smaller number of patients available for validation in this study, the c-statistic was 0.71, indicating sufficient accuracy for predicting 5-year survival (309).

The decision to treat AAA with either OAR or EVAR remains a complex one. Long-term outcomes of EVAR and OAR (>15 years) have shown no difference in overall survival between the two modalities in controlled and observational studies (317, 326), but aneurysm-related mortality was higher in the EVAR group (64, 326). The decision-aid tool developed in this thesis might assist in this selection process by estimating individualised life expectancies.

As the developed model provides an estimate of the background mortality of patients based on their comorbidities, the potential for using such tools might be a useful public health initiative. For example, if a form of an AAA

detection program is to be developed, a pre-screening test by using the AAA model might determine if a patient would benefit from screening based on existing comorbidities and therefore utilising health resources efficiently.

7.3 Topical questions related to potential AAA screening in New Zealand

7.3.1 Should AAA screening be introduced to NZ?

In Sweden nearly ten years after introducing a national aneurysm screening program, the overall annual number of intact AAA repairs increased while the number of ruptures decreased by 50%, as expected from such a program (327). In NZ, where aneurysm detection still relies on incidental radiological findings and physician-led referral systems, the number of aneurysm repairs remained fairly constant for both scheduled and rupture presentations during the last decade.

In Sweden, there was a gradual uptake by counties for AAA screening, and there was a significant reduction in both AAA-related and cardiovascular mortality when comparing those screened with those not screened (321). Similarly, in the UK, a decline of aneurysm rupture was observed in 65-74 year old men at a higher rate that those older than 75 years old, which could be due to the national screening programme (328).

The information from this thesis has highlighted that the prevalence of AAA was high in a selected population undergoing CTC in the South Island of NZ. This population had a lower expected survival than an age-and-sex-matched population, but after adjusting for age and sex, the presence of AAA was not associated with any statistical difference in overall survival.

Given the impact of screening in other countries, the prevalence of AAA and the number of deaths related to AAA in NZ, it seems that national population screening for AAA will likely result in a reduction of premature deaths in men. The barrier to such a programme remains to be the costs in implementation.

7.3.2 Who and how to screen for an AAA?

In New Zealand, the viability of screening for AAA is being investigated and it is of big importance to be able to provide an accurate estimate of local figures. The change of AAA epidemiology and the relatively lower early mortality achieved nowadays with elective repair can alter the clinical decision-making for AAA management in comparison to evidence-based norms established two decades ago (329).

In this study, patients living in higher deprived areas where more likely to have an AAA and they also had a higher representation in those undergoing aneurysm repair. Lower income and SES have been associated with a higher AAA prevalence (145). It is therefore of some concern that geographical regions with low average incomes and SES appear to have lower attendance rates to national AAA screening (112, 114). A more targeted approach that aims to improve the capture of higher-risk individuals might decrease AAA-related mortality rates through earlier detection and enabling greater cardiovascular risk-factor management opportunities.

Other methods for increasing the detection rate of AAA would be to utilize other radiological modalities for aortic assessments in those undergoing abdominal imaging, then linking the information regarding abdominal aortic size to a central database were people over the age of 50 get their aorta measured. This might be the most cost-effective strategy and "smartest" method to ensure that the majority of people who undergo incidental imaging are screened, hence reserving screening to those with less access to healthcare.

One issue which might arise is that patients would not have directly consented to have their aorta measured, which might potentially be associated with a psychological burden for some of them (330). Data from screening trials suggest that there was a small impact on health status after detecting aneurysms in men compared to those who did not have an aneurysm detected, but this association was no longer evident after 1 year (331). It remains the patient's choice if an incidental AAA was discovered

whether they wished to have this treated or monitored after being appropriately counselled. The rates of incidental findings will continue to mirror the use of radiological modalities used for diagnostic and therapeutic purposes, therefore understanding the implication of an aneurysm diagnosis on the patient's quality of life is an important area and requires further work (332).

7.4 Limitations

There were some limitations discussed at the end of each chapter relating to the study design, data collection and assumptions where applicable. This section will discuss the overall limitations of this thesis.

7.4.1 CTC study

The biggest limitation in using the CT colonography cohort as a surrogate for an ultrasound screening population was the selection process for patient inclusion, which might have created a bias towards those with higher comorbidities and gastrointestinal symptoms. Another weakness was the retrospective nature of the study design, which has resulted in some missing data points. However, using this approach had an advantage of including individuals from all socioeconomic groups who sought medical attention. An alternative prospective approach may have resulted in avoidance from some (low socioeconomic group) individuals as observed in other studies (112, 115).

Longitudinal population-based studies have provided most of the data on the natural history of AAA. Such studies can take a considerable amount of time to complete and can be associated with high costs due to the necessity to collect long-term follow-up. Indeed, this was apparent in the CTC data examined in this thesis, in which it was apparent that at least 5 years of follow-up were required to provide meaningful observations that could be translated to the clinical setting. In NZ, a general population longitudinal study has not been performed and is unlikely to be undertaken in the near

future, therefore using this large CTC cohort provided some information at little additional costs or risks to the patients.

In order for more reliable information on AAA to be gathered from different ethnic groups in NZ, collaboration with other existing cardiovascular research groups to provide further information in this field is required, as it was noted that the absolute numbers included in this study were small.

7.4.2 New Zealand AAA data

To provide information on national AAA trends and outcomes, all available datasets were used. From 2010 to 2014, the Australasian Vascular Audit (AVA) was used to supplement the National Minimum Data Set. For the 2000 to 2009 period, the previous Otago Surgical Audit was not accessible and the information was not consistently recorded. This might correspond to 150 to 200 patients that could be missing from the pre-2010 period, and more likely to present patients undergoing aortic repair at a private institution. Fortunately, it has become mandatory that private hospitals report operative cases to the NMDS with a lag time in data of 2 years.

Another limitation of this study was that it was not possible to gather further information and validate the quality of data provided in the mortality collection database to a similar standard as that to which the administrative and clinical datasets were scrutinised. It appears that there is significant under-reporting as pre-hospital deaths only contributed to a small proportion (21%) of ruptured AAA presentations compared to the estimated 32% figure that was previously reported (6).

7.4.3 Systematic review and meta-analysis

The systematic review had some inherent weaknesses mostly due to information and publication bias, which might have limited the understanding of some of the impacts on survival. There was some inconsistency in defining the risk factors studied, which was reflected by a high heterogeneity in some instances. The comorbidities were considered in a binary (yes/no) manner and information such as the duration and severity

of each comorbidity could not always be quantified. In addition, duration and doses of the medications used were not reported, therefore limiting the translational knowledge to patient care. These hazard risk estimates might have led to the model's over-prediction of mortality.

7.4.4 Model development

As with any model development, there is susceptibility to simulating 'real world' environment and therefore some assumptions had to be made. Some of the risk factors were collected retrospectively, which might have resulted in inaccurate sample representation. With regards to testing the performance of this tool, there was limited available data to use for external validation of the discrete event-simulation AAA-management model. This was partly attributed to requiring a minimum of five years follow-up to avoid right censor biases in the validation process. Despite this, the model's predictability performance was considered sufficiently accurate.

7.4.5 Future research & direction

This work has laid some foundation for further research into this field. The advantage of conducting population research in NZ is the ability to link some databases to improve the quality and accuracy of the data. In addition, the survival status can also be updated, which would increase the duration of follow-up.

The model developed in this thesis is still in its infancy and requires further external validation and refinement. Further work has begun to test the validation of the model in different clinical settings, such as those of Australia, Netherlands and Hong Kong.

Another example where model inputs can be adjusted would be in the AAA expansion rates. In the DES model, the growth rates of AAA were assumed to be similar in all age groups, as age was not found to be an independent predictor of AAA growth (32). However, the meta-analyses have not included any octogenarians, as historically this group of patients was not routinely offered repair. Work has begun to explore the expansion rate of

AAA in the octogenarian population. If a substantial difference in growth is found, the DES AAA management tool can be updated to represent this and therefore simulate a more accurate representation of patients with an AAA. Potentially the DES AAA model can be used for selecting patients for aneurysm detection, surveillance and for repair consideration.

While the model has been shown to be relatively accurate at predicting 5-year survival, the influence of the DES AAA model on clinician and patient decision- making is an area that warrants further exploration. As the model generates 10 year survival curves adjusted to individual patient comorbidities, these can be presented to patients and their families, the decision surrounding the management options could potentially be improved and hence steer the outcome towards the strategy that is more likely to achieve the agreed desired patient outcome.

Some of the data generated in this thesis has been used in developing a National Health Committee document on Models of Care for AAA. Furthermore, I have collaborated with the Burden of Disease, Epidemiology, Equity and Cost Effectiveness Programme (BODE^3) in developing a cost-effective screening model for screening AAA in New Zealand. There were several inputs into the model that used the data presented in this thesis.

The development of a robust national AAA preoperative and outcome database used in this thesis allowed the collaboration with some international vascular registries such as the VASCUNET. This is likely to generate future international work and shed some light into AAA management across different areas.

7.5 Conclusions

In conclusion, based on the prevalence, trends of presentations and mortality, AAA remains a significant burden on the NZ population and their health care system. The prognostic factors that reduce survival may help in decision-making when managing patients with AAA, and cardiovascular risk-factor modifications with antiplatelet and statin use appear to improve

the overall survival. Ethnic and social deprivation inequality still occurs in a universal health-care system and therefore requires further targeted attempts to reduce this apparent disparity. The discrete event-simulation tool developed was a useful predictor of 5-year survival for patients who underwent AAA repair and might have other uses in management of small aneurysms and selecting treatment strategies. Understanding the limitations of the existing datasets and what information is already available might help future-reporting of AAA outcome data. Also, the findings from this study may provide information that could assist in decision-making related to the prospect of a national AAA screening programme. The work generated in this thesis has not only informed our contemporary understanding of AAA on New Zealand society but, given the effect of our aging population, will likely play an important role in the necessary future work to be conducted in this field.

"Are you saying there is no basis for doing a trial or for introducing a screening programme and including a control group?"

"There would be if there was an important question that such trial would answer but I'm not aware that there is."

Law et al. responding to R A P Scott (principal investigator of Chichester AAA screening study) in one of the earliest articles promoting and arguing the case for AAA screening (84)

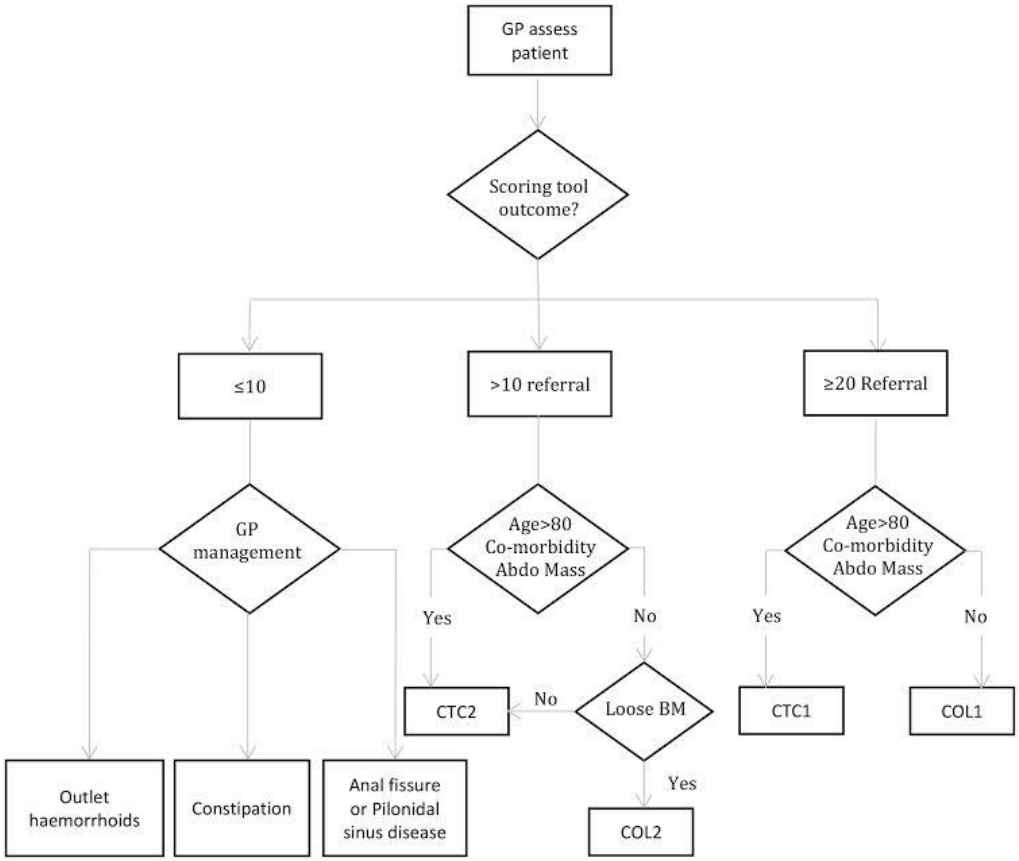
Chapter 8: Appendix

8.1 Triaging Patients with Gastrointestinal Symptoms

8.1.1 The Canterbury Colorectal System Pathway scoring tool

Covariate	Score
Age	
<40	-5
40-59	0
>60	10
Personal history	
CRC	5
adenoma	2.5
Family History	
1	0
2	5
3	10
Symptoms (>6 weeks)	
Rectal bleeding:	
- Sinister	12.5
- Outlet	5
Change in bowel habit:	
- Loose	10
- Constipation	5
Weight loss (>5kg)	5
Examination findings	
Abdominal mass	20
PR pass	20
Bloods	
Unexplained Iron deficiency Anemia	20
Faecal occult blood positive	10
If diarrhea/loose motions	10
CRP>10	10

8.1.2 Pathway of undergoing investigation depending on The Canterbury Colorectal System Pathway scoring tool



Adapted from Sanders *el al.* A novel pathway for investigation of colorectal symptoms with colonoscopy or computed tomography colonography N Z Med J 2013 (123)

8.2 Search History for Systematic Review

EMBASE

1. exp abdominal aortic aneurysm/
2. abdominal aortic aneurysm.tw.
3. infrarenal aortic aneurysm.mp.
4. aneurysm surgery/ or Endovascular aneurysm repair/
5. elective surgery/ or abdominal aorta aneurysm/ or aneurysm surgery/
6. exp risk reduction/
7. exp long term survival/
8. exp survival prediction/
9. exp predictor variable/
10. exp survival/
11. 1 or 2 or 3
12. 4 or 5
13. 6 or 7 or 8 or 9 or 10
14. 11 and 12 and 13

Total: 4061

Medline

1. Abdominal aortic Aneurysm.mp.
2. Abdominal aortic Aneurysm/
3. Aortic Aneurysm, Abdominal/su [Surgery]
4. Risk Factors/ or Risk Adjustment/ or Risk/ or Risk Management/ or Risk assessment.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. Survival Rate/
6. time factors/
7. time factors.mp.
8. risk factors.mp.
9. postoperative complication/
10. 4 or 5 or 6 or 7 or 8
11. 1 or 2 or 3
12. 9 and 10 and 11

Total: 1108

Cochrane

Abdominal aortic aneurysm

Total: 580

8.3 Codes Extracted from the International Classification of diseases (ICD-10)

8.3.1 Diagnosis and Procedural Codes Extracted from Administrative Databases

I71.3	Abdominal aortic aneurysm, ruptured
I71.4	Abdominal aortic aneurysm, without mention of rupture
9022800	Endoluminal repair of aneurysm
9020902	Direct closure of wound of aorta
9021302	Repair of wound of aorta by interposition graft
3308000	Repair of intra-abdominal aneurysm
3318100	Repair of ruptured intra-abdominal aneurysm
3310900	Replacement of thoraco-abdominal aneurysm with graft
3311200	Replacement of suprarenal abdominal aorta aneurysm with graft
3311500	Replacement of infrarenal abdominal aortic aneurysm with tube graft
3311800	Replacement of infrarenal abdominal aortic aneurysm with bifurcation graft to iliac arteries
3312100	Replacement of infrarenal abdominal aortic aneursym with bifurcation graft to femoral arteries
3312400	Replacement of iliac artery aneurysm with graft, unilateral
3312700	Replacement of iliac artery aneurysm with graft, bilateral
3314800	Replacement of ruptured thoraco-abdominal aneurysm with graft
3315100	Replacement of ruptured suprarenal abdominal aortic aneurysm with graft
3315400	Replacement of ruptured infrarenal abdominal aortic aneurysm with tube graft
3315700	Replacement of ruptured infrarenal aortic aneurysm with bifurcation graft to iliac arteries
3316000	Replacement of ruptured infrarenal abdominal aortic aneurysm with bifurcation graft to femoral arteries

3316300	Replacement of ruptured iliac artery aneurysm with graft
3416000	Repair of aorto-enteric fistula with direct closure of aorta
3416300	Repair of aorto-enteric fistula with insertion of aorta graft
3416600	Repair of aorto-enteric fistula with oversewing of abdominal aorta and axillo- femoral bypass graft

8.3.2 Codes Used to Identify Comorbidities and Risk Factors

Comorbidities	**ICD-10**
Ischaemic heart disease	I200, I201, I208, I209-I214, I219, I221, I229, I234, I240, I248-9, I2510-I2512, I252-3, I255, I258-9
Hypertension	I10, I110, I130
Atrial fibrillation	I48
Diabetes	E1120, E1130, E1140, E1150, E1160, E1170, E1180, E1190, E1450, E1490
Respiratory disease	J40, J410, J42, J438-J441, J448-J449, J459, J47
Cerebrovascular disease	I602, I608, 1611, I615, I620, I632, I634-5, I638-9, I64, I652-3, I658, I661, I664, I671-2, I678-9, I690, I692-4, I698
Ex-smoker/personal history of tobacco use	Z8643
Current smoker/tobacco use	Z720
Peripheral artery disease	I700, I7020-4, I708-9

8.4 Grants and Awards

Best Trainee presentation, Australia and New Zealand Society of Vascular Surgery Maui, Hawaii, USA September 2015
"*Does the diameter of abdominal aortic aneurysm influence late survival following abdominal aortic aneurysm repair? A systematic review and meta-analysis"*

Best registrar prize, Vascular Society of New Zealand Dunedin, NZ February 2015
"Factors affecting survival following abdominal aortic aneurysm repair"

Royal Australasia College of Surgeons- Foundation for Surgery Research New Zealand Research Scholarship 2016

University of Otago, Doctoral Scholarship 2015

University of Otago, Doctoral Scholarship 2014

Summer Studentship University of Otago, Christchurch 5,000 NZD per grant
November 2014 to January 2015 "Determining the prevalence of normal and sub aneurysmal aortic diameters in patients undergoing CT colonography" November 2015 to January 2016 "A targeted quality of life analysis following abdominal aneurysm repair - Influence on treatment method" November 2016 to January 2017 "What is the expansion rate of abdominal aortic aneurysms in the octogenarian population?"

ANZSVS Cook Medical Travel Scholarship
Attended the 8th Annual Introduction to Academic Vascular Surgery Tampa Florida

8.5 Publications, Citations, Conference Proceedings and Posters

8.5.1 Publications

The list below is for publications related to this thesis but not included directly into main chapters. The list of publications directly related to chapters is listed at the beginning of the thesis.

1) Khashram M, Jenkins JS, Jenkins J, Kruger AJ, Boyne NS, Foster WJ, et al. Long-term outcomes and factors influencing late survival following elective abdominal aortic aneurysm repair: A 24-year experience. Vascular. 2016; 24(2):115-25. DOI: 10.1177/1708538115586682

2) Khashram M, Tiong LC, Jones GT, Roake JA. The impact of CT colonography on abdominal aortic aneurysm referrals in a tertiary hospital. Journal of medical imaging and radiation oncology. 2016. DOI: 10.1111/1754-9485.12535

3) Peek KN, Khashram M, Wells JE, Roake JA. The costs of elective and emergency abdominal aortic aneurysm repair: a comparative single centre study. The New Zealand medical journal. 2016; 129(1433):51-61.

4) Khashram M, Jones GT, Roake JA. Re: 'Self-referral to the NHS Abdominal Aortic Screening Programme'. European journal of vascular and endovascular surgery 2016;52(2):270-1. DOI: 10.1016/j.ejvs.2016.05.023

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8.5.2 Citations between January 2015 and December 2016

Excluding self-references

Prevalence of Abdominal Aortic Aneurysm (AAA) in a Population Undergoing Computed Tomography Colonography in Canterbury, New Zealand
Cited: 3 times

Systematic Review and Meta-analysis of Factors Influencing Survival Following Abdominal Aortic Aneurysm Repair
Cited: 5 times

Long-term outcomes and factors influencing late survival following elective abdominal aortic aneurysm repair: A 24-year experience
Cited: 4 times

Abdominal aortic aneurysm repair in New Zealand: a validation of the Australasian Vascular Audit. ANZ journal of surgery
Cited: 1 time

8.5.3 Manuscripts in preparations

Khashram M, Pitama S, Williman JA, Jones GT, Roake JA. Survival disparity following Abdominal Aortic Aneurysm repair highlights inequality in socioeconomic status.

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Khashram M, Khashram Z, Sandiford P, Jones GT, Roake JA. Incidence and management of abdominal aortic aneurysms in New Zealand

8.5.4 Oral presentations

Khashram M, Jones GT, Roake JA, Abdominal Aortic Aneurysm screening in New Zealand: a pilot prevalence study. Royal Australasian College of Surgeons Annual Scientific Congress Singapore

Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Factors influencing survival following AAA repair- Systematic review & meta-analysis VEITH 41st Symposium 2014 November 2014

Khashram M, Hider PN, Williman JA, Jones GT, Roake JA What Factors influence survival following AAA repair? Vascular Society of New Zealand. February. Dunedin, New Zealand 20th -22nd February 2015.

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DOI: http://dx.doi.org/10.1016/j.jvs.2015.06.045

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8.5.5 Poster presentations

Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Systematic review and meta-analysis of factors influencing survival following abdominal aortic aneurysm repair. International Society for Vascular Surgery. Athens, Greece. 10th – 12th, September 2015.

Khashram M, Gupta A, Osman M, Jones GT, Roake JA. Evaluation of aortic diameters in a population undergoing CT colonography: Prevalence and effect on survival. International Society for Vascular Surgery. Athens, Greece. 10th – 12th, September 2015.

8.6 Published Manuscripts

8.6.1 Prevalence of abdominal aortic aneurysm (AAA) in a population undergoing computed tomography colonography in Canterbury, New Zealand

Eur J Vasc Endovasc Surg (2015) 50, 199–205

Prevalence of Abdominal Aortic Aneurysm (AAA) in a Population Undergoing Computed Tomography Colonography in Canterbury, New Zealand

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WHAT THIS PAPER ADDS
In a previously unscreened population, computed tomography colonography was used as a surrogate for an abdominal ultrasound, at no extra cost or increased risk of radiation, to determine the prevalence of abdominal aortic aneurysm (AAA). The prevalence of AAA in men was similar to that in published randomised AAA screening trials. Knowledge of contemporary AAA prevalence in women and octogenarians—two groups that have not been included in screening programmes—is extended. The data presented highlight the high prevalence of AAA, particularly in the elderly, and the challenges that health services might encounter from the AAA burden.

Objective/Background: There is compelling level 1 evidence in support of screening men for abdominal aortic aneurysm (AAA) to reduce AAA mortality. However, New Zealand (NZ) lacks data on AAA prevalence, and national screening has not been implemented. The aim of this study was to determine the prevalence of AAA in a population undergoing a computed tomography colonography (CTC) for gastrointestinal symptoms.
Methods: This was an observational study; all consecutive CTCs performed in three regions of the South Island of NZ over a 4 year period were reviewed. Data on abdominal and thoracic aorta diameters ≥30 mm, and iliac and femoral aneurysms ≥20 mm were recorded. Previous aortic surgical grafts or endovascular stents were also documented. Demographics, survival, and AAA related outcomes were collected and used for analysis.
Results: Included were 4,893 scans on 4,644 patients (1,933 men [41.6%], 2,711 women [58.4%]) with a median age of 69.3 years (range 17.0–97.0 years). There were 309 scans on 289 patients (75.4% men) who had either an aneurysm or a previous aortic graft with a median age of 79.6 years (range 57.0–96.0 years). Of these, 223 had a native AAA ≥30 mm. The prevalence of AAA rose with age from 1.3% in men aged 55–64 years, to 9.1% in 65–74 year olds, 16.8% in 75–84 year olds, and 22.0% in ≥85 year olds. The corresponding figures in women were 0.4%, 2%, 3.9%, and 6.2%, respectively.
Conclusion: In this observational study, the prevalence of AAA was high and warrants further evaluation. The results acquired help to define a population that may benefit from a national AAA screening programme.

Article history: Received 26 January 2015, Accepted 20 April 2015, Available online 11 June 2015
Keywords: Abdominal aortic aneurysm, CT colonography, New Zealand, Prevalence, Screening

INTRODUCTION

Abdominal aortic aneurysm (AAA) screening using an abdominal ultrasound (US) has been shown to reduce AAA mortality in asymptomatic men over the age of 65 years.[1] The uptake of national screening programmes has been slow for several reasons, including changing epidemiology,[2,3] lack of funding or awareness, and varying AAA prevalence among different populations and ethnicities. In New Zealand (NZ), the true prevalence of AAA is unknown and detection still relies on incidental findings from radiological modalities and referrals from other physicians. The global AAA burden has changed between 1990 and 2010. However, the incidence of AAA has been highest in Australasia, despite a decrease in trends in NZ.[4]

In Canterbury, NZ, a pathway to triage patients with gastrointestinal (GI) symptoms was introduced in 2008. Depending on clinical symptoms, physical examination findings, family history, and laboratory results, a high score directs referrals to an endoscopic colonoscopy, while a low score directs referrals to a computed tomography

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http://dx.doi.org/10.1016/j.ejvs.2015.04.023

colonography (CTC) first approach.[5] Owing to constraints on the public health system in providing colonoscopy for symptomatic patients, the use of CTC for the detection of colorectal diseases and colonic surveillance has gained popularity in NZ as an alternative to optical colonoscopy. It has also been used when colonoscopy could not be completed and in the surveillance of colonic diseases. A CTC (also referred to as "virtual colonoscopy") is a non-invasive, low dose CT that assesses the entire colon by inflating air via the rectum to allow distension of the colon and visualisation of colonic pathology. Other potential advantages of CTC include visualisation of extra-colonic pathologies such as AAA at no additional cost or radiation risk. CT also permits assessment of the entire aorta (usually the descending thoracic aorta to femoral bifurcation) and precise measurement of the aortic wall without hindrance from bowel gas or obesity.

Previous model studies revealed that dual screening for colorectal cancer (CRC) and AAA using CTC was more cost effective in a hypothetical population when compared with optical colonoscopy and an abdominal aortic US.[6,7] While randomised trials of AAA screening used US to measure the abdominal aorta, in the absence of a national US screening programme, the aim of this study was to use CTC as a surrogate for US to document the prevalence of AAA in a population undergoing CTC for GI symptoms.

METHODS

This was a retrospective observational study. From 1 January 2009 to 1 April 2013 all consecutive CTCs performed in the Canterbury, West Coast, and Timaru regions of South Island, NZ, were retrieved from the picture archiving computer system (PACS) database. The retrospective nature of the study precluded individual patient consent. The study was approved by the national Health and Disability Ethics Committee.

The CTC examination was performed at seven different centres with similar protocols. A rectal or stomal tube was inserted for air inflation; a helical CT with 2.5 mm slices was performed in the prone and supine positions, with a large field of view. Intravenous contrast was used if the diagnosis of malignancy was known, or as indicated clinically. The presence of a distended distal bowel and rectal or stomal tube was confirmed to ensure that the scan was a CTC.

Measurements

The entire available aorta from the series—usually from the descending aorta into the femoral bifurcation—was meticulously assessed. Any dilatation or abnormal change in aortic calibre triggered aortic measurements of the dilated segments. Measurements were performed with a digital magnified view—at eye level to avoid any parallax—using outer wall to outer wall lengths using fine electronic callipers, also ensuring that the line of measurement passed through the centre of the aneurysm.[8] Maximum short axis diameters were recorded to 0.1 mm. The presence of a thoracic and abdominal aorta $\geq$30 mm, iliac and femoral arteries $\geq$20 mm, and a visceral artery $\geq$1.5 mm were recorded. The presence of previous aortic prosthetic grafts or endovascular stent grafts was also documented. All measurements were carried out by the same investigator (M.K.).

Demographical data for all patients, including dates of death, deprivation index, and ethnicity, were obtained from the Ministry of Health's database. Deprivation index was defined as the measure of the socioeconomic status of geographical areas based on 2013 NZ census data, where 1 is least deprived and 10 is most deprived.[9] Clinical risk factors, aneurysm location, colorectal cancer (CRC) diagnosis, and causes of death were collected from patients with aneurysms or previous aortic surgery. CTC radiologist reports were viewed to determine whether the presence of aneurysms was commented on and whether patients were in a AAA surveillance programme. The aneurysm with the largest diameter was defined as the primary aneurysm; other aneurysms detected were referred to as secondary. Estimated predicted life expectancy figures were obtained from the NZ life tables 2010—12 (www.stats.govt.nz) for a fictive population matched to age and sex.[10]

Preliminary analysis indicated that the continuous explanatory variables (age and deprivation) were related to the presence of AAA (binary) on a linear rather than a logarithmic scale; therefore, linear regression models were used to calculate unadjusted and adjusted rate differences.[11] Rate ratios were also calculated for categorical variables using Poisson regression with robust standard errors due to non-convergence of log binomial models.[12] Kaplan—Meier methodology was used for survival analysis, and the log rank test was used for univariate group comparison. The Cox proportional model was used to calculate adjusted and unadjusted hazard ratios (HRs) for variables influencing survival. Survival data were censored on 1 October 2014. Statistical significance and 95% confidence intervals (CIs) were calculated with an alpha of 0.05. Statistical analyses were performed using SPSS 22 for Mac (IBM, Armonk, NY, USA).

RESULTS

During the study period, 4,915 CTC scans were performed on 4,665 patients. Of these scans, 22 were coded on the PACS database as CTC but when the scans were reviewed, the CT was not a CTC or the raw axial images were not stored and were therefore excluded from any further analysis. Hence, 4,893 scans on 4,644 patients (male: female ratio = 1.0: 1.4) and a median age of 69.3 years (range 17.0—97.0 years) were reviewed. Excluded from further analysis were 925 patients aged <55 years old who had no AAA detected. The median age of the remaining 3,719 individuals was 72.9 years (range 55.0—97.4 years). The number of CTC scans performed in the years 2009—12 was 1,039, 1,174, 1,169, and 1,178 scans, respectively.

There were 309 scans on 289 patients who had either an aneurysm in any location or a previous abdominal aortic graft repair. The location of aneurysms and abnormal aortas

Table 1. Number of thoracic/abdominal aneurysms ≥30 mm and iliac/femoral/visceral aneurysms ≥20 mm.

Location	*n*
AAA (native)	223
AAA (graft)[a]	26
Iliac	23
Thoracic	5
Femoral	1
Prosthetic graft[b]	9 (6 open, 3 EVAR)
Visceral	2
Total	289

Note. AAA = abdominal aortic aneurysm; EVAR = endovascular aneurysm repair.
[a] Graft diameter ≥30 mm.
[b] Diameter <3 cm.

detected are summarised in Table 1. Two hundred and fifty eight patients had either a ≥30 mm AAA or an abdominal aortic graft present. Of these, 223 had a native AAA, 26 had either a dilated prosthetic graft or a residual post-endovascular aneurysm repair (EVAR) AAA sac ≥30 mm, and nine had an aortic graft <30 mm. The CTC identified 165 (74%) new incidental AAAs; the remainder had a known AAA on prior imaging. The median age was 79.7 years (range 57.4—96.2 years), 74.4% were men, and 94.2% were NZ Europeans or Europeans. A native AAA in the infrarenal position was the most common site. Demographics and risk factors are presented in Table 2.

The overall prevalence (95% CI) of all AAAs ≥30 mm was 258/3,719 (6.9%; 95% CI 6.1—7.8); after excluding 35 prosthetic AAA grafts, prevalence was 223/3,684 (6.1%; 95% CI 5.3—6.9). The prevalence of native AAA in men and women aged 55.0—64.9, 65.0—74.9, 75.0—84.9, and ≥85.0 years was 1.3%, 9.1%, 16.8%, and 22.0%, and 0.4%, 2.0%, 3.9%, and 6.2% respectively (Fig. 1). The distribution of native AAA diameter according to sex is presented in Fig. 2; 72.2% (161/223) had a 30—39-mm AAA and 10.3% (23/223) had an AAA ≥50 mm.

There was a significant association with having an AAA and advanced age (>55 years), with an increase in prevalence rate of 4% (95% CI 3.0—5.0; $p < .01$) for each 10 year increase. Male sex was also a strong predictor for the presence of AAA, with a rate ratio of 4.08 (95% CI 3.1—5.4; $p < .01$). In this model, deprivation indices and ethnicity were not significant predictors of AAA presence (Table 3).

Of the 223 patients with native AAA, 23 (10.3%) had an AAA ≥50 mm, and 12 had subsequently undergone AAA repair (nine open repair and three EVAR) during the follow up period. Nine patients were thought not to benefit from repair: five owing to medical comorbidities (primarily cognitive impairment), and four owing to suprarenal extension of the aneurysm who were deemed unfit for complex procedures. Two patients were on surveillance (AAA < 55 mm). In all, 13 (56.5%) of those participants with an AAA >50 mm were still alive at study completion. Six died without repair, three died post-repair (>30 days post-operatively), and one died of an AAA rupture without repair.

The median follow up period was 3.16 years (interquartile range 1.23 years). Fig. 3 shows the Kaplan—Meier

Table 2. Demographics and baseline characteristics of patients ($n = 223$) with abdominal aortic aneurysms (AAAs).

Median age, y (range)	79.7 (57.4—96.2)
Men	166 (74.4)
Ethnicity	
NZ European/European	210 (94.2)
Maori	4 (1.8)
Other/unknown	9 (4.0)
Median AAA diameter, cm (range)	3.3 (3.0—9.4)
AAA neck location	
Infrarenal	203 (91.0)
Juxtarenal	14 (6.3)
Suprarenal	6 (2.7)
IHD[a]	113 (50.7)
Statin[a]	139 (62.3)
Hypertension[a]	195 (87.4)
COPD[a]	51 (22.9)
Creatinine (mean ± SD)	106.7 ± 34.6
Diabetes[a]	43 (19.3)
Colorectal cancer	19 (8.5)
Smoking[b]	
Never	49 (22.3)
Ex-smoker	137 (62.6)
Current	33 (15.1)
Deprivation index	
1—2 (better SES)	30 (13.5)
3—4	36 (16.1)
5—6	46 (20.6)
7—8	91 (40.8)
9—10 (worse SES)	21 (9.4)
AAA in surveillance	84 (37.6)
Secondary aneurysm	20 (9.0)
AAA reported	158 (70.9)

Note. Data are given as *n* (%) unless otherwise indicated. NZ = New Zealand; IHD = ischaemic heart disease; COPD = chronic obstructive pulmonary disease; SES = socioeconomic status.
[a] One missing patient.
[b] Four missing patients.

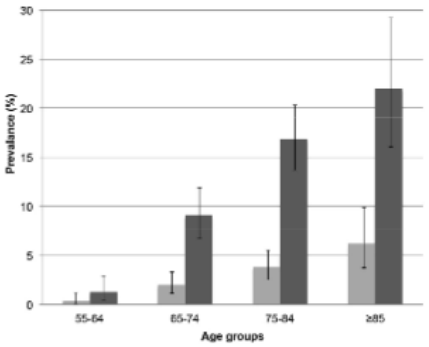

Figure 1. Prevalance of abdominal aortic aneurysm stratified to age bracket and sex ($n = 233$) with 95% confidence intervals (light grey bars indicate women; dark grey bars indicate men).

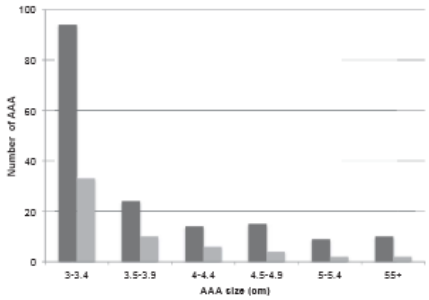

Figure 2. Distribution of abdominal aortic aneurysm (AAA) size stratified to sex ($n = 223$). Light grey bars indicate women; dark grey bars indicate men.

survival curves for the study participants with AAA compared with those without AAA. The 5 year observed survival (SE) of those with AAAs was 55.1% (5.0) compared with 77.4% (0.9) in those without AAA (log rank $p < .01$). When adjusting for age and sex, the presence of AAA did not influence late survival (HR 1.24, 95% CI 0.97—1.58; $p < 0.09$) (Table 4). There were 78 deaths in the AAA group; the causes of death during the study period were unknown causes ($n = 25$), cardiovascular ($n = 19$), cancer related ($n = 14$), respiratory ($n = 11$), multi-organ failure ($n = 5$), sepsis ($n = 2$) and AAA rupture ($n = 2$; both women, with AAA diameters of 38 and 94 mm, respectively). For comparison, estimated predicted life expectancy figures from the NZ life tables 2010—12 were also plotted on Fig. 3 .

DISCUSSION

In this study, the prevalence of AAA in patients undergoing investigation with CTC in South Island, NZ, was estimated. The prevalence of AAAs in men aged ≥55 years of 6.1% is similar to that found in a randomised controlled screening trial conducted in Australia approximately 10 years ago.

This study specifically aimed to use CTC to determine AAA prevalence. Previous studies reporting extra-colonic findings from CTC varied with respect to AAA prevalence, ranging from 1.4% to 5.0%, despite the similar demographics of the groups included.[13—15] In contrast to previous studies, which did not focus primarily on the status of the abdominal aorta, the current study represents the largest series to date to detect AAAs specifically within a CTC patient cohort.

In NZ, prior to a recent study, the prevalence of AAA in the population was unknown. In the study by Majeed et al.,[16] 10,403 patients undergoing a transoesophageal echo were also examined for the presence of AAA. In men aged 65—74 years the prevalence of AAA was 4.7%, rising to 8.5% in those aged 75—84 years.[16] In the present study, CTC was associated with similar age group specific AAA prevalence rates to that of those undergoing echocardiography. Although increased AAA prevalence has been reported in association with severe (angiographically confirmed) coronary artery disease,[17] the large proportion of angiographically normal patients under evaluation for valvular disease in an "echo cohort" would most likely mask a coronary disease driven prevalance effect. In addition, some of the differences between the echo studied population might be due to differences in AAA measurement between CT and US. Nevertheless, both studies highlight the burden of AAA in NZ.

Table 3. Predictors of abdominal aortic aneurysm presence using a linear regression model.

Continuous variables	Unadjusted				Adjusted[a]		
	Median (IQR)	Rate difference (%)	95% CI	*p*	Rate difference (%)	95% CI	*p*
Age (y)	79.7 (10.3)	4.0	3.0—5.0	<.01	4.0	3.0—5.0	<.01
Deprivation index	6.0 (5.0)	0.3	0—0.6	.08	0.2	−0.1 to 0.5	.20
Categorical variables	*n* (%)	Rate ratio	95% CI	*p*	Rate ratio	95% CI	*p*
Age (y)							
55—64	7.0 (0.7)	1 (ref.)	—	—	1 (ref.)	—	—
65—74	59.0 (5.0)	6.69	3.07—14.57	<.01	6.75	3.11—14.64	<.01
75—84	123.0 (9.2)	12.47	5.84—26.65	<.01	12.29	5.77—26.18	<.01
85—94	48.0 (11.9)	16.08	7.34—35.23	<.01	16.71	7.64—36.51	<.01
Sex							
Male	166.0 (10.7)	4.06	3.03—5.45	<.01	4.08	3.05—5.46	<.01
Female	57.0 (2.6)	1 (ref.)	—	—	1 (ref.)	—	—
Deprivation index							
1—5	91 (5.1)	1 (ref.)	—	—	1 (ref.)	—	—
6—10	132 (6.9)	1.35	1.04—1.75	.02	1.25	0.97—1.61	.08
Ethnicity							
NZ European	210 (6.1)	1 (ref.)	—	—		—	—
Maori	4 (5.1)	0.83	0.32—2.18	.55	1.45	0.55—3.84	.64
Other and unknown	9 (4.8)	0.79	0.41—1.51	.51	.87	0.46—1.66	.82

Note. IQR = interquartile range; CI = confidence interval; NZ = New Zealand.
[a] Adjusted for other variables in the model.

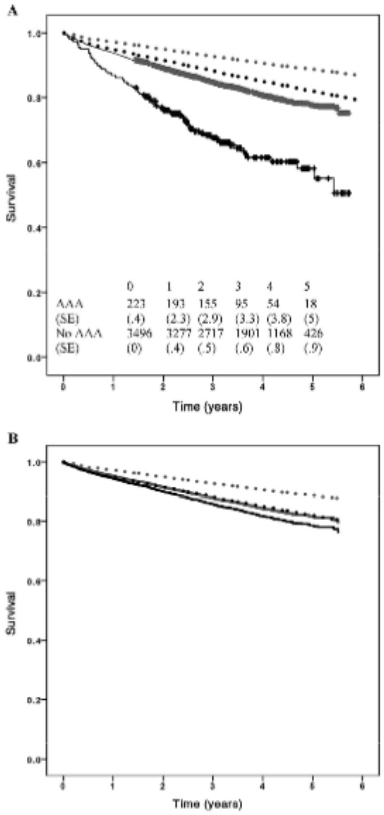

Figure 3. (A) Kaplan—Meier observed (solid) and expected (dotted) survival curves of patients with an abdominal aortic aneurysm (AAA; black line) and without an AAA (grey line). Log rank of observed survival $p < .01$. (B) Cox proportional hazard of adjusted (age and sex) survival with dotted expected survival curves (hazard ratio 1.24; $p < .09$).

A systematic review and meta-analysis of 14 AAA screening population studies revealed a prevalence range of 4.2—14.2% in men and 0.35—6.2% in women.[18] The estimated prevalence in the current study is similar to previous population studies. In the present study, 942 patients, of whom 554 (58.8%) were women, were >80 years of age. This particular group has not been previously included in the screening trials. This study has therefore extended the knowledge of AAA prevalence in octogenarians, a group with an improved life expectancy that has not been included in AAA population studies. It is expected, given that the prevalence of AAA increases with age, that more people will require management in terms of risk factor modification, decisions surrounding screening and surveillance, and counselling family members for AAA screening.

Variations with international AAA screening programmes differ with respect to the targeted population, interval of surveillance scans, and size prior to consideration for surgical treatment.[19] The epidemiology of AAA is changing globally, with a decrease in AAA mortality observed in countries such as England, Australia, and NZ, whereas an increase in mortality has been reported in Hungary, Denmark, Austria, and Romania.[20] Despite a lower AAA prevalence reported from Sweden and England, screening for AAA remains cost-effective.[21]

Variations in diameter measurements between CT and US have been reported, with CT measurements giving a larger diameter and that this might not represent the "true" maximal difference.[22] During an US measurement, the transducer can be tilted to measure a true diameter, even in the presence of aortic tortuosity. However, the cardiac cycle phase during a CT is unknown and is not routinely controlled for. The use of CT to measure an AAA might lead to underestimation of AAA size owing to the unknown phase of the cardiac cycle. US measurements carry a 1.9 mm average difference between systolic and diastolic peak recordings.[23]

It is unclear whether the study population is truly representative of the general South Island, NZ, population. A direct "cause and effect" between colorectal cancer (CRC) and AAA prevalence has not been established; however, it has been estimated that approximately 0.3—3.8% of AAAs will have a concomitant CRC present at the time of the diagnosis.[24] CRC and AAA share some risk factors such as smoking, age, and male sex. Cardiovascular risk factors for those without an AAA and the prevalence of CRC were not available to allow such analysis.

CT was used for AAA diagnosis, whereas the randomised screening studies used US and in some a targeted AAA US scan was used. The advantage of CT for screening AAA was noted in this study with the detection of 23 isolated iliac aneurysms, five thoracic aneurysms, two visceral aneurysms, and late graft complications following AAA repair. A study from a Veterans Affairs centre, where dedicated vascular technicians included the iliac arteries in AAA screening US scans, detected 0.1% of isolated iliac aneurysms.[25] The results of the present study revealed an isolated iliac aneurysm in 23/3,719 (0.6%) patients undergoing CTC.

Survival following elective AAA repair is lower than the expected survival of the age and sex matched population,[26] and the presence of an AAA is an independent predictor of decreased survival. Previous studies have reported that non-AAA related deaths are more common in patients undergoing small AAA surveillance than AAA related deaths.[27] The current study is consistent with these observations, with the leading causes of death among patients

Table 4. Cox proportional model of variables affecting late survival.

Variable	Unadjusted			Adjusted[a]		
	HR	95% CI	*p*	HR	95% CI	*p*
Age per decade	2.46	2.25–2.69	<.01	2.46	2.25–2.7	<.01
Sex (female)	0.61	0.53–0.71	<.01	0.59	0.51–0.69	<.01
Presence of AAA	2.28	1.8–2.88	<.01	1.24	0.97–1.58	.08
Deprivation index	1.02	0.99–1.06	.16	1.00	0.97–1.03	.83
Ethnicity						
NZ European	Ref.	–	–	Ref.	–	–
Maori	0.82	0.46–1.45	.49	1.35	0.76–2.4	.30
Other and unknown	0.52	0.33–0.82	.01	0.66	0.42–1.04	.07

Note. HR = hazard ratio; CI = confidence interval; AAA = abdominal aortic aneurysm; NZ = New Zealand.
[a] Adjusted for other variables in the model.

undergoing CTC with AAA being cardiovascular and oncological conditions.

Of the 4,644 patients identified in this study, 65 (1.4%) of the AAAs detected did not have a formal diagnosis, nor was the presence of an AAA noted during the CTC reporting process. Such under-reporting of incidental AAA has been observed previously in 4,112 patients undergoing CT, of whom 53 (1.3%) did not have the aortic dilatation recognised or reported.[28] Based on these findings, it is recommended that the abdominal aorta should be specifically screened for an AAA when people undergo abdominal CT scans, particularly those over the age of 55 years.

Limitations of this study were the retrospective collection of clinical risk factors, and that the population selected might not represent the true population as seen with lower observed survival than expected from the total population. In addition, some of the patients might have a reduced life expectancy owing to a diagnosis of CRC. However, this population sought medical attention for symptoms or clinical concerns, which is different from invited participants included in screening studies. This was also reflected by a representative sample from all socioeconomic groups. It is widely accepted that people with lower socioeconomic status and from more deprived areas have low compliance with AAA screening.[29]

In conclusion, the prevalence of AAA in a population undergoing CTC for GI symptoms in South Island, NZ, is high and warrants further evaluation, despite the relatively lower percentage of men included. The results of this observational study seem to support a national AAA screening programme.

ACKNOWLEDGEMENTS

We thank Jonathan Williman for his statistical advice and support during the study.

CONFLICT OF INTEREST

None.

FUNDING

None.

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8.6.2 Abdominal aortic aneurysm repair in New Zealand: a validation of the Australasian Vascular Audit. ANZ journal of surgery

ORIGINAL ARTICLE

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Abdominal aortic aneurysm repair in New Zealand: a validation of the Australasian Vascular Audit

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Key words
abdominal aortic aneurysm, Australasian Vascular Audit, surgical audit.

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This study was presented at the Vascular Society of New Zealand meeting on 20 February 2016.

Accepted for publication 23 June 2016.

doi: 10.1111/ans.13702

Abstract

Background: In New Zealand (NZ), there are two major sources of operative data for abdominal aortic aneurysm (AAA) repair: the Australasian Vascular Audit (AVA) and the National Minimum Data Set (NMDS). Since the introduction of the AVA in NZ, there has not been any attempt at the validation of outcome data. The aims of this study were to report the outcomes of AAA repair and validate the AAA data captured by AVA using the NMDS.

Methods: AAA procedures performed in NZ from January 2010 to December 2014 were extracted from the AVA and NMDS. Patients identified from the AVA had their survival status matched to the NMDS. Only primary AAA procedures were included for the analysis, with re-interventions and graft infections excluded. Demographical, risk factors and outcome data were used for validation.

Results: The number of patients undergoing primary AAA procedure from AVA and NMDS was 1713 and 2078, respectively. The AVA inpatient mortality for elective and rupture AAA was 1.6 and 32.2%, respectively. The NMDS 30-day mortality from AAA was 2.5 and 31.5%. Overall, 1604 patients were available for matching, and the NMDS correctly reported 98.1% of endovascular aneurysm repair and 94.2% of elective AAA repairs; however, there were major differences in comorbidity reporting between the data sets.

Conclusion: Both data sets were incomplete, but combining administrative (NMDS) and clinical (AVA) data sets provided a more accurate assessment of mortality figures. More than 80% of AAA repairs are captured by AVA, but further work to improve compliance and comorbidity documentation is required.

Introduction

Clinical governance and accountability requires that operative outcome data is now routinely collected by national health bodies. The majority of surgical units are also required to collect their own data for reporting, audit and research purposes.

Broadly, there are two types of data sources: administrative and clinical. The accuracy and reliability of each is an important issue, and surgeons need to understand the differences between them. The main purpose of each data set differs, and therefore, the variables recorded, the quality and accuracy are likely to differ.[1]

Surgeons and health policy decision makers rely on end outcomes such as 30-day or 1-year mortality for reporting outcomes. This relatively simple measure can differ depending on the data source. Specifically with cases of abdominal aortic aneurysm (AAA), there is documented variation in 30-day mortality figures for elective repairs depending on the source of the data: prospective population-based reported 8.2% compared to 3.8% from prospective hospital-based.[2]

The Australasian Vascular Audit (AVA) is a bi-national web-based audit and is the official audit for the Australian and New Zealand Society of Vascular Surgery.[3] It collects demographical data, risk factors, operative details and outcomes for all inpatient events on vascular patients. Data entry was commenced in January 2010 with gradual uptake from the majority of vascular units at both private and public hospitals in New Zealand (NZ) and has replaced several individual hospital databases and the Otago Clinical Audit from that date. Since 2012, it has been compulsory

for vascular surgery trainees to use AVA to generate their operative logbook.

Understanding the quality and accuracy of data captured by the AVA is important as this audit can provide a useful record of AAA repair. Recently, data quality from Australia submitted to the AVA was subjected to internal validation using a random 5% of major arterial cases, and a reported error rate of 2.6% was found. With regards to external validation, the AVA in Australia captures 63% of the data in the public sector and only 51.6% in the private sector.[4]

The NZ outcome data submitted to the AVA have not been subjected to any form of validation since its introduction. Furthermore, there are very few published contemporary studies of AAA repair outcomes in NZ; the most recent published information reported a 30-day mortality of 6.7% for elective AAA repaired between 2002 and 2006.[5] It is unknown whether this figure included endovascular aneurysm repair (EVAR) or symptomatic but non-rupture AAA. In addition, this figure is considered relatively high compared to contemporary figures, and greater reliance on EVAR in recent practice is likely to have reduced overall operative mortality rates following elective AAA repair.[6]

Therefore, the aim of this study was to validate the quality and accuracy of demographic and outcome AAA repair data recorded on the AVA using the Ministry of Health National Administrative Data set.

Methods

The Health and Disability Ethics Committee approved this observational study and the obtaining of data from the Ministry of Health National Minimum Data Set (NMDS) for matching purposes. Written individual patient consent was not possible due to the nature of the study design.

Data sources

National Minimum Data Set

In NZ, each patient has a unique seven-digit National Health Index (NHI) that allows matching. A data request enquiry was made for all International Classification of Diseases (ICD)-10 AAA diagnostic codes and procedures from 1 January 2010 to 31 December 2014 (Appendix S1). Patient demographics of up to 20 comorbidity diagnoses and 20 procedures were provided for each hospital encounter. Following this, a data set of unique patients that had a diagnosis of AAA and an AAA-related procedure was developed to represent the number of primary AAA procedures performed.

Australasian Vascular Audit

Between 1 January 2010 and 31 December 2014, all AAA procedures identified from the AVA were obtained. Duplicate patients and secondary procedures were removed, and the primary AAA procedure was considered the index case. The database was checked for procedures performed for graft infections, mycotic aneurysms, isolated iliac aneurysms, EVAR conversions and all re-interventions, and these were excluded from analysis and matching (Fig. S1). Of the NHI identified, all except one was matched with the NMDS database, and three additional fields were returned and added into the AVA data set: ethnicity, deprivation from the 2013 census data and date of death for patients that died and were registered in NZ.

Definitions

Risk factors were defined as outlined in the AVA manual. Inpatient mortality as recorded in the AVA was defined as a death occurring while under the vascular team or if the death occurred in the same hospital admission. The NZ deprivation index is a measure of the level of socioeconomic status (SES) and is measured on a scale from 1 to 10, where 1 is least deprived (better SES) and 10 is the most deprived (worse SES). For the purposes of the validation, it was assumed that demographical and survival status was correctly coded in NMDS, and clinical risk factors and operative details were correctly recorded in the AVA. Hospital volume was categorized into two groups: individual hospitals performing >10% of total AAA repair and individual hospitals performing <10%.

The following information was used for data validation: patient demographics (age and gender), date of admission, length of hospital stay, mode of presentation (acute/arranged) and risk factors (ischaemic heart disease (IHD), diabetes, smoking history and hypertension). For admission dates and dates of birth differences $>\pm 1$ day, a manual check across the data sets was performed to ensure that procedures matched.

Statistical analysis

The first 5 years of AVA capture with a minimum 1-year follow-up was chosen as the study duration and follow-up period, respectively. Data validation, cleaning and initial coding was carried out on Microsoft Excel (Microsoft, Redmond, WA, USA), and statistical analyses were performed using SPSS 23 for Mac (SPSS Inc, Chicago, IL, USA). Odds ratio (OR) and 95% confidence intervals (CI) of comorbidities recorded by NMDS compared with AVA data were analysed, and a P-value of <0.05 was considered statistically significant.

Results

During the 5-year period, 1804 AAA procedures were recorded, and following data cleaning and applying the inclusion criteria, 1713 patients were included in the analysis from AVA. There were 6690 hospital encounters in the NMDS, and after removal of duplicates and identifying patients diagnosed with an AAA and had an AAA-related procedure, 2078 patients were included. The overall number of AAA repairs stratified to type of presentation over the years is presented in Figure 1. On average, AVA captured 82.4% of the AAA diagnosis and procedures identified by the NMDS during the 5-year period. Between 2012 and 2014, the AVA capture rate increased to 87.9%. The trend of AAA presentation by method of repair is shown in Figure S2.

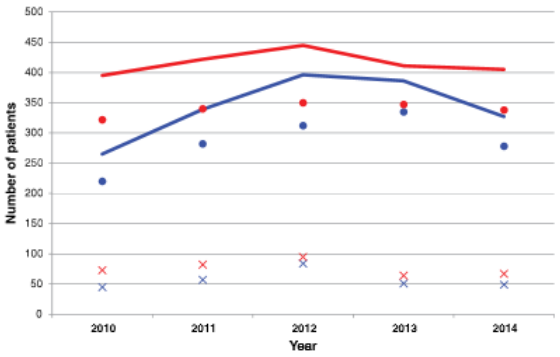

Fig. 1. Comparison of abdominal aortic aneurysm (AAA) repairs stratified into type of repair between the Australasian Vascular Audit (AVA) and the Ministry of Health (MOH) National Minimum Data Set (NMDS) during the study period. —, AVA total; —, MOH total; ●, AVA elective; ●, MOH elective; ×, AVA rupture; ×, MOH rupture.

AVA summary

AVA reported 1713 patients who underwent AAA repair: 1220 (71.2%) elective, 207 (12.1%) symptomatic and 286 (16.7%) ruptures. Of the patients who underwent elective repair, 677 (55.5%) had an EVAR. The baseline demographics, comorbidities and operative details of the AVA patients are presented in Table 1. There were no missing risk factors or AAA diameter data as these are mandated fields in AVA data capture.

AAA repair outcomes

There were 121 deaths recorded on the AVA. Following matching and verification with the NMDS, an additional six inpatient deaths were discovered but not recorded on AVA: one elective and five ruptured AAA. The overall 30-day mortality obtained from the NMDS was 134/1713 (7.8%): seven patients died between discharge and 30 days after operation (four elective, two symptomatic and one rupture). Mortality stratified for type of repair and presentation is presented in Table 2. The overall 30-day mortality for AVA cases was 2.0% for elective, 5.3% for symptomatic and 34.3% for ruptures. Of the 2078 patients from the NMDS during the study period, the 30-day mortality for non-ruptured and ruptured AAA was 2.5 and 31.5%, respectively.

Data matching and validation

Of the 1713 patients from the AVA, 1604 matched the hospital episode recorded in the NMDS (93.6%). There were 109 patients that could not be matched, of which 80 patients had an AAA repair at a private hospital, 11 had an AAA repair but were not recorded as an AAA repair or diagnosis in the NMDS, and 18 patients were found on the NMDS, but the AAA encounter did not match the AVA data.

Of the recorded patients who underwent repair in the private sector, 97 patients were recorded in the AVA. There were 57 patients who underwent open aneurysm repair, and 40 patients underwent EVAR with no 30-day mortality observed.

AVA comparison with NMDS data

There were some demographic data errors identified in the AVA. Thirty-nine patients (2.4%) had an incorrect date of birth (error of greater than ±2 days) recorded, and 14 (0.9%) patients had

Table 1 Demographics and baseline characteristics of the 1714 patients from AVA

	Number (%)
Age* (median, range)	75 (34–93)
Males*	1389 (79.9)
Ethnicity	
NZ European	1496 (87.3)
Maori	122 (7.1)
Pacific Islanders	40 (2.3)
Other/unknown	55 (3.2)
Deprivation status†	
1–2 (least deprived)	216 (12.6)
3–4	277 (16.2)
5–6	402 (23.5)
7–8	433 (35.3)
9–10 (most deprived)	374 (21.8)
AAA presentation	
Elective	1220 (71.2)
Symptomatic but non-ruptured	207 (12.1)
Rupture	286 (16.7)
IHD	824 (48.1)
Renal impairment	172 (10.0)
Diabetes	198 (11.6)
Hypertension	1333 (77.8)
Smoking status	
Never	535 (31.2)
Ex-smoker	935 (54.6)
Current	243 (14.2)
AAA diameter (median, range)	6.0 cm (3–13.5)
EVAR	778 (45.4)
Length of hospital stay (median, IQR)	
EVAR	5 (4–7)
OAR	9 (7–14)
Private hospitals	97 (5.7)
High-volume hospitals	1177 (68.7)

*Corrected demographics from NMDS. †Missing 11 patients. AAA, abdominal aortic aneurysm; AVA, Australasian Vascular Audit; EVAR, endovascular aneurysm repair; IHD, ischaemic heart disease; IQR, interquartile range; NZ, New Zealand; OAR, open aneurysm repair.

Table 2 Operative mortality stratified into type of repair and presentation from the AVA and NMDS returns

	Elective 1220	Symptomatic 207	Rupture 286
OAR	19/543 (3.5%)	10/135 (7.4%)	92/257 (35.8%)
EVAR	6/677 (0.9%)	1/72 (1.4%)	6/29 (20.7%)
Total (AVA 30 day from NMDS)	25/1220 (2.0%)	11/207 (5.3%)	98/286 (34.3%)
IP deaths from AVA (verified from NMDS)	21/1220 (1.7%)	9/207 (4.3%)	97/286 (33.9%)
IP deaths recorded on AVA	20/1220 (1.6%)	9/207 (4.3%)	92/286 (32.2%)

AVA, Australasian Vascular Audit; EVAR, endovascular aneurysm repair; IP, inpatient; NMDS, National Minimum Data Set; OAR, open aneurysm repair. IP deaths as defined by AVA (discharged from AVA).

incorrect gender identification. Admission date and length of stay details (error of greater than ±2 days) were incorrect in 33 (2.1%) and 113 (7.0%) patients, respectively.

The NMDS correctly identified 98.1% of the patients as an EVAR and 94.2% as an elective (arranged) admission. Of the comorbidities cross-checked, there was major underreporting in the presence of IHD and hypertension in the NMDS compared to the AVA. The proportion of patients with a smoking history was similar between the two data sets, but there was a 32.8% lack of concordance between them, OR 1.56 (95% CI: 1.34–1.83) $P < 0.001$. The presence of diabetes, however, was more consistently recorded in both databases (Table 3).

Discussion

In this study, by interrogating both the national data set and the vascular surgery audit, we were able to provide accurate 30-day outcomes, describe the national burden of AAA on health services and present sources of error. Both data sets were incomplete but the early mortality was similar. Regulatory bodies are very likely to use the most accessible data rather than the 'best' available data when policy decisions are made; therefore, understanding the limitations of each data set is important.

In NZ, the viability of screening for AAA is being investigated, and being able to provide an accurate estimate of local figures is important. The change of AAA epidemiology and the relatively lower early mortality achieved nowadays can alter the clinical decision making for AAA management in comparison to evidence-based norms established two decades ago.[7]

The mortality rates for AAA repairs from both data sets were very similar, and the results compare favourably with reported contemporary international elective AAA repair figures.[6] However, differences between the two data sets might be attributable to the unclassified diagnosis of 'symptomatic' but non-rupture AAA, which occurred in about 12% of AAA presentations. The majority of private AAA procedures performed were not found on the NMDS. Therefore, the total number of repairs performed in the private sector is unknown. Excluding private AAA repairs from national figures could also partially account for the 0.5% increase in mortality reported in the NMDS.

This type of validation study has been assessed in other studies in different geographical settings. Several similar studies linking administrative and clinical databases have been conducted in the UK, and conflicting results have been reported. Holt *et al.* compared 1102 elective AAA patients from the English Hospital Episode statistics with clinical case records, and 86% of the cases were confirmed as an elective AAA repair.[8] Johal *et al.* reported that of patients undergoing AAA replacement, the diagnosis of AAA was consistent in >90%.[9] However, a study from Scotland highlighted that such a discrepancy between clinical and national data can lead to a significant reduction in reported mortality from national figures.[10] Our results were similar to these studies, but including both data sets allowed us to present more accurate outcome data.

As with the majority of databases, the quality and accuracy of data depend on those entering data. There has been a gradual uptake of AVA usage in some NZ vascular units and among surgeons; hence, the low capture in the first 2 years can be expected.

Table 3 Validation of 1604 verified patients between the NMDS and the AVA

	NMDS (%)	AVA (%)	Discrepancy (%)	Odds ratio* (95% CI)	*P*-value
Males	1278 (79.7)	1284 (80.0)	14 patients	0.98 (0.82–1.16)	0.79
Age, mean (SD)	74.3 (7.8)	74.2 (8.2)	39 patients†	—	0.72‡
Date of admission	—	—	33 patients§	—	—
Length of stay, median (IQR)	6 (4–10)	6 (3.8–10)	113 patients¶	—	—
IHD	161 (10.0)	774 (48.3)	687 (42.9)	0.12 (0.10–0.14)	<0.001
Diabetes	198 (12.3)	187 (11.7)	148 (9.2)	1.07 (0.86–1.32)	0.55
Hypertension	563 (35.1)	1236 (77.1)	829 (51.7)	0.16 (0.14–0.19)	<0.001
Smoking history	1241 (77.4)	1100 (68.6)	514 (32.8)	1.56 (1.34–1.83)	<0.001
Admission type (elective/non-acute)	1117 (69.6)	1124 (70.1)	93 (5.8)	0.98 (0.84–1.14)	0.79
EVAR	745 (46.4)	737 (45.9)	30 (1.9)	1.02 (0.89–1.17)	0.77

*Odds ratio of data recorded by NMDS compared with AVA data. †(> ±2 days), range difference: (–5330 to 31 047) days. ‡*T*-test. §(> ±2 days), range difference: (–173 to 590) days. ¶(> ±2 days), range difference: (–39 to 365) days, excluding 31 non-discharged patients. AVA, Australasian Vascular Audit; CI, confidence interval; EVAR, endovascular aneurysm repair; IHD, ischaemic heart disease; IQR, interquartile range; NMDS, National Minimum Data Set.

In Australia, the AVA compliance dropped by about 10% in 2013.[4] In NZ, data compliance in 2014 decreased without a notable systematic reason. Continued auditing of the AVA data requires future monitoring and improvement.

With regards to the comorbidities comparison, where there was a wide range of definitions, large differences were observed (such as in hypertension and IHD), resulting in high discrepancy rates, whereas with comorbidities with a clearer definition (such as the presence of diabetes), the differences were smaller. The consistency of diabetes coding has been also been shown in a similar study.[8] This might be due to the coding nature of diabetes that coders are well trained to enter from case and discharge notes.

Strengths and limitations

The relatively large patient number during the study period to represent the vascular surgeon workload for AAA disease is of high importance to governing bodies. For this reason, we decided to include all AAA repairs (complex and standard) to provide realistic estimates of mortality and increase the generalizability of these figures that would more accurately reflect contemporary clinical practice.

The AVA webpage form is currently not linked to hospital coding software, and therefore, human typing errors are very likely to occur, particularly in the demographics section of the free typing, that is, date of birth and gender. These errors could potentially be avoided by amalgamating existing software platforms. However, with numerous different software used in each institution it is unlikely that this will occur.

Some important prognostic information such as AAA diameter and renal impairment could not be verified as these variables are not recorded on the NMDS. In addition, the timing of data entry into the AVA with respect to the admission details was not available. Further work to determine if such delays in data entry might lead to a source of error is of merit.

Information on aspirin and statin use is not collected in the AVA; given the importance of risk factor modification, inclusion of such variables would be useful in auditing and model development. Other recorded data such as hypertension is not considered to be a significant risk factor *per se*, but rather whether it is treated or not. Hence, routine collection of 'hypertension' is perhaps no longer an important comorbidity for mortality prediction. Respiratory disease and cardiac failure have greater impact on short- and long-term outcomes, and inclusion into the data requirement might better inform risk models and decision making.[11]

Conclusions

Both AAA data sets were incomplete, but this analysis has allowed us to understand the differences. The AVA captures more than 82% of AAA repairs performed in NZ. Matching clinical databases and national administrative data sets provides a better representation of absolute national workload, provides accurate survival status and increases the utility of a single data set to reflect real-world outcomes.

Acknowledgements

Manar Khashram is a PhD candidate supported by the Foundation for Surgery New Zealand Research Scholarship. The authors acknowledge the Analytical Services at the Ministry of Health, New Zealand for providing the data extracts used for analysis in this study and Mr Ziad Khashram for data preparation and presentation. We thank all the vascular surgeons and vascular trainees who have contributed their time and effort in submitting data into the AVA particularly the following vascular surgeons: A. Hill, S. Caldwell, P. Haggart and R. Evans for assisting with data retrieval.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. ICD codes used for data extraction from the NMDS.
Fig. S1. Flow diagram of data synthesis and validation.
Fig. S2. Trends of AAA repair by presentation and method of repair.

8.6.3 Systematic Review and Meta-analysis of Factors Influencing Survival Following Abdominal Aortic Aneurysm Repair

Eur J Vasc Endovasc Surg (2016) 51, 203–215

REVIEW

Systematic Review and Meta-analysis of Factors Influencing Survival Following Abdominal Aortic Aneurysm Repair

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WHAT THIS PAPER ADDS?
Predicting late survival before elective abdominal aortic aneurysm (AAA) repair remains the Achilles heel of AAA management. Models predicting 30 day mortality are well established but determining late survival is not fully understood. This systematic review reports the determinants of late survival following open and endovascular AAA repair and suggests significant factors that influence late survival. The need for standardisation in current reporting of AAA survival data has been highlighted. Knowledge and quantification of such factors may assist in clinical decision making when assessment surrounding AAA management is made.

Background: Predicting long-term survival following repair is essential to clinical decision making when offering abdominal aortic aneurysm (AAA) treatment. A systematic review and a meta-analysis of pre-operative non-modifiable prognostic risk factors influencing patient survival following elective open AAA repair (OAR) and endovascular aneurysm repair (EVAR) was performed.
Methods: MEDLINE, Embase and Cochrane electronic databases were searched to identify all relevant articles reporting risk factors influencing long-term survival ($\geq$1 year) following OAR and EVAR, published up to April 2015. Studies with $<$100 patients and those involving primarily ruptured AAA, complex repairs (supra celiac/renal clamp), and high risk patients were excluded. Primary risk factors were increasing age, sex, American Society of Anaesthesiologist (ASA) score, and comorbidities such as ischaemic heart disease (IHD), cardiac failure, hypertension, chronic obstructive pulmonary disease (COPD), renal impairment, cerebrovascular disease, peripheral vascular disease (PVD), and diabetes. Estimated risks were expressed as hazard ratio (HR).
Results: A total of 5,749 study titles/abstracts were retrieved and 304 studies were thought to be relevant. The systematic review included 51 articles and the meta-analysis 45. End stage renal disease and COPD requiring supplementary oxygen had the worst long-term survival, HR 3.15 (95% CI 2.45–4.04) and HR 3.05 (95% CI 1.93–4.80) respectively. An increase in age was associated with HR of 1.05 (95% CI 1.04–1.06) for every one year increase and females had a worse survival than men HR 1.15 (95% CI 1.07–1.27). An increase in ASA score and the presence of IHD, cardiac failure, hypertension, COPD, renal impairment, cerebrovascular disease, PVD, and diabetes were also factors associated with poor long-term survival.
Conclusion: The result of this meta-analysis summarises and quantifies unmodifiable risk factors that influence late survival following AAA repair from the best available published evidence. The presence of these factors might assist in clinical decision making during discussion with patients regarding repair.

Article history: Received 16 May 2015, Accepted 9 September 2015, Available online 23 October 2015
Keywords: Abdominal aortic aneurysm, Endovascular aneurysm repair, Systematic review, Survival factors, Hazard rates

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http://dx.doi.org/10.1016/j.ejvs.2015.09.007

INTRODUCTION

Determinants of a patient's late survival following AAA repair mostly depend on pre-existing co-morbidities rather than the AAA repair method chosen. The results of a meta-analysis that included four randomised controlled trials (RCT) comparing open AAA repair (OAR) with endovascular aneurysm repair (EVAR) showed that the modality chosen for AAA repair does not influence survival at 4 years (OR 0.92, 95% CI 0.75—1.12).[1] When the results from three propensity score matched studies were included in the meta-analysis, the main conclusion did not change (HR 0.97, 95% CI 0.9—1.04).[2]

Prognostic demographic and clinical variables associated with poor late survival following AAA repair have been well described but are often reported as single outcomes in multiple studies. The aim of this study was to perform a systematic review and meta-analysis of prognostic factors on individual outcomes against one another for their associated impact on late survival following AAA repair.

METHODS

This was a systematic review performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)[3] and the meta-analysis and systematic reviews of observational studies in epidemiology (MOOSE),[4] guidelines as most of the anticipated studies included were of an observational design. Two researchers (M.K. and J.R.) independently conducted the study selection, data extraction, and assessment of methodological quality. This topic was defined in the PICOT[5,6] format as the Population is patients undergoing elective AAA repair (via either OAR or EVAR); Intervention and comparison: presence/absence or magnitude of non-modifiable clinical pre-operative risk factors, Outcome: all cause mortality and Time: greater than or equal to 1 year.

Search strategy

Medline, EMBASE, and the Cochrane Library Database were searched via the OVID SP database. With the assistance of a clinical librarian, "exploded" medical subject headings (MeSh) terms for MEDLINE and Cochrane, and EMTREE terms for EMBASE were used to broaden the key word search: "abdominal aortic aneurysm", "risk factors", "long term survival" and "survival rate" along with their synonyms. Two independent researchers conducted the search and when disagreement arose the reviewers met to resolve any issues.

There were no date restrictions and no limitations on publication language or study type applied to the search. The first search was conducted in May 2014 and updated in April 2015. A manual search of additional articles was conducted using references from relevant articles and review papers. The journals *Annals of Vascular Surgery, European Journal of Endovascular and Vascular Surgery, Journal of Endovascular Therapy, Journal of Vascular Surgery and Vascular* were searched for any relevant articles published "online first". Abstracts of conference proceedings were searched for full text publication. Eligible titles or abstracts where imported into Endnote X7 (Thomson Reuters) library and full text articles were obtained.

Inclusion and exclusion selection criteria

Two independent reviewers adhered to the following inclusion criteria: any studies reporting survival data and information about non-modifiable factors that may influence survival following elective AAA repair (OAR or EVAR), with at least 1 year follow up with the primary outcome endpoint being all cause mortality; studies with greater than a 100 patients; studies including symptomatic or rupture AAA in the analysis were included if the total number of symptomatic/rupture AAA was less than 20% of study participants. Studies containing up to a small proportion of patients (<40%) undergoing complex open (suprarenal clamping/visceral debranching) or fenestrated EVAR were included. Studies that included AAA repair and other vascular operations were included if the analysis was done separately for each type of surgery. However, the other vascular operations were not included. The exclusion criteria included studies that were limited to small AAA (<5 cm), high risk patients, octogenarians, and studies reporting intra- or post-operative factors rather than pre-operative factors, and non-patient related factors such as hospital/surgeon volume status.

Study selection

When studies from large registries or known databases were included, the most recent study or the paper that contained the largest number of patients and relevant data was used. Data from national databases were also checked to ensure data from individuals were not duplicated in other published series. If two articles presented data from the same database, but different variables were reported, then both studies were included for the two variables. Study authors were contacted when clarification was required.

Data extraction and quality assessment

Data extraction from studies meeting the inclusion criteria were entered into a Microsoft Excel spreadsheet. This review presents the unmodifiable demographic factors and clinical determinants that may influence long-term survival: age, sex, and clinical assessment information represented by the American Society of Anaesthesiologist (ASA) score, and information about the presence of potentially important co-morbidities: ischaemic heart disease (IHD), cardiac failure, hypertension, chronic obstructive pulmonary disease (COPD), renal impairment, cerebrovascular disease, peripheral vascular disease (PVD), and diabetes.

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The quality of the observational studies was assessed using the Newcastle—Ottawa Scale (NOS).[7] This scale employs a 9 point system that assesses three domains: patient selection, comparability of the study groups and the ascertainment of study outcome. Studies with a score of 9 stars indicate a low risk of bias whereas scores of 7—8 indicate medium bias risk and a score of ≤6 indicates a high chance of bias. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the quality of evidence and strength of each outcome identified, and this was conducted using GradePro (www.gradepro.org).

Statistical analysis

A meta-analysis of time to event data was undertaken. Reported HRs (statistically significant and non-significant) from multivariate Cox proportional models were extracted from individual studies. Pooled estimates together with 95% CI were calculated using a random effects model, chosen due to expected heterogeneity among the studies. Heterogeneity was expressed with the I^2 statistic with more than 25%, 50%, and 75% defined as low, moderate, and high degrees of heterogeneity respectively.[8] Statistical significance was set at $p = .05$. Subgroup analyses were performed according to *a priori* groupings related to study design, duration of follow up, type of repair (EVAR vs. OAR), location, and number of participants (<1,000 vs. >1,000). When CIs were not reported, estimates were calculated using reported ratios and p values. The meta-analysis was performed using Review Manager (RevMan) Version 5.2 (The Nordic Cochrane Centre, Copenhagen; http://tech.cochrane.org/revman).

RESULTS

A total of 304 articles were assessed in full and 51 studies met the inclusion criteria and were included in the analysis (Fig. 1). Six studies were included in the systematic review but were excluded from the meta-analysis as their data were descriptive without any reported hazard risk ratios,[9–11] ambiguous without any variables defined,[12] or they included factors not relevant to this review.[13,14] In all, 21 authors were contacted and 11 provided information regarding the data or the study.

The individual study design, location, and setting of the studies, number of participants, and follow up duration are presented in Table 1. Of the 51 studies, 25 were based in North America, 20 in Europe, four in Asia, one from Australia and one from South America. Forty-nine studies were observational and two were *post hoc* analyses from prospective controlled trials. The majority of the studies

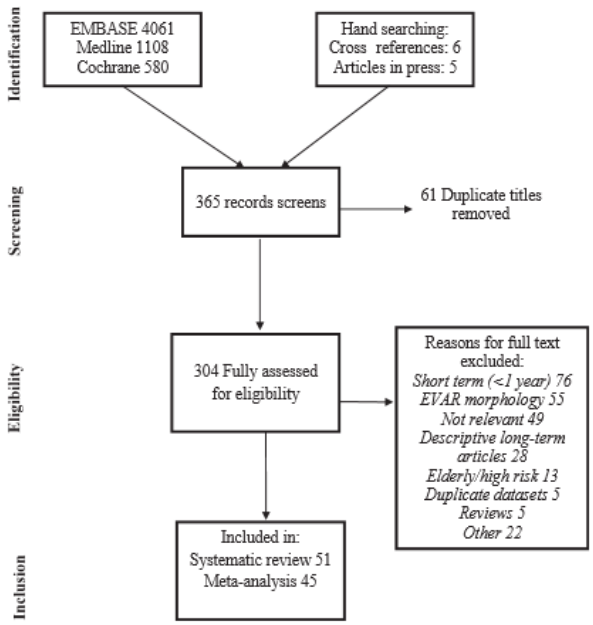


Figure 1. PRISMA search flow diagram.

Table 1. Summary of the included studies.

First author	Journal	Year	Country	Type of study	Area/region	Number of patients	Treatment	Setting	Duration of study/follow up (months)	No.
Khashram[22]	*Vascular*	2015	Australia	Observational	Brisbane	1340	EVAR and OAR	Elective	1990–2013	78 OAR & 48 EVAR 9
Teufelsbauer[29]	*Circulation*	2002	Austria	Observational	Vienna	454	EVAR and OAR	Elective	1995–2000	30 7
Espinosa[9]	*JEVT*	2009	Brazil	Observational	Rio de Janeiro	337	EVAR	Elective	1997–2007	58.7 7
Johnstone[42]	*J Vasc Surg*	1994	Canada	Observational	Multicentre	680	OAR	Elective	1986	NR 8
Grootenboer[16]	*J Vasc Surg*	2013	Europe	Eurostar registry	Multicentre	9227	EVAR	Elective	1996–2006	12.6[a] 8
Jaakkola[41]	*Ann Chir Gynaecol Fe*	1996	Finland	Observational	Kuopio	135	OAR	Elective	1976–1985	72 9
Biancari[56]	*Br J Surg*	2003	Finland	Observational	Oulu	433	OAR	Elective	1979–2002	54[a] 8
Koskas[23]	*Ann Vasc Surg*	1997	France	Observational	Multicentre	794	OAR	Elective	1989	60 9
Batt[36]	*EJVES*	1999	France	Observational	Nice	176	OAR	Elective	1987–1991	71 9
Tsilimparis[30]	*Vasc Endovasc Surg*	2012	Germany	Observational	Berlin	119	EVAR	Elective	4 years	34 6
Saratzis[28]	*J Vasc Surg*	2013	Greece	Observational	Thessaloniki	383	EVAR	Elective	2008–2011	34 7
Bonardelli[15]	*Ann Ital Chir*	2007	Italy	Observational	Brescia	1111	OAR	Elective	1992–2004	43.7 8
Lomazzi[25]	*Ann Vasc Surg*	2011	Italy	Observational	Varese	235	EVAR	Elective	2000–2008	26.3 7
Piffaretti[55]	*Arch Med Sci*	2014	Italy	Observational	Varese	276	EVAR and OAR	Elective and acute	2000–2005	70[a] 8
Yasuhara[59]	*Br J Surg*	1999	Japan	Observational	Tokyo	338	OAR	Elective	1980–1997	30 7
Komori[44]	*Surgery*	1999	Japan	Observational	Fukuoka	332	OAR	Elective	1979–1995	NR 9
Moro[12]	*Surg Today*	1998	Japan	Observational	Niigata City	125	OAR	Elective and acute	NR-1986	NR 6
Lim[43]	*J Vasc Surg*	2015	Korea	Observational	Seoul	247	EVAR	Elective	2006–2013	33.9 7
Welten[31]	*Am J Kidney Disease*	2007	Netherlands	Observational	Rotterdam	1324	OAR	Elective	1995–2006	72 9
Kertai[69]	*AM J Med*	2004	Netherlands	Observational	Rotterdam	510	OAR	Elective	1991–2001	56.4[a] 9
Schlosser[19]	*Ann Surg*	2010	Netherlands	Observational	Multicentre	3457	EVAR and OAR	Elective	1997–2001	60 9
Winkel[32]	*J Vasc Surg*	2009	Netherlands	Observational	Rotterdam	220	EVAR	Elective	2003–2008	34.8 7
Zeebregts[47]	*Br J Surg*	2004	Netherlands	Observational	Enschede	286	EVAR and OAR	Elective	1993–2003	42.7 6
De Bruin[37]	*J Vasc Surg*	2014	Netherlands/ Belgium	RCT *post hoc*	DREAM	351	EVAR and OAR	Elective	7 years	76.8[a] 9
Berge[17]	*Scand Cardiovasc J*	2008	Sweden	Observational	Multicentre	1041	EVAR and OAR	Elective and acute	1983–2002	NR 9
Carlisle[13]	*Br J Surg*	2007	UK	Observational	Torquay	130	OAR	Elective	1999–2006	35[a] 7
Grant[35]	*Health Technol Assess*	2015	UK	Observational	VGNW	4070	EVAR and OAR	Elective	2000–2013	NR 9
Hertzer[40]	*J Vasc Surg*	2005	USA	Observational	Cleveland Clinic	855	OAR	Elective	1976–2003	NR 9
Hertzer[46]	*J Vasc Surg*	2002	USA	Observational	Cleveland Clinic	1135	OAR	Elective	1989–1998	44 9
Starr[53]	*J Vasc Surg*	1996	USA	Observational	Cleveland Clinic	582	OAR	Elective	1983–1988	131 8
De Martino[50]	*J Vasc Surg*	2013	USA	Observational	VSGNE	2367	EVAR and OAR	Elective	2003–2011	29 9
Stone[45]	*J Vasc Surg*	2013	USA	Observational	VSGNE	3455	EVAR and OAR	Elective	2003–2011	NR 9
Lifeline collaborators[33]	*J Vasc Surg*	2005	USA	LIFELINE Registry	IDE Clinical trial	2664	EVAR	Elective	5 year	34 7

Zarins[51]	*J Vasc Surg*	2006	USA	LIFELINE Registry	IDE Clinical trial	923	EVAR	Elective	1998–1999	60		8
Conrad[20]	*J Vasc Surg*	2007	USA	Observational	Massachusetts General Hospital	540	OAR	Elective	1994–1998	87		9
Gloviczki[21]	*J Vasc Surg*	2015	USA	Observational	Rochester	934	EVAR	Elective and acute	1997–2011	45.6		8
Lee[24]	*World J Surg*	2013	USA	Observational	Cleveland Clinic	440	EVAR and OAR	Elective	1996–2004	83.4[a]		9
Mastracci[54]	*J Vasc Surg*	2010	USA	Observational	Cleveland Clinic	412	EVAR	Elective	1998–2005	48		8
McFalls[57]	*J Vasc Surg*	2007	USA	Observational	VA centres	1598	EVAR and OAR	Elective	1999–2003	NR		8
Parmar[18]	*J Vasc Surg*	2013	USA	Observational	Alabama	2063	EVAR and OAR	Elective	1985–2010	31		9
Rettke[26]	*J Cardiothorac Vasc Anesth*	1991	USA	Observational	Rochester	348	OAR	Elective	1979–1981	55.2[a]		7
Roger[27]	*JACC*	1989	USA	Observational	Olmstead, Rochester	131	OAR	Elective	1971–1987	NR		9
Yuo[18]	*J Vasc Surg*	2015	USA	Observational	US Renal Data System	1557	EVAR and OAR	Elective	2005–2008	NR		6
Feinglass[38]	*Surgery*	1995	USA	Observational	VA centres	280	OAR	Elective	1985–1987	NR		7
Gallinanes[39]	*Vascular*	2015	USA	Observational	Medicare & Medicaid	19323	EVAR and OAR	Elective	2007–2008	12		7
Matsumura[58]	*Ann Vasc Surg*	2009	USA	Prospective trial *post hoc*	Multicentre	334	EVAR and OAR	Elective	NR	NR		6
Brewster[11]	*Ann Surg*	2006	USA	Observational	Massachusetts	873	EVAR	Elective	1995–2005	27		6
Menard[10]	*J Vasc Surg*	2003	USA	Observational	Massachusetts	572	OAR	Elective	1990–2000	47.3		9
De Virgilio[14]	*Arch Surg*	2006	USA	Observational	California	468	EVAR	Elective	1996–2005	78[a]		6
Diehm[52]	*Vasa*	2008	USA/ Switzerland	Observational	NR	731	EVAR	Elective	1994–2007	48		7
Diehm[34]	*J Vasc Surg*	2007	USA/ Switzerland	Observational	NR	711	EVAR	Elective	1994–2006	48		7

Note. Follow up was reported as a mean unless otherwise stated. NR = not reported; VSGNE = Vascular Surgery Group of New England; VA = Veteran Affairs; VGNW= Vascular Governance North West.

[a] Median follow up.

were of high quality with an average NOS (standard deviation) score of 7.8 (1.1). There were 11 major prognostic factors analysed and the GRADE quality of evidence was low for most outcomes (Table 2).

Demographic variables

Age. Age was the most common covariate identified and was reported as a continuous variable in 21 eligible studies[15–35] and as a categorical variable in 11 other studies.[36–46] Two studies were excluded as one study did not define how age was categorised[47] and the other used patients aged over 80 years old as the reference category and meaningful HRs were not obtainable.[48] The pooled HR from the 21 studies was 1.05 (95% CI 1.04–1.06), $I^2 = 81\%$ related to each 1 year increase in age. When the studies were stratified into groups of less than or greater than 1,000 participants, heterogeneity was confined to the group of studies with more than 1,000 participants (Fig. 2). When the participants' age groups were categorised up to 75 years ($n = 8$) and >75 years old ($n = 5$) versus the reference category (<65years), the estimated pooled HRs were 1.77 (95% CI 1.36–2.30), $I^2 = 77\%$ and 2.32 (95% CI 1.93–2.80), $I^2 = 37\%$ respectively.

Sex. Sex was the second most reported covariate and all reported hazard ratios were adjusted for age differences. Sixteen studies reported on the influence of gender on late survival.[16–19,21,22,25,27,28,33,35,37,39,48–50] Females had a worse overall survival than males with HR 1.15 (95% CI 1.07–1.27), $I^2 = 45\%$.

Clinical assessment

ASA. ASA classification, although a 5 score categorical variable, was kept in an ordinal (continuous) form in three studies[15,22,51] and categorised as greater than ASA 3 or 4 versus less than 3 in one study.[16] Pooled HR related to each successive increase in ASA score and high ASA (3 and 4) was 1.30 (95% CI 1.16–1.47), $I^2 = 0\%$ and 1.63 (95% CI 1.42–1.87) respectively.

Co-morbidities

Ischaemic heart disease. IHD was inconsistently defined among the included studies. Definitions included a history of angina or myocardial infarction (MI), the presence of coronary disease on angiogram, and signs from ECG findings or cardiac stress test results. Eighteen studies reported the influence of IHD however defined, on late survival with a pooled HR 1.29 (95% CI 1.18–1.48), $I^2 = 46\%$.[15–20,23,30,32,33,35,37,42,44,45,49,52,53] Seven studies reported specifically on the influence of a previous history of MI.[20,23,26,28,42,49,50] When the analysis was confined to the presence of IHD based on a history of MI or ECG findings,

Table 2. GRADE assessment for outcomes influencing survival following abdominal aortic aneurysm repair.

Outcome	No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Age	21	Observational	Not serious	Very serious	Not serious	Not serious		Very low
Age (studies <1000 patients)	12	Observational	Not serious	Not serious	Not serious	Not serious		Low
Age cat ≤75	8	Observational	Not serious	Very serious	Not serious	Not serious	Dose response	Very low
Age cat >75	5	Observational	Not serious	Serious	Not serious	Not serious	Dose response, Large effect	Moderate
Sex (females)	16	Observational	Not serious	Serious	Not serious	Not serious		Very low
ASA	3	Observational	Not serious	Not serious	Serious	Serious		Very low
IHD	18	Observational	Not serious	Serious	Not serious	Not serious		Very low
MI	7	Observational	Not serious	Not serious	Not serious	Not serious		Low
Cardiac failure	14	Observational	Not serious	Very serious	Not serious	Not serious		Very Low
Cardiac failure (OAR)	5	Observational	Not serious	Not serious	Not serious	Not serious		Low
Hypertension	9	Observational	Not serious	Serious	Serious	Very Serious		Very low
LVH on ECG	3	Observational	Not serious	Not serious	Serious	Serious	Dose response	Very low
COPD	18	Observational	Not serious	Very serious	Not serious	Not serious		Very low
COPD long-term follow up (>4 years)	9	Observational	Not serious	Not serious	Not serious	Not serious		Low
COPD on O_2	3	Observational	Not serious	Serious	Not serious	Serious	Large effect, dose response	Moderate
Renal impairment	16	Observational	Not serious	Not serious	Not serious	Not serious		Low
ESRF	5	Observational	Not serious	Not serious	Not serious	Serious	Large effect	Low
Cerebrovascular disease	9	Observational	Not serious	Not serious	Not serious	Not serious		Low
Carotid disease	2	Observational	Not serious	Not serious	Not serious	Very serious		Very low
PVD	3	Observational	Not serious	Not serious	Not serious	Not serious		Low
Diabetes	14	Observational	Not serious	Not serious	Not serious	Not serious		Low

ASA = American Society of Anaesthesiologist; COPD = chronic obstructive pulmonary disease; ESRF = end stage renal failure; IHD = ischaemic heart disease; LVH = left ventricular hypertrophy; MI = myocardial infarction; OAR = open aortic repair; PVD = peripheral vascular disease.

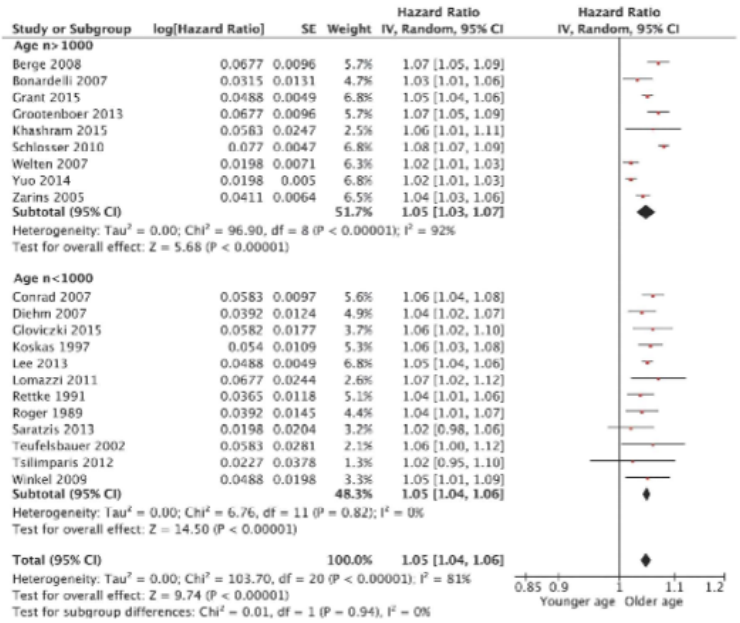


Figure 2. Forest plot of age (continuous) with sub analysis of number of participants included.

heterogeneity disappeared (I^2 = 0%) but the pooled HR remained broadly consistent at 1.52 (95% CI 1.32–1.73) (Fig. 3).

Cardiac failure. The impact of cardiac failure or congestive heart failure was also variably defined in the studies and was based on a mixture of clinical, radiological, and echocardiographic criteria. The impact of heart failure however defined, was reported in 14 studies.[19,20,22,33,39,41,43,45,46,49,54–57] The pooled HR was 1.91 (95% CI 1.58–2.30), I^2 = 70%. Subgroup analysis into type of repair reduced heterogeneity in OAR with an I^2 = 22% but heterogeneity for EVAR and both type of repairs remained high I^2 = 77%.

Hypertension. Of the nine[16–18,27,28,33,37,48,49] studies reporting on the influence of hypertension on survival, only two attempted to define hypertension or comment on treatment.[48,49] The pooled HR of the nine studies was 0.90 (95% CI 0.79–1.03), I^2 = 60%. When a history of hypertension was confined to the presence of left ventricular hypertrophy (LVH) on ECG, the effect on survival was harmful and heterogeneity was eliminated HR 2.25 (95% CI 1.66–3.04), I^2 = 0%.[26,38,42]

COPD. There were 18 studies reporting the influence of COPD on long-term mortality following AAA repair.[15–17,22,29,31,33,37–40,44,45,47,52,54,56,58] The pooled HR was 1.53 (95% CI 1.37–1.70), I^2 = 70% (Fig. 4). Three studies reported on COPD patients requiring supplementary oxygen therapy with a HR 3.05 (95% CI 1.93–4.80), I^2 = 63%.[24,43,45] A subgroup analysis was undertaken to determine if the average duration of follow up could explain the high heterogeneity. Studies with longer than 4 year follow up resulted in I^2 = 0% compared with shorter follow up studies with heterogeneity of I^2 = 82%.

Renal impairment. There was inconsistency among the studies in the methods used to report renal impairment and differences in the units of measurement. Some of the differences were overcome by converting creatinine units in mg/dL into µmol/L. Creatinine values were either reported as categorical data or kept in a continuous form. Three separate analyses were performed: (a) a categorical group was defined based on creatinine levels between 150 and 200 µmol/L, (b) creatinine clearance or estimated glomerular filtration rate (eGFR) data were used for another analysis, and (c) studies reporting on patients receiving haemodialysis or patients with end stage renal disease (ESRD) (creatinine > 350 µmol/L) were assessed. The results from the first analysis which included 16 studies[15–17,20,22,27,29,33–37,40,45,49,59] indicated that the presence of renal impairment was associated with increased mortality

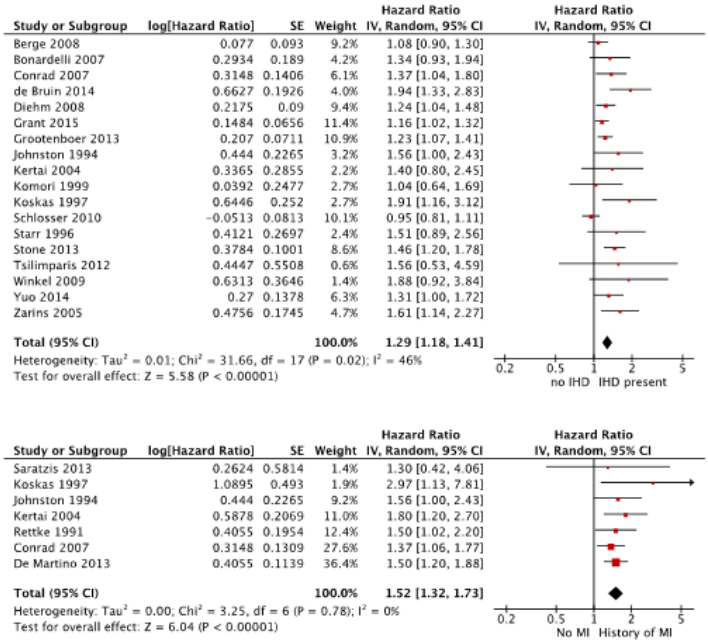


Figure 3. Forest plot of ischaemic heart disease and myocardial infarction.

risk HR of 1.54 (95% CI 1.43—1.67), I^2 = 11%. Four studies reporting on eGFR or creatinine clearance had a HR of 0.98 (95% CI 0.96—0.99), I^2 = 88%, for each increase in measurement unit (mL/min).[28,30,31,52] Five studies included patients with severe disease on dialysis or with ESRD and had a resulting HR of 3.15 (95% CI 2.45—4.04) I^2 = 0% (Fig. 5).[24,31,43,46,57]

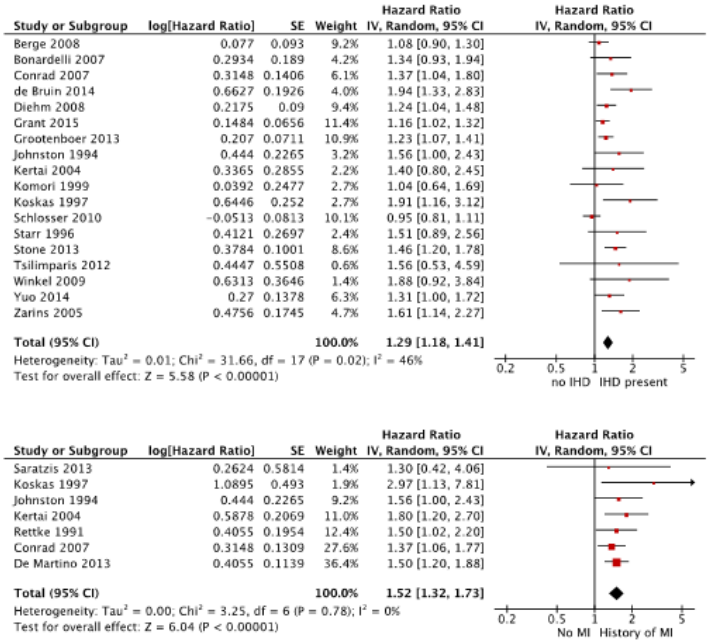
Cerebrovascular disease. Cerebrovascular disease when defined was reported as a history of a previous stroke or transient ischaemic attack. Two studies reported the influence of carotid disease but these were not included in this group as carotid disease is not primarily associated with all strokes and carotid disease was poorly defined.[16,37] Nine studies[17,19,24,27,28,31,38,44,59] reported the influence of cerebrovascular disease on late survival resulting in a pooled HR 1.57 (95% CI 1.40—1.77) I^2 = 0%. The presence of carotid disease had a HR 1.27 (95% CI 0.93—1.73) I^2 = 0%.

PVD. Three studies reported the influence of PVD on the overall survival following AAA repair.[22,28,51] The pooled HR 1.36 (95% CI 1.18—1.58), I^2 = 0%. One additional study included ankle brachial pressure indices (ABPI) with lower ABPI values predicting worse survival.[58] However, given differences in the definitions, the results could not be pooled.

Diabetes. Fourteen studies[16—19,27—29,33—35,37,39,44,49] reported on the influence of diabetes in relation to survival. The type of diabetes, the treatment and the presence of any complication was only defined in one study.[49] One study included "diabetes with complications" but this was not described.[39] The pooled HR was 1.34 (95% CI 1.20—1.49), I^2 = 26%.

DISCUSSION

In this comprehensive review, the best available prognostic data from studies reporting on late AAA repair survival during the past 25 years were pooled. It included 65,557 individuals. COPD requiring supplementary oxygen and ESRD/dialysis were associated with the highest risks of long-term mortality. In addition, the presence of the identified demographic (increasing age and female gender) and clinical factors (cardiac failure, renal impairment, COPD, cerebrovascular disease, PVD, diabetes and IHD) all significantly increased mortality to a lesser extent. The presence of hypertension, which arguably is a risk factor rather than a co-morbidity, was a notable exception as it appears to confer survival advantage. However, when there is hypertension with end organ damage (represented as LVH), mortality was significantly increased (Table 3).



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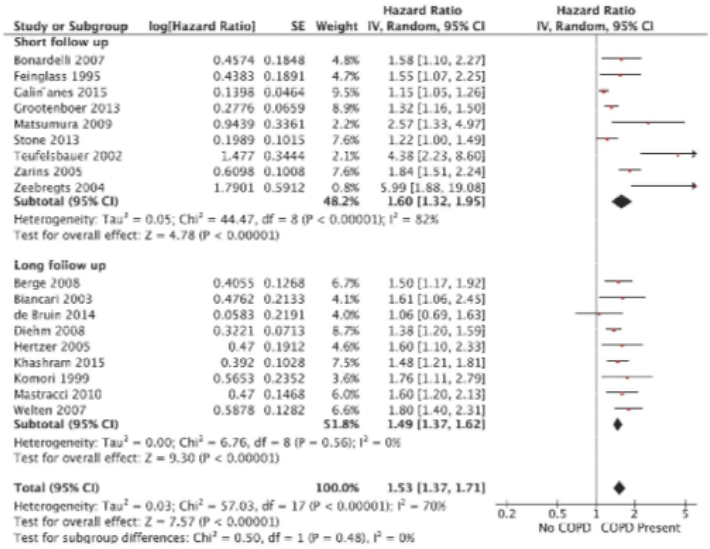

Figure 4. Forest of plot of chronic obstructive pulmonary disease presence with a sub-analysis according to length of follow up.

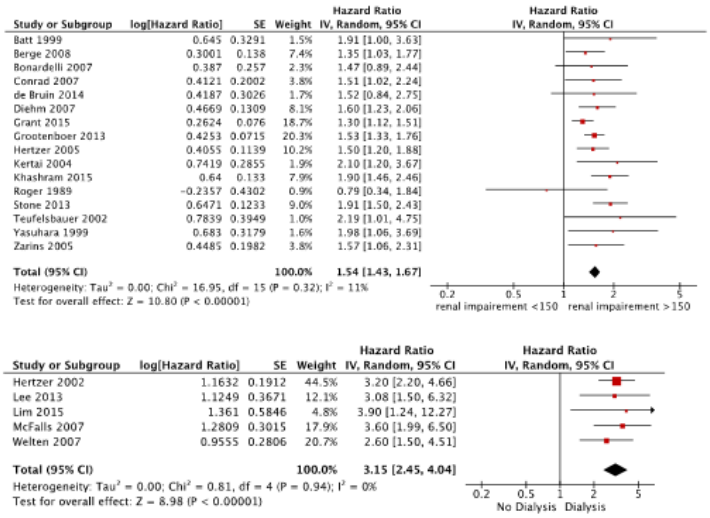

Figure 5. Forest plot of renal impairment (150—200 µmol/L) and end-stage renal disease/dialysis use.

Table 3. Summary of factors identified in this review that influence long-term survival following abdominal aortic aneurysm repair.

Factor	Number of patients	Number of studies	HR (95% CI)	I^2 (%)	Overall Z-Test effect	*p*
Demographic						
Age (continuous)/year	31,100	21	1.05 (1.04–1.06)	81	9.74	<.00001
Age category						
Up to 75 years old	22,047	8	1.77 (1.36–2.30)	77	4.24	<.0001
>75 years old	24,492	5	2.32 (1.93–2.80)	57	8.79	<.00001
Females	49,653	16	1.15 (1.07–1.27)	45	3.42	<.0006
Clinical assessment						
ASA	3,374	3	1.30 (1.16–1.47)	0	4.32	<.0001
Comorbidity						
IHD	31,441	18	1.29 (1.18–1.48)	46	5.58	<.00001
MI	5,433	7	1.52 (1.32–1.73)	0	6.04	<.00001
Cardiac failure	35,525	14	1.91 (1.58–2.30)	70	6.77	<.00001
Hypertension	17,927	9	0.90 (0.79–1.03)	60	1.55	0.12
LVH on ECG	1,308	3	2.25 (1.66–3.04)	0	5.28	<.00001
COPD	43,953	18	1.53 (1.37–1.70)	70	7.58	<.00001
COPD on O_2 supplement	4,142	3	3.05 (1.93–4.80)	63	4.8	<.00001
Renal impairment						
Creatinine (>150–200 µmol/L)	26,974	16	1.54 (1.43–1.67)	11	10.8	<.00001
Dialysis or ESRF	4,744	5	3.15 (2.45–4.04)	0	8.98	<.00001
Cerebrovascular disease	7,726	9	1.57 (1.40–1.77)	0	7.49	<.00001
Carotid disease	9,578	2	1.27 (0.93–1.73)	0	1.5	0.13
PVD	2,646	3	1.36 (1.18–1.58)	0	4.17	<.0001
Diabetes	44,211	14	1.34 (1.20–1.49)	26	5.35	<.00001

ASA = American Society of Anaesthesiologist; COPD = chronic obstructive pulmonary disease; ESRF = end stage renal failure; IHD = ischaemic heart disease; LVH = left ventricular hypertrophy; MI = myocardial infarction; PVD = peripheral vascular disease.

The results from this review highlight several important issues in relation to long-term survival following AAA repair. There is some debate about whether gender influences survival following AAA repair. Data from the EUROSTAR and Lifeline registries and the Mayo Clinic revealed no difference in late survival between genders.[16,21,33] In the general population, women have been shown to have a higher life expectancy than males. However, following AAA repair, this difference appears to be negated and females had a significantly higher risk of death than males (HR 1.16, 95% CI 1.07–1.27) after adjusting for age. Recent evidence from the United States Renal Data System suggests that late survival after AAA repair among patients with ESRD receiving dialysis may be poor, with an estimated 3 year survival of 23.1% compared with 41.9% survival of patients with ESRD without an AAA.[18] This conclusion is consistent with the results from this review that also report that late mortality is high among these patients (HR 3.15, 95% CI 2.45–4.04), and questions the long-term benefits of elective AAA repair for this group.

In this review, the prevalence of the reported prognostic factors that influence survival have also been reported. Sometimes clinical variables collected in operative registries have no clinical value and can lead to incomplete datasets.[60] This analysis has also identified important demographic and clinical factors that influence late survival and such factors should be considered in predictive late survival modelling tools and clinical decision making.[35,54]

Varying definitions of major co-morbidities, such as cardiac failure and COPD in published studies, markedly hinder the evaluation of the influence of these conditions on outcomes such as long-term survival after AAA repair. The findings from this review highlight the major contribution from these differing definitions to the occurrence of heterogeneity in the various results. When study results could be included where definitions were clearly defined or simplified to reporting the presence or absence of a co-morbidity, then heterogeneity was either eliminated or greatly reduced. Despite the presence of heterogeneity observed in some factors, there was evidence of increasing mortality with an increase in the severity of the co-morbidity. Worse renal impairment and more severe forms of COPD were consistently associated with increased long-term mortality. In keeping with international agreements to standardise key aspects of the design and reporting of epidemiological and observational studies such as STROBE,[61] attention should be paid to gaining some consistency in the measurement and reporting of co-morbidities among clinical trials and observational research.

The findings from the subgroup analyses gave some helpful insights into other sources of heterogeneity among the studies. For example, heterogeneity is no longer apparent when the results from studies that have investigated survival after AAA repair among patients with COPD are restricted to those that have reported longer term outcomes (>3 years). When these studies are separated out then the deleterious effect of COPD on long-term survival is evident (HR 1.49 95% CI 1.37–1.62), I^2 = 0%. In another example, the reduction of heterogeneity among study results when cardiac failure was grouped into type of repair

suggests that the presence of the comorbidity may already influence the choice of operative procedure, OAR (HR 1.58, 95% CI 1.23—2.03), $I^2 = 22\%$) and EVAR (HR 1.91, 95% CI 1.58—2.68), $I^2 = 77\%$).

In this review the search and patient selection was broadened to quantify risks from the literature that would enable presentation of generalizable hazard ratios for each factor analysed. In so doing, a lack of consistency in risk factor definitions was noted, together with a tendency towards categorising continuous variables or reporting categorical data as a continuous variable. These factors may have reduced the statistical power of subsequent meta-analysis.[62] To improve future studies the need for standardisation in reporting variables that might influence survival following AAA repair has been highlighted.

Limitations

As with most systematic reviews, this analysis is not immune to selection, publication, and reporting bias. A key limitation of this study was that each of the factors have been analysed in isolation from any others, whereas in practice patients have more than one demographic and co-morbid factors to be considered in any decisions about their care. It is possible that the effects of the various factors may be additive or multiplicative on the risk of late survival. Alternatively, the risks associated with some co-morbidities may even be subsumed into the risks associated with another co-morbidity. Publication bias is a concern with any systematic review and studies from centres with good or excellent results are more likely to publish their data than units with poor outcomes. However, it is notable that the data included in this review also included reports from national registries, *post hoc* RCT data, along with the data provided by smaller groups of surgeons based at specialist institutions. The GRADE score was low for the majority of outcomes and this was predominantly due to the high the risk of bias and types of study included.

This review suggests that decision making regarding AAA treatment and long-term survival needs to consider patient related factors including age and gender along with a range of important clinical co-morbidities. Further work is needed to determine the relative importance of each and how the risks from different combinations of the co-morbidities may interact. Attention needs to be given to ensuring these factors are consistently measured and reported in future studies so that updated and improved estimates can be readily obtained in future assessments and the obtained estimates could then be validated against AAA datasets.

In conclusion, using the best available estimates of risk from the literature, it was possible to identify important pre-operative risk factors and calculate effect estimates for factors influencing late survival among patients undergoing elective AAA repair. COPD requiring supplementary oxygen and ESRD had the highest impact on survival which raises questions with regards to the benefits of the elective AAA repair in their presence.

CONFLICT OF INTEREST

None.

FUNDING

None.

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8.6.4 Does the diameter of abdominal aortic aneurysm influence late survival following abdominal aortic aneurysm repair? A systematic review and meta-analysis

Review Article

Vascular

Vascular
2016, Vol. 24(6) 658–667

DOI: 10.1177/1708538116650580
vas.sagepub.com
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Does the diameter of abdominal aortic aneurysm influence late survival following abdominal aortic aneurysm repair? A systematic review and meta-analysis

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Abstract

Background: Studies reporting the influence of preoperative abdominal aortic aneurysm diameter on late survival following abdominal aortic aneurysm repair have not been consistent.

Aim: To report the influence of abdominal aortic aneurysm diameter on overall long-term survival following abdominal aortic aneurysm repair.

Methods: Embase, Medline and the Cochrane electronic databases were searched to identify articles reporting the influence of abdominal aortic aneurysm diameter on late survival following open aneurysm repair and endovascular aneurysm repair published up to April 2015. Data were extracted from multivariate analysis; estimated risks were expressed as hazard ratio.

Results: A total of 2167 titles/abstracts were retrieved, of which 76 studies were fully assessed; 19 studies reporting on 22,104 patients were included. Preoperative larger abdominal aortic aneurysm size was associated with a worse survival compared to smaller aneurysms with a pooled hazard ratio of 1.14 (95% CI: 1.09–1.18), per 1 cm increase in abdominal aortic aneurysm diameter. Subgroup analysis of the different types of repair was performed and the hazard ratio (95% CI), for open aneurysm repair and endovascular aneurysm repair were 1.08 (1.03–1.12) and 1.20 (1.15–1.25), respectively, per 1 cm increase. There was a significant difference between the groups $p < 0.02$.

Conclusions: This meta-analysis suggests that preoperative large abdominal aortic aneurysm independently influences overall late survival following abdominal aortic aneurysm repair, and this association was greater in abdominal aortic aneurysm repaired with endovascular aneurysm repair.

Keywords

Abdominal aortic aneurysm, endovascular aneurysm repair, systematic review, survival factors, hazard rates, size

Introduction

Abdominal aortic aneurysm (AAA) rupture is associated with high surgical mortality worldwide,[1] yet AAA can be effectively managed by either open aneurysm repair (OAR) or endovascular aneurysm repair (EVAR) in an elective setting with a 10-fold decrease in perioperative mortality. Regardless of the repair method chosen, results from four randomized trials and two large cohort studies indicate that survival is similar between EVAR and OAR.[2,3]

Previous research has identified several independent prognostic variables associated with lower survival following AAA repair with varying size effects. These include demographic such as age, gender and clinical comorbidities including cardiac, renal or pulmonary impairment.[4] Furthermore, population studies have also shown that an increase in infra-renal abdominal

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aortic size above the normal aortic diameter or the presence of an AAA (defined as greater than or equal to 3 cm) are independent predictors of increased cardiovascular and overall late mortality.[5,6]

Koskas and Kfeifer[7] were the first to report that the diameter of the AAA negatively predicted late survival following OAR in a multicenter prospective trial consisting of 794 patients. The hazard ratio (HR), 95% confidence interval (CI) was 1.1 (95% CI: 1.04–1.08) for each 1 cm increase in AAA diameter.[7] Following the emerging use of EVAR in the early 2000s, endovascular registries from Europe (EUROSTAR) and the United States (Lifeline registry) both reported that larger AAA were independently associated with worse late survival.[8,9] However, other studies have observed no difference in late survival between small and large AAA diameter.[10,11]

Since late survival following AAA repair is determined by preoperative factors such as AAA diameter, quantifying the individual risk is necessary in clinical decision-making. This systematic review and meta-analysis aimed to report the influence of preoperative AAA diameter on late survival of patients undergoing elective AAA repair.

Methods

The systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA).[12] Individual patient consent was not possible, as this review will analyze published literature only. The Health and Disability Ethics committee has approved this project. This topic was defined in the PICOT[13] format as: the population are patients undergoing elective AAA repair (via either OAR or EVAR); intervention and comparison: preoperative AAA diameter, Outcome: all cause mortality and time: greater than or equal to one year.

Search strategy

EMBASE, Medline and the Cochrane Library Database were searched via the electronic OVID SP database. With the assistance of a clinical librarian, "exploded" medical subject headings (MeSH) terms for MEDLINE and Cochrane, and EMTREE terms for EMBASE were used to broaden the key word search: "abdominal aortic aneurysm," "size," "blood vessel diameter," "long term survival" and "survival rate" along with their synonyms. Two independent researchers (MK and JR) conducted the search and when disagreement arose the reviewers met to resolve any issues.

There was no date restriction and no limitations on publication language or study type applied to the search. The last search was completed in April/May 2015. An additional manual search of articles was conducted using references from relevant articles and review papers. The journals of Annals of Vascular Surgery, European Journal of Endovascular and Vascular Surgery, Journal of Endovascular Therapy, Journal of Vascular Surgery and Vascular were searched for any relevant articles published "online first." Abstracts of conference proceedings were searched for full text publication. Eligible titles or abstracts where imported into Endnote X7 (Thomson Reuters) library and full text articles were obtained.

Study selection

Inclusion and exclusion selection criteria

Two independent reviewers adhered to the following inclusion criteria: any studies with greater than a 100 patients, reporting survival data and information about preoperative AAA diameter following elective AAA repair (OAR or EVAR) with at least one year follow-up with the primary endpoint of outcome being all-cause mortality. There were no restrictions to operative repair methods and complex repairs (suprarenal clamping/visceral debranching or fenestrations). The exclusion criteria were studies that were solely limited to small AAA (<5 cm), rupture AAA, first generation/early custom-made stent grafts, high-risk patients and octogenarians.

Study selection and data extraction

Two researchers independently performed the data extraction. Studies that met the inclusion criteria were entered into a Microsoft Excel spreadsheet. When studies from large registries, or known databases were included, only the most recent study that contained the largest number of patients or the study that kept AAA diameter as a continuous variable was used in the analysis. Study authors were contacted when clarification was required.

The quality of the observational studies (cohort) was assessed using the Newcastle-Ottawa Scale (NOS).[14] This tool employs a 9-point system that assesses three domains: patient selection, comparability of the study groups and the ascertainment of study outcome. Studies with a score of 9 indicate a lower risk of bias whereas scores of 7–8 indicate medium risk of bias and a score of ≤6 indicates a higher chance of bias.

Statistical analysis

Reported baseline risk factors were extracted from baseline tables, group means and standard deviations

(SD) were weighted and combined for descriptive purposes. A meta-analysis of time-to-event data was undertaken. Reported HR (statistically significant and non-significant) from multivariate Cox proportional models were extracted from individual studies. Pooled estimates together with 95% CI were calculated using a random effects model, chosen due to expected heterogeneity among the studies. Heterogeneity was expressed with the I^2 statistic with greater than 25%, 50% and 75% defined as low, moderate and high degrees of heterogeneity. Statistical significance was set at a *p*-value 0.05. Sub group analyses were performed according to *a priori* groupings related to type of repair (EVAR vs OAR). The meta-analysis was performed using Review Manager (RevMan) [Computer program] Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012. Meta-regression was performed in *R* using the package metafor, with heterogeneity estimated using the DerSimonian–Laird method with inverse variance weights.[15,16]

Results

The literature search flow chart results are summarized in Figure 1. Of 2167 titles, 72 were thought to be relevant after screening titles and abstracts. Following duplication removal, 66 articles were assessed of which 10 met the inclusion criteria.[17–26] The hand searching identified seven additional studies[7,11,27–30] and searching vascular journals for ahead of print/ "Online first" articles identified two additional studies.[31,32] Nineteen articles were included in the

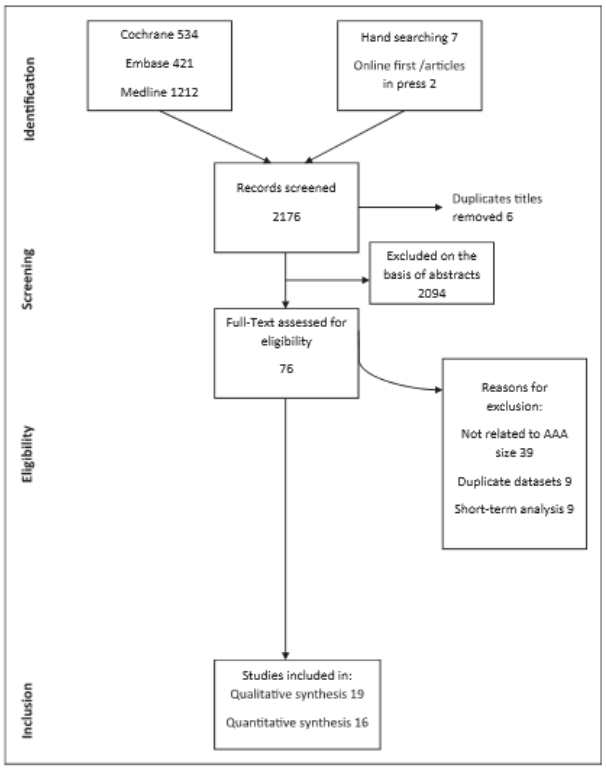

Figure 1. PRISMA Diagram showing flowchart of study selection.

systematic review of which three did not include sufficient data to allow inclusion into the meta-analysis. One study provided descriptive results only[27] and two studies included univariate (unadjusted) risk ratios.[25,26]

Nineteen studies published between 1989 and 2015 were included in this review. Ten studies were from the United States, eight were from Europe and one was from Australia. Repairs of AAA were done with EVAR in 10 studies and OAR in 5 studies. Three studies included both OAR and EVAR and one study did not state the method of repair. "Raw" data from one study was obtained and analyzed according to type of repair.[31] The average (SD) NOS was 7.7 (1.4) indicating a high overall quality of observational studies (Table 1).

A total of 22,104 patients were included in the systematic review. Baseline demographics, clinical risk factors and AAA diameter descriptions are presented in Table 2; 13 studies reported AAA diameter as a continuous variable (per cm, mm or 5 mm increments), 1 study transformed aortic sizes into a logarithmic scale[20] and 4 studies categorized AAA diameter;[17,23,26,33] 15 studies that comprise 20,205 patients, provided baseline mean/median aneurysm diameter measurements (range 5.1–6.4 cm).

The full meta-analysis included 16 studies and 19,722 patients. All of the studies adjusted for age while several also adjusted for comorbid conditions (Table 1). Larger AAA diameter measured prior to AAA repair was associated with lower reported survival compared with smaller aneurysms. A 1-cm increase in AAA diameter was associated with a pooled HR of 1.14 (95% CI: 1.10–1.18), $I^2 = 48\%$ (Figure 2). Excluding four studies with either categorical[17,23,33] or logarithmic[20] AAA diameter conversions did not influence the overall risk – HR 1.13 (95% CI: 1.09–1.18), $I^2 = 50\%$ for each increase in 1 cm of AAA diameter.

Thirteen studies were included in a subgroup analysis according to AAA repair type that included an equal weight (50%) for each category (Figure 3). EVAR was associated with a significantly higher mortality risk compared with OAR for each 1 cm increase in AAA diameter, pooled HR was EVAR 1.20 (95% CI: 1.15–1.25), $I^2 = 0\%$ and OAR 1.08 (95% CI: 1.03–1.12), $I^2 = 12\%$, respectively (Figure 3). This subgroup analysis excluded two studies that included both EVAR and OAR in the same analysis,[17,32] one study that categorized AAA diameter[23] and one that did not report how the AAA was repaired.[20]

Meta-regression was undertaken to determine if the between-study heterogeneity could be accounted for by the mid-year of study or duration of follow-up; 16 studies contributed to mid-year of the study and 15 studies contributed to the duration of follow-up. There was an association for a decrease in log(HR) by duration of follow up ($\beta = 0.998$, 95% CI: 0.996–1.000, $I^2 = 24\%$, $p < 0.013$; Figure 4). There was no evidence of a change in log(HR) by mid-year study ($\beta = 1.004$, 95% CI: 0.999–1.010, $I^2 = 47\%$, $p = 0.13$).

Discussion

Individualizing patient treatment to their specific demographics and comorbidities is warranted to improve long-term outcomes. This systematic review found that larger AAAs were independently associated with a lower survival following elective AAA repair and this observation was greater for EVAR than OAR.

AAA size has also been shown to be an important independent predictor of perioperative morbidity and mortality. Schouten et al.[34] reported on 500 patients undergoing elective open AAA repair and larger AAA diameter had a significantly higher risk of cardiovascular complications and mortality. A recent report from the Vascunet database included 5895 patients from six countries and concluded that the size of AAA was associated with higher perioperative mortality with an adjusted odds ratio of perioperative mortality for a 1-cm increase in AAA size in patients undergoing either OAR or EVAR of 1.14 (95% CI: 1.03–1.27) and 1.28 (95% CI: 1.06–1.55), respectively.[35] The diameter of AAA at the time of repair has also been associated with a decreased five-year survival as demonstrated by a recent meta-regression analysis including 13,281 patients treated between 1978 and 2011.[36]

Why are larger AAAs associated with worse survival?

Based on the results from this meta-analysis, there appears to be two factors that could explain why larger AAAs may have a worse survival. First, this association was found in both types of repairs; therefore, a biological cause seems plausible. Larger AAA might exhibit more inflammatory mediators or larger size AAA might be associated with more advanced cardiovascular disease.[8,23,34] Five studies provided group comparison between small and large AAA. The results from three large studies[8,9,26] suggest that patients with larger AAA were older and had a greater burden of cardiovascular disease than patients with small AAA. In the two other smaller studies,[10,23] there was no difference in morbidities between the groups. However, patient co-morbidities were adjusted for in the survival models and the influence of AAA size was an independent predictor of late survival.

Second, the effect estimate of AAA size of EVAR treatment was significantly higher in this analysis compared to the OAR group.

Nevertheless, this does not adequately explain why the association was greater in EVAR than OAR.

Table 1. Study characteristics of included studies.

First author	Year	Country	Area	NOS	N at start	Repair type	Duration of study	Average follow-up (months)	Adjustors
Beck et al.[33]	2009	USA	VSGNNE	7	639	EVAR	2003–2007	12	Age, COPD, supra-renal clamp and renal impairment
Brady et al.[20]	2001	UK	Multicenter	9	1139	NR	1991–1995	43.2	Age, sex, PVD, angina, IHD smoking status, cholesterol, diabetes, hypertension, BMI, WBC, creatinine and COPD
Brewster et al.[27]	2006	USA	Massachusetts	6	873	EVAR	1995–2005	27	NR
Carlisle and Swart[25]	2007	UK	Torquay	5	130	OAR	1999–2006	35[a]	NR
De Bruin et al.[17]	2014	Netherlands/ Belgium	DREAM (RCT *post hoc*)	9	351	EVAR and OAR	Seven years	76.8	Age, sex, reintervention, tobacco, statin, antiplatelet, hypertension, cardiac, pulmonary, renal and carotid disease
Diehm et al.[22]	2007	USA/Switzerland	NR	7	711	EVAR	1994–2006	48.3	Age, hemoglobin, diabetes, statin use, renal and pumonary scores,
Grootenboer et al.[18]	2013	Europe	Eurostar Registry Multicentre	8	9227	EVAR	1996–2006	12.6[a]	Age, sex, ASA scale, cardiovascular comorbidities, AAA and treatment characteristics
Hertzer and Mascha[19]	2005	USA	Cleveland Clinic	9	855	OAR	1976–2003	NR	Age, preliminary coronary revascularization, COPD, renal, impairment and graft configuration
Huang et al.[32]	2015	USA	Mayo Clinic	9	1116	EVAR and OAR	2000–2011	91.2[a]	Age, sex, type of repair, history of cancer and surgical risk score
Kabbani et al.[21]	2014	USA	Detroit	9	245	OAR	1986–2013	54[a]	Age, smoking, IHD, COPD, renal, hyperlipidemia, renal impairment, diabetes, history of smoking and stroke
Keith et al.[26]	2013	USA	Alabama	8	740	EVAR	2000–2011	40	NR
Khashram et al.[31]	2015	Australia	Brisbane	9	1340	EVAR and OAR	1990–2013	78 OAR and 48 EVAR	Age, sex, ASA scale, type of repair. COPD, PVD, renal impairment and HF
Koskas and Kieffer[7]	1997	France	Multicentre	9	794	OAR	1989	60	Age, thrombosis of IVC, iliac involvement, carotid artery occlusion, IHD, renal impairment, neck aneurysm and incision method
Lomazzi et al.[30]	2011	Italy	Varese	7	235	EVAR	2000–2008	26.3	Age. ASA scale and sex
Mastracci et al.[24]	2010	USA	Cleveland Clinic	8	412	EVAR	1998–2005	48	Age, HF, COPD, statin and aspirin use,
Roger et al.[29]	1989	USA	Olmstead, Rochester	9	131	OAR	1971–1987	NR	Age, sex, diabetes, uncorrected IHD, hypertension, creatinine, history of stroke, cancer and smoking
Saratzis et al.[11]	2013	Greece	Thessaloniki	7	383	EVAR	2008–2011	34	Age, WBC, hemoglobin, creatinine, cancer history, C reactive protein and endoleak type I
Tsilimparis et al.[23]	2012	Germany	Berlin	6	119	EVAR	Four years	34	Age, current smoking, IHD and renal function
Zairis[28]	2005	USA	IDE trial (LIFELINE Registry)	7	2664	EVAR	Five year	34	Age, sex, IHD, HF, hypertension, COPD, diabetes and renal failure

RCT: randomized controlled trial; VSGNNE: Vascular Study Group of Northern New England; IDE: investigative device exemption; NOS: Newcastle-Ottawa Scale; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; ASA: American society of anesthesiology; BMI: body mass index; WBC: white blood count; HF: heart failure.
[a]Median follow-up.

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RCT: randomized controlled trial; VSGNNE: Vascular Study Group of Northern New England; IDE: investigative device exemption; NOS: Newcastle-Ottawa Scale; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; ASA: American society of anesthesiology; BMI: body mass index; WBC: white blood count; HF: heart failure.
[a]Median follow-up.

Table 2. Patient and AAA baseline characteristics.

Author	Age (SD)	Males (%)	No of groups	AAA diameter in mm (SD)	Method of measurement	Units/ presentation	IHD[a]	Smoking history[b]	Renal impairment	Diabetes	COPD
Beck et al.[23]	74 (NR)	82	1	57.0 (10)	NR	≥65 mm	31.0	90.1	7.0	18.0	39.0
Brady et al.[20]	NR	NR	1	51.0 (32–92)	US	per logarithmic unit (0.8 cm)	NR	NR	NR	NR	NR
Brewster et al.[27]	75.7 (7.6)	81.4	1	56.8 (10.6)	CT	NR	57.2	65.1	7.0	12.4	24.1
Carlisle and Swart[25]	NR	NR	1	NR	NR	per 10 mm	NR	NR	NR	NR	NR
De Bruin et al.[17]	70.2 (6.7)	91.7	1	60.4 (8.7)	CT	≥70 mm	44.2	59.0	8.3	10.0	23.1
Diehm et al.[22]	75.8 (7.5)	90.9	1	58.2 (10.6)	NR	per 1 mm	45.0	77.6	21.8	15.0	32.1
Grootenboer et al.[18]	72.2 (7.8)	93.2	1	58.1 (12.2)	CT	per 1 mm	60.4	48.7	19.1	13.0	41.9
Hertzer and Mascha[19]	69 (47–94)	86	1	59.0	CT and US	per 10 mm	NR	NR	NR	NR	6.2
Huang et al.[32]	73 (7.6)	86	1	58.0 (14.9)	CT, MRI or US	per 1 cm	NR	NR	NR	NR	NR
Kabbani et al.[21]	71 (7.9)	68.8	1	64 (19)	NR	per 1 cm	42.0	85.0	N/A	14.0	36.0
Keith et al.[26]	71.4	84.6	3	NR	CT	<5, 5–5.9 and >6 cm	52.5	73.5	10.8	16.2	27.4
Khashram et al.[31]	72.4 (7.4)	81.7	1	59.4 (11.9)	CT	per 1 cm	47.3	90.4	8.1	13.0	27.5
Koskas and Kieffer[7]	67.8 (8.4)	92.9	1	NR	NR	per 1 cm	42.8	NR	10.8	9.2	21.2
Lomazzi et al.[30]	71.9 (8)	92.7	1	NR	CT	per 1 mm	48.0	NR	11.0	NR	53.2
Mastracci et al.[24]	75.4 (7.5)	88	1	64.0 (11.6)	CT	per 5 mm	58.0	19[b]	28.0	16.0	38.0
Roger et al.[29]	NR	79	1	60.0 (NR)	NR	per 1 cm	42.7	44.0[b]	12.0	8.0	NR
Saratzis et al.[11]	68.9 (8.2)	91.7	1	61.8 (14)	CT	per 1 cm	9.7	72.6	N/A	18.8	NR
Tsilimparis et al.[23]	71.3 (8.2)	91.6	2	58 (34–93)	CT	≥60 mm	36.1	47.0	14.3	14.3	20.0
Zairns[28]	73.1 (7.8)	88.6	1	55.8 (10.2)	CT	per 1 mm	82.7	NR	3.4	12.4	29.2
Range	68.9–75.8	68.8–93.2		51–64 mm			9.7–82.7	19.0–90.4	7.0–28.0	8.0–18.8	6.2–53.2

SD: standard deviation; NR: not reported; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease.
[a]Various definitions used.
[b]Current smokers.

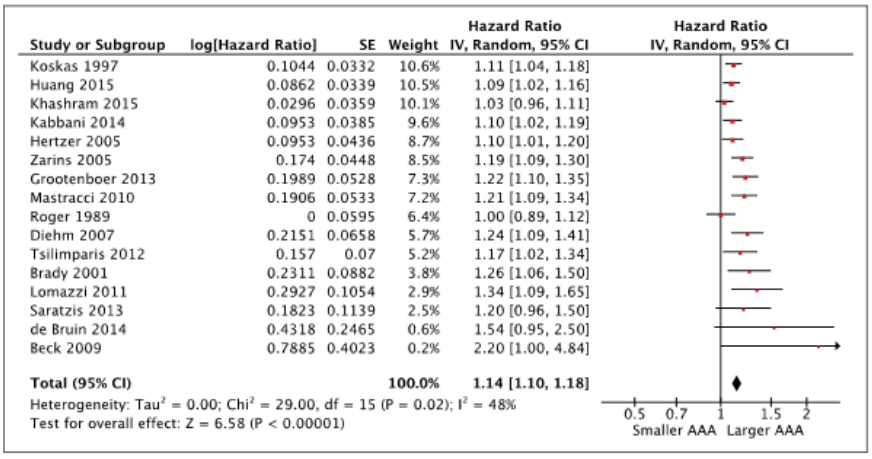

Figure 2. Meta-analysis of the effect of AAA size of late mortality following elective AAA repair (per 1 cm increase).

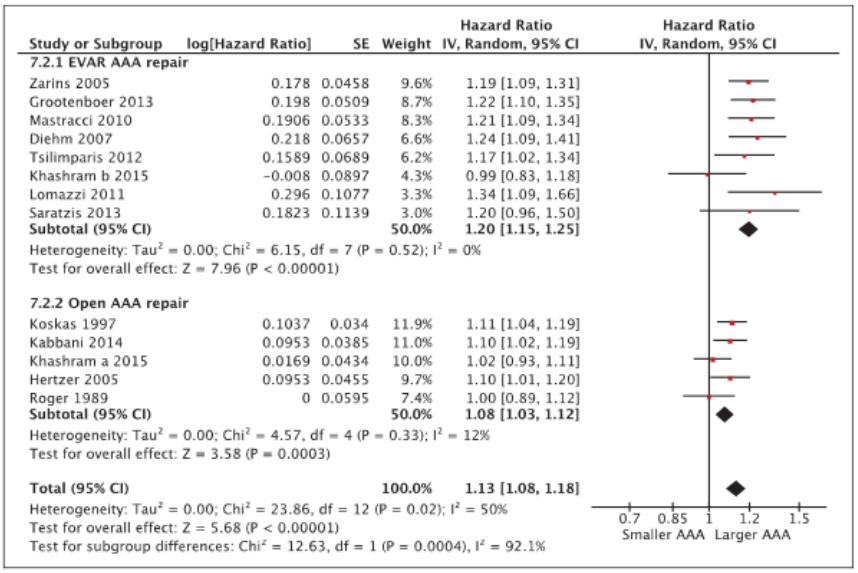

Figure 3. Subgroup analysis of AAA size according to type of repair (per 1 cm increase, EVAR: endovascular aneurysm repair, OAR: open aneurysm repair).

Results from the Lifeline and EUROSTAR registries have also shown that an increase in AAA diameter was independently associated with a higher AAA related mortality, higher rupture post repair, re-intervention and surgical conversion to OAR.[8,9,28] One might speculate that each re-intervention might have an additive mortality risk.

Roger et al.[29] were the first to include AAA size in a multivariate model, but AAA diameter was not a significant mortality predictor in their study. Almost a decade later, Koskas and Kfieifer[7] were the first to show that preoperative AAA size was an independent predictor of poor late survival. Interestingly, this finding appeared to generate little discussion, including within the reporting paper. It was not until subsequent EVAR data began to emerge, highlighting morphological aortic neck and iliac artery differences between small and large AAA that interest in this area has increased.[8,9]

Limitations

This systematic review has a number of potential limitations related to study selection and potential biases in reporting and publication. Specifically, as AAA diameter (>5.5 cm) has not been subjected to any randomized trials, it is possible that higher risk patients were selected to undergo EVAR and hence were more likely to experience higher late mortality. However, it was notable that three studies[7,19,29] in the OAR group recruited patients prior to the EVAR era, and AAA diameter remained a negative predictor of late survival.

Furthermore, potential confounders that were not adjusted for in the analysis might have contributed to the findings of this review. For example, other anatomical features of AAAs such as short proximal necks or juxta/supra-renal aneurysms have been associated with worse outcomes and lower survival following AAA repair. Some of the earlier studies might have included first generation endovascular stent grafts that were associated with higher mortality and endoleak rates and might have influenced the results.[37] We excluded studies that only included such grafts to minimize the selection bias.

The outcome of interest in this analysis was overall patient survival during the reported follow-up period. This period ranged from 12 to 91.2 months and the metaregression at univariable level suggests an

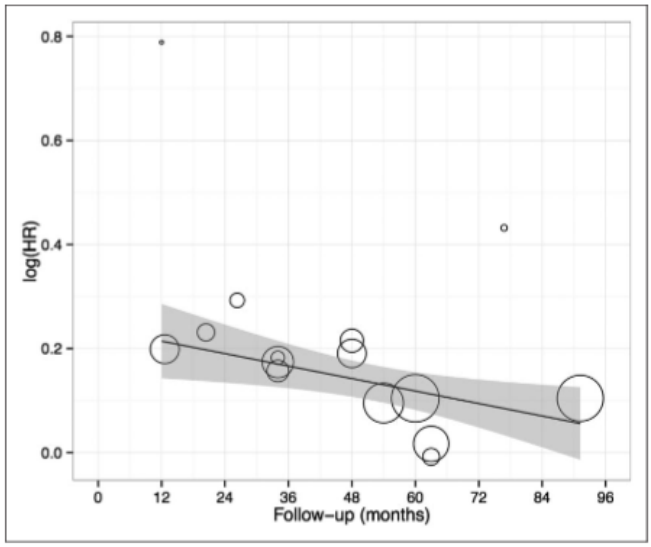

Figure 4. Log(HR) of AAA size vs study follow-up. The solid line represents the regression line and the shaded gray area corresponds to the 95% CI. Each circle represents a different study and the size of the circle is proportional to the weight of study (inverse variance = 1/standard error^2 of the HR).

association of a decreased risk with larger AAA during follow-up. In addition, the long-term success of the index EVAR procedure and variations in endoleak rates and reporting is not accounted for. Future studies comparing endoleak rates, AAA diameter and the effect on aneurysm related mortality is warranted to better understand this relationship.

In addition, this review contains a mixture of study designs: single surgeon series, tertiary single center studies, national registries, treatment specific registries and post hoc randomized trials. Therefore, heterogeneity is expected in such an analysis. We were able to reduce heterogeneity by grouping studies into type of repair (OAR and EVAR).

As more AAA are repaired with endovascular therapy and open repair is reserved for a selected population,[38] estimating the influence of AAA diameter in relation to repair method will be susceptible to selection biases. We recommend that future studies reporting on late predictors of survival following AAA repair should include AAA diameter within the predictive modeling. In addition, AAA measurements should be kept as continuous data.[39] When applicable, separating the analysis according to type of repair might shed further light on the influence of repair type in relation to late survival.

Conclusion

In conclusion, best estimate from the published literature appears to indicate that preoperative AAA diameter influences late survival following elective AAA repair. Larger AAA is associated with poorer survival and this association is greater for EVAR than OAR.

The inclusion of AAA diameter in the clinical decision-making process, therefore, seems warranted when considering the most appropriate surgical management option for individualizing patient care.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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8.6.5 Management of Modifiable Vascular Risk Factors Improves Late Survival following Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-Analysis. Annals of vascular surgery

ELSEVIER

General Review

Management of Modifiable Vascular Risk Factors Improves Late Survival following Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-Analysis

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Background: The main determinants of survival following abdominal aortic aneurysm (AAA) repair are preexisting risk factors rather than the method of repair chosen. The main aim of this meta-analysis was to assess the effect of modifiable risk factors on late survival following AAA repair.

Methods: Electronic databases were searched to identify all relevant articles reporting the influence of modifiable risk factors on long-term survival (≥1 year) following elective open aneurysm repair and endovascular aneurysm repair.

Results: Twenty-four studies which comprised 53,118 patients, published between 1989 and 2015, were included in the analysis. The use of statin, aspirin, beta-blockers, and a higher hemoglobin level was all significant predictors of improved survival following repair with a hazard ratio (HR) and 95% confidence interval (CI) of 0.75 (0.70–0.80), 0.81 (0.73–0.89), 0.75 (0.61–0.93), and 0.84 (0.74–0.96), respectively. Smoking history and uncorrected coronary disease were associated with a worse long-term survival of HR 1.27 (95% CI 1.07–1.51) and HR 2.59 (95% CI 1.14–5.88), respectively.

Conclusions: Addressing cardiovascular risk factors in patients preoperatively improves long-term survival following AAA repair. Global strategies to improve risk factor modifications in these patients are warranted to optimize long-term outcomes.

Conflict of interest: The authors declare no conflict of interests.

Funding: No funding has been received.

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Ann Vasc Surg 2016; ■: 1–11
http://dx.doi.org/10.1016/j.avsg.2016.07.066

Manuscript received: February 8, 2016; manuscript accepted: July 27, 2016; published online: ■ ■ ■

INTRODUCTION

Weighing the risks of abdominal aortic aneurysm (AAA) rupture against the risks of operative mortality remains one of the most challenging decisions in AAA management. In the clinical setting, this judgment is usually part of a shared medical decision process between clinicians and patients. Ideally, this process would take into account comorbidities and estimates of life expectancy with or without repair. Unfortunately, predictive models to identify high-risk patients and to aid this process are not available.[1]

Results from a large Medicare database and a meta-analysis of randomized controlled trials have shown that there is no difference in overall long-term patient survival between endovascular

aneurysm repair (EVAR) or open aneurysm repair (OAR).[2,3] Therefore, existing comorbidities and cardiovascular risk factors appear to have the strongest impact on overall late mortality following AAA repair.

Nonmodifiable demographical factors, such as age, female gender, and several clinical risk factors (cardiac failure, renal impairment, chronic pulmonary obstructive disease, cerebrovascular disease, peripheral vascular disease, diabetes, and ischemic heart disease [IHD]), have been associated with a worse survival after AAA repair as documented and quantified in a recent systematic review.[4]

Given the importance of risk factor modification, the aim of this meta-analysis was to quantify and compare the impact of modifiable cardiovascular factors with long-term survival after AAA repair.

METHODS

A systematic review of published articles was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[5] In the PICOT[6,7] format, this topic was defined as follows:

Population: Patients undergoing elective AAA repair (via either OAR or EVAR)
Intervention and comparison: Presence/absence or magnitude of modifiable clinical preoperative risk factors
Outcome: All-cause mortality
Time frame: ≥1 year

Modifiable cardiovascular risk factors were defined as factors that could potentially be changed, addressed to any extent, or eliminated by the patient or physician preoperatively.

Two researchers (M.K. and J.R.) independently conducted the study selection, data extraction, and assessment of methodological quality. When disagreement arose, the reviewers met to resolve any issues. MEDLINE, EMBASE, and the Cochrane Library Database were searched via the OVID SP database. With the assistance of a clinical librarian, "exploded" medical subject heading terms for MEDLINE and Cochrane and EMTREE terms for EMBASE were used to broaden the keyword search for "abdominal aortic aneurysm," "risk factors," "long-term survival," and "survival rate" along with their synonyms.

The search did not have any date restriction, and no limitations on publication language or study type were applied. The first search was conducted in May 2014, and it was updated in April 2015. A manual search of additional articles was conducted using references from relevant articles and review papers. The journals *Annals of Vascular Surgery*, *European Journal of Endovascular and Vascular Surgery*, *Journal of Endovascular Therapy*, *Journal of Vascular Surgery*, *Vascular Medicine* and *Vascular* were searched for any relevant articles published "online first." Abstracts of conference proceedings were searched for full-text publication. Eligible titles or abstracts were imported into Endnote X7 (Thomson Reuters) library, and full-text articles were obtained.

Both reviewers adhered to the following inclusion criteria: any studies reporting survival data and information about modifiable factors that may influence survival following elective AAA repair (OAR or EVAR); a primary outcome being all-cause mortality (survival) with at least 1-year follow-up; and sample size >100 patients. Studies containing a small proportion of patients (<40%) undergoing complex open (suprarenal clamping/visceral debranching) or fenestrated EVAR were included. The exclusion criteria were studies that only included small AAA (<5 cm), nonelective repairs, and octogenarians.

Study Selection

When known databases or studies from large registries were included, the most recent study containing the largest number of patients and relevant data was used. Data from national databases were also checked to ensure that data from individuals were not duplicated in other published series. If 2 or more studies presented data from the same database but different risk factors, then both studies were included in the review. Study authors were contacted when clarification was required.

Data Extraction and Quality Assessment

Data extracted from studies meeting the inclusion criteria were entered into a Microsoft Excel spreadsheet. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the quality of evidence and strength of each factor identified; this was conducted using GradePro (www.gradepro.org). The Newcastle–Ottawa Scale was also used to assess study quality, as it was anticipated that the majority would be observational studies.[8] This scale employs a 9-point (star) system that assesses 3 domains: patient selection, comparability of the study groups, and the ascertainment of study outcome. Studies with a score of 9 stars indicate a

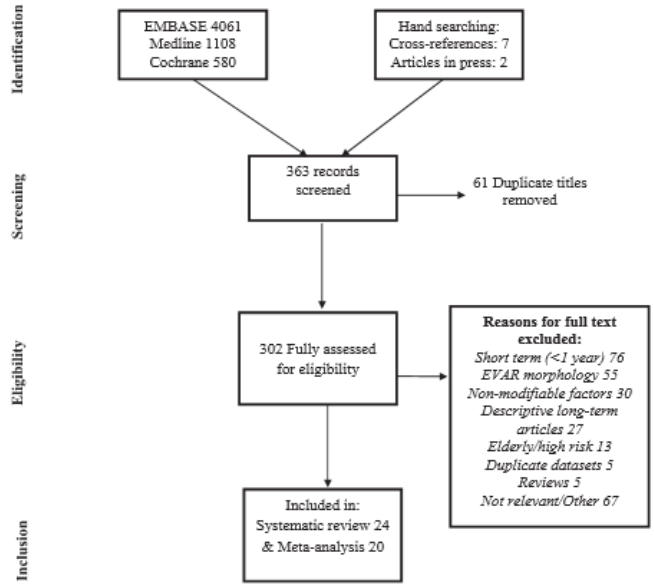

Fig. 1. PRISMA literature search flow diagram.

low risk of bias, whereas 7–8 stars indicate medium bias risk, and a score of ≤6 stars indicates a high chance of bias.

Statistical Analysis

A meta-analysis of time-to-event data was performed. Reported hazard ratios (HRs) and confidence intervals (CIs) from multivariable Cox proportional hazard models were extracted from individual studies. Pooled estimates with 95% CIs were calculated using a random effects model, due to expected heterogeneity among the studies. Heterogeneity was expressed with the I^2 statistic; degrees of heterogeneity were defined as greater than 25%, 50%, and 75%, respectively.[9] When CIs were not reported, estimates were calculated using reported ratios and *P* values.[10] Meta-regression was performed in R using inverse variance weights[11] for meta-analysis containing 10 or more studies. Statistical significance was set at a *P* value <0.05. The meta-analysis was performed using Review Manager Version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

RESULTS

The electronic search identified 5749 studies, of which 302 studies were included for full-text assessment (Fig. 1). Ten studies were identified from manually searching references[12–19] and "articles in press."[20,21] The systematic review included 24 studies consisting of 53,118 patients[12–35] (Table I).

All 24 studies were observational, of which 2 studies were *post hoc* analyses of prospective trials. Twelve studies were from the USA, 11 from Europe, and 1 from Asia. The year of publication ranged from 1989 to 2015. Ten studies included EVAR only, 6 studies included OAR, and 8 studies included both types of repair. There were 12 studies that reported mean[12,13,15,18,20,26,28,29,31–34] follow-up and 6 studies reported median follow-up information.[14,19,21–23,25] The mean (range) follow-up for studies reporting mean and median was

Table I. Summary of the included studies

Author	Country	Type of study	Number of patients	Repair type	Duration of study/follow-up (months)		Newcastle–Ottawa scale	Modifiable factor included	Adjusters/confounders
De Bruin[22]	Netherlands/Belgium	RCT *post hoc*	351	EVAR and OAR	7 years	76.8[a]	9	Statin use, antiplatelet/anticoagulation and tobacco use	Age, sex, reintervention, AAA size, hypertension, and cardiac, pulmonary, renal, and carotid disease
Diehm[12]	USA/Switzerland	Observational	731	EVAR	1994–2007	49.8	7	Statin use	Creatinine, cardiac and pulmonary disease
Diehm[13]	USA/Switzerland	Observational	711	EVAR	1994–2006	48	7	Hemoglobin	Age, AAA size, diabetes, statin use, renal and pulmonary scores
Galinanes[20]	USA	Observational	19,323	EVAR and OAR	2007–2008	12	7	Statin use	Age, sex, race, HF, COPD, and renal impairment
Grant[21]	UK	Observational	4070	EVAR and OAR	2000–2013	97.2[a]	9	Statin use	Age, sex, heart disease, renal impairment, diabetes, and anemia
Grant[19]	UK	Observational	506	EVAR and OAR	2007–2012	26[a]	8	Hemoglobin	Age, sex, diabetes, IHD, statin, renal impairment, and cardiopulmonary exercise variables
Grootenboer[23]	Europe	Eurostar registry	9227	EVAR	1996–2006	12.6[a]	8	Smoking and obesity	Age, sex, ASA scale, cardiovascular comorbidities, and AAA treatment characteristics
Hertzer[35]	USA	Observational	855	OAR	1976–2003	NR	8	Planned coronary revascularization	Age, AAA size, COPD, renal impairment, and graft configuration
Kertai[14]	Netherlands	Observational	510	OAR	1991–2001	56.4[a]	9	B-blockers and aspirin use	Age, sex, IHD, HF, diabetes, statin use, COPD, and renal impairment
Komori[24]	Japan	Observational	332	OAR	1979–1995	NR	9	Smoking	Age, hypertension, diabetes, and cardiac, pulmonary, renal, and cerebrovascular diseases

Lee[25]	USA	Observational	440	EVAR and OAR	1996–2004	83.4[a]	9	Statin, anticoagulation use, and smoking history	Age, COPD, stroke, steroids, dialysis, and enlarged heart
Leurs[26]	Europe	Eurostar registry	5892	EVAR	NR	17	7	Statin	Age, ASA, and cardiac disease
Masiracci[15]	USA	Observational	412	EVAR	1998–2005	48	8	Aspirin use	Age, HF, COPD, AAA size, and statin use
Matsumura[27]	USA	Prospective trial *post hoc*	334	EVAR and OAR	NR	NR	6	Smaller BMI	Pulmonary score, erectile dysfunction, platelet count, PVD, valve replacement, type of repair
Parmar[28]	USA	Observational	2063	EVAR and OAR	1985–2010	31	9	Smokers and statin use	Age, type of repair, sex, ethnicity, hypertension, and other atherosclerotic diseases/diabetes
Roger[16]	USA	Observational	131	OAR	1971–1987	NR	9	Smoking and uncorrected IHD	Age, sex, diabetes, hypertension, AAA size, creatinine, history of stroke, and cancer
Saratzis[18]	Greece	Observational	383	EVAR	2008–2011	34	7	Statin use	Age, sex, AAA size, renal impairment, hypertension, diabetes, IHD, PVD, and stroke
Saratzis[17]	Greece	Observational	224	EVAR	2008–2011	NR	7	Hemoglobin	Age, WBC, creatinine, AAA diameter, cancer history, C reactive protein, and endoleak type I
Starr[29]	USA	Observational	582	OAR	1983–1988	131	8	Uncorrected coronary disease	Age, renal impairment, IHD, and coronary angiographic findings
Stone[30]	USA	Observational	3455	EVAR and OAR	2003–2011	NR	9	Statin and aspirin use	Age, renal disease, IHD, heart failure, and COPD with and without oxygen
Tsilimparis[31]	Germany	Observational	119	EVAR	4 years	34	6	Current smoking	Age, IHD, and renal function

(*Continued*)

Table I. Continued

Author	Country	Type of study	Number of patients	Repair type	Duration of study/ follow-up (months)		Newcastle–Ottawa scale	Modifiable factor included	Adjusters/confounders
Welten[32]	Netherlands	Observational	1324	OAR	1995–2006	72	9	Statin use	Age, COPD, renal impairment, and dialysis
Winkel[33]	Netherlands	Observational	220	EVAR	2003–2008	34.8	7	Statin use	Age, perioperative troponin release, IHD, and renal failure
Zarins[34]	USA	LIFELINE Registry	923	EVAR	1998–1999	60	8	Obesity	Age, AAA diameter, ASA grade, family history of AAA, COPD, PVD, and other surgical procedures

Follow-up was reported as a mean unless otherwise stated.
ASA, American Society of Anesthesiologist; COPD, chronic pulmonary obstructive disease; HF, heart failure; NOS, Newcastle–Ottawa Scale; NR, not reported; PVD, peripheral vascular disease; RCT, randomized controlled trial; WBC, white blood cell.
[a]Median follow-up.

46.4 (12–131) and 58.7 (12.6–97.2) months, respectively. There were 7 modifiable factors reported and analyzed. The GRADE score of evidence was low for most of the factors (Table II).

Lipid-Lowering Agent Use

There were a total of 11 studies reporting the influence of statin/lipid-lowering use on survival.[12,18,20–22,25,26,28,30,32,33] There was some variation in the definition of use; 9 studies reported "statin use," 1 study examined "medication for hypercholesterolemia,"[25] and another included all types of "lipid modifying drug therapy."[28] Statin/lipid-lowering use had a protective role on overall survival, with a pooled HR of 0.75 (95% CI 0.70–0.80), I^2 = 14% (Fig. 2). When analysis was confined to the 9 studies reporting statin use, heterogeneity was reduced: HR 0.76 (95% CI 0.71–0.81), I^2 = 6%. In those studies, the proportion of patients using statins varied from 12.4% to 69.9%. In 2000, approximately 38% (95% CI 28–48) of participants in AAA studies used statins. Since 2000, the proportion of participants who used statins increased at a rate of about 2.7% each year (95% CI 0.7–4.8, $P = 0.016$) (Fig. 3).

Cardiac Revascularization

One study reported the survival advantage of planned coronary revascularization before AAA repair (HR 0.76, 95% CI 0.59–0.98)[35] and 2 studies specified the risk associated with uncorrected IHD (HR 2.59, 95% CI 1.14–5.88).[16,29]

Hemoglobin

Three studies included information on preoperative hemoglobin concentration, and the levels were analyzed as a continuous variable.[13,17,19] A higher baseline hemoglobin level was a protective factor, with an HR of 0.84 (95% CI 0.74–0.96), I^2 = 47%.

Aspirin and Anticoagulant Use

Six studies reported[14,15,21,22,25,30] the effect of antiplatelet or anticoagulation use after AAA repair. Definition of use varied by study; 3 studies[14,15,30] specified antiplatelet use as "aspirin," and the other 3 defined it as "antiplatelet,"[21] "antiplatelet/anticoagulant,"[22] or "Coumadin" use.[25] Antiplatelet use in 4 of these studies was associated with an overall protective effect, with an HR of 0.81 (95% CI 0.73–0.89), I^2 = 9% when compared with

Table II. GRADE assessment for outcomes influencing survival following AAA repair

Risk factor	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Statin use	11	Observational	Not serious	Not serious	Not serious	Not serious	Low
Obesity	2	Observational	Not serious	Not serious	Not serious	Very serious	Low
Antiplatelet	4	Observational	Not serious	Not serious	Not serious	Not serious	Low
Increase in hemoglobin	3	Observational	Not serious	Serious	Not serious	Serious	Low
Beta-blockers	2	Observational	Not serious	Not serious	Not serious	Not serious	Low
History of smoking	7	Observational	Not serious	Serious	Not serious	Not serious	Very low
Uncorrected coronary revascularization	2	Observational	Not serious	Very serious	Not serious	Serious	Very low

nonaspirin/antiplatelet users. In one study, antiplatelet/anticoagulation use was combined and 76.6% of the patients were receiving either one or both drugs[22] and thus was not included in the analysis as they were inseparable. Anticoagulation (Coumadin) use was associated with reduced survival compared with nonanticoagulation users, with an HR of 1.41 (95% CI 1.07−1.85) in one study.[25]

Beta-Blockers

Two studies reported the effects of preoperative beta-blocker use[14,22] compared with patients not receiving beta-blockers. Information on specific beta-blocker agents or doses was not specified. The pooled HR was 0.75 (95% CI 0.61−0.93) indicating a protective role following AAA repair.

Body Mass Index

Anthropometric measurements were reported as body mass index (BMI) in 3 studies.[23,27,34] However, there was inconsistency in the assessments and a lack of definitions for BMI categories. The Eurostar[23] and the Investigational Device Exemption trial[34] reported BMI as "obesity," whereas Matsumura et al. reported body measurements as "smaller BMI." The combined HR for these 2 studies was 0.86 (95% CI 0.76−0.99), revealing a protective effect with obesity. However, Matsumura et al.[27] reported that a smaller BMI was associated with improved survival (HR 0.29, 95% CI 0.12−0.69). Given the differences and lack of definitions for BMI, the pooled estimates of all 3 studies could not be performed.

Smoking History

Seven studies[16,22−25,28,31] used various definitions for smoking, which ranged from current smokers to history of smoking/nicotine use to ever smoked. Two studies specified "current smokers/smokers" rather than history of smoking.[28,31] The pooled HR for any history of smoking and current use was 1.27 (95% CI 1.07−1.51), $I^2 = 45\%$.

DISCUSSION

This systematic review has identified important modifiable risk factors published in the literature and quantified the pooled HRs for each factor using the reported estimates (Table III). The uses of lipid-lowering agents (statins), beta-blockers and aspirin were predictors of improved survival. Any smoking history, low preoperative hemoglobin

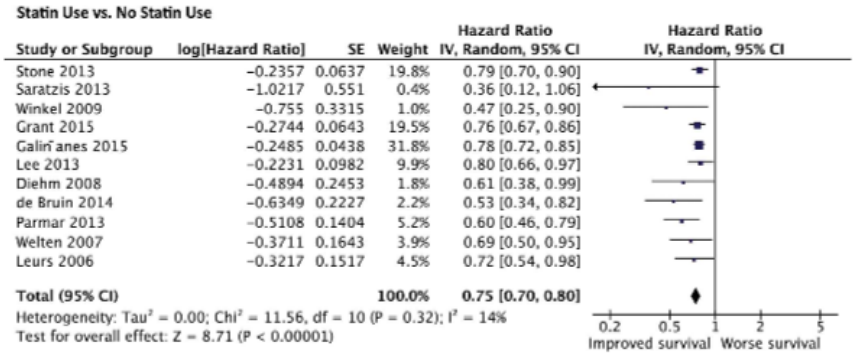

Fig. 2. Forest plot of statin use according to proportion of patients using statin in each study (top to bottom = highest to lowest percentage).

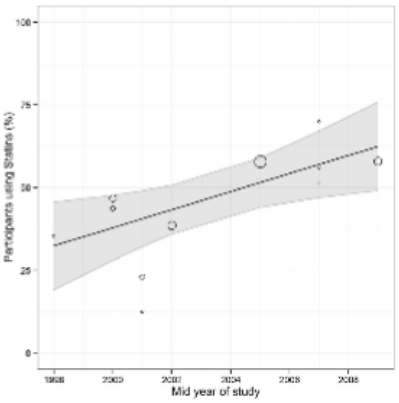

Fig. 3. Weighted linear regression of mid-year study and proportion of patients using statin (size of circle proportional to study size, and *shading* represents 95% confidence intervals).

levels, and uncorrected coronary artery disease were predictors of worse survival following elective AAA repair. The influence of BMI could not be determined.

The results from this study underline the importance of making efforts to improve patient cardiovascular risk factors before AAA repair to increase survival. Despite improvements in medical therapy and operative repair technology, a systematic review reported that estimated 5-year survival following elective AAA repair (OAR and EVAR) remained at about 69% (95% CI 67–71) for over 40 years.[36] Further improvements in survival may require better utilization of medical therapy, and future studies need to follow established guidelines to improve reporting of specific medications, doses, and durations of therapy and assess whether medical therapy has been optimized.

Although there has been an increase in statin use during the past 2 decades,[26] the proportion of patients receiving statins is still not optimal. The benefits of statin use in vascular surgery have been well documented. A meta-analysis by Antoniou et al.[37] observed that statin therapy reduced perioperative mortality and myocardial infarction in a population undergoing vascular procedures. In addition, a meta-analysis by Twine and Williams[38] concluded that patients receiving statin therapy had lower 5-year mortality following AAA repair than those who were not on statin treatment at the time of AAA repair. Our findings confirm these benefits in relation to long-term survival.

The results related to some factors are difficult to explain. BMI was observed to be both protective and harmful. In all studies, the categorization of obesity was not defined. This makes interpretation of the findings difficult. These results are also not consistent with those related to short-term (30-day) mortality, where obesity does not appear to have an influence after AAA repair.[39] Future reporting and definitions of BMI in AAA repair outcome studies is required to determine if an association exists.

Table III. Modifiable factors that influence long-term survival following AAA repair

Modifiable factor	Number of patients	Number of studies	HR (95% CI)	I^2 (%)	*P* value
Statin	38,252	11	0.75 (0.70–0.80)	14	<0.0001
Obesity	10,150	2	0.86 (0.76–0.99)	NA	0.03
Antiplatelet	8447	4	0.81 (0.73–0.89)	9	<0.0001
Increase in hemoglobin	1441	3	0.84 (0.74–0.96)	47	0.008
Beta-blockers	861	2	0.75 (0.61–0.93)	NA	<0.01
History of smoking (any)	12,663	7	1.27 (1.07–1.51)	45	<0.005
Uncorrected coronary revascularization	713	2	2.59 (1.14–5.88)	NA	0.02

NA, not applicable.

Two studies identified that uncorrected IHD was associated with worse outcomes; however, the results from a randomized trial suggest that there were no observed benefits when cardiac revascularization was performed before vascular surgery.[40] It is notable that the 2 studies were published before 1996, before the availability of statins and when interventional coronary procedures were in their early phases.

The association of low hemoglobin levels reported in 3 studies was interesting. The proinflammatory markers of AAA biology might be a direct cause of lower hemoglobin levels due to potential circulatory cytokines. In 2 studies, there was no difference in the proportion of patients with a history of cancer, indicating an unlikely association related to an oncological cause.[13,17] Two of these studies using similar data have defined low hemoglobin as anemia in other studies, which was reported to be a predictor of worse outcome. Further research in this field is warranted.

In this review, the use of antiplatelet therapy was beneficial, whereas the use of anticoagulation might be associated with a worse survival following AAA repair. However, data on the type of antiplatelet treatment and what other antiplatelet or anticoagulation therapy patients were receiving were not provided in the studies. Given the findings of this review, future studies should avoid combining antiplatelet and anticoagulation use in predictive modeling, as their effects appear to be opposing. Moreover, with newer antiplatelet and anticoagulation medications being utilized, reporting of individual drug type and dosage is required to shed further light on the influence of such drugs on long-term survival.

We noted high heterogeneity in the meta-analyses of 2 studies with a small number of patients (low power). However, heterogeneity in these instances needs to be interpreted with caution.[41] Another explanation for the heterogeneity may relate to differences in the definitions employed by the studies. When the differences were minimized, heterogeneity was decreased or eliminated, as was observed in the statin use groups.

Because randomized trials of preoperative risk factor modifications are unlikely to be conducted, it is important that observational studies follow established guidelines such as STROBE and strengthen the quality and reporting of these factors, so that associated risks or benefits of each factor can be more accurately quantified.[42]

Limitations

This review is strengthened by the large combined population included, but there were some limitations that should be mentioned.

The majority of the studies included were observational, and the inherited risks of bias and unknown confounder effects are likely present. The observational study design contributed to the predominantly low GRADE score for the individual factors reported.

Publication bias is another concern, as large centers with very good results are more likely to report such findings than smaller centers with average outcomes. Our review included studies of national databases, stent-graft registries, multi- and single studies, each with inherent weaknesses and strengths.

The inconsistency of definitions for risk factors reported also makes analysis and interpretation difficult in some instances, in particular when studies did not specify the timing of initiating medications. These data are usually presented in baseline patient characteristics format and it is unknown whether these medications were started pre- or postoperatively. Also, patient compliance or changes to medications are not recorded routinely in the studies included. Only one study verified the statin usage during follow-up and accounted for patients starting therapy during follow-up.[14]

This review documented the prevalence of modifiable factors that have been published. Apart from statin use and smoking history, few studies reported on the other modifiable risk factors included. Other factors that might be associated with improved survival such as physical activity, diet, and exercise tolerance have not been reported in the AAA literature.

CONCLUSIONS

Addressing modifiable cardiovascular risk factors in patients before elective AAA repair offers a clear, long-term survival advantage. Improved survival was associated with the use of statins, beta-blockers, and aspirin, while smoking and uncorrected coronary disease were associated with worse survival following AAA repair. These data are particularly useful in preoperative assessment and model development to aid clinical decision making.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.avsg.2016.07.066.

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