CLINICAL EPIDEMIOLOGY OF ANEURYSMS

OF THE ABDOMINAL AORTA

HJCM PLEUMEEKERS

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CLINICAL EPIDEMIOLOGY OF ANEURYSMS

OF THE ABDOMINAL AORTA

Klinische epidemiologie

van het aneurysma van de abdominale aorta

PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de rector magnificus

Prof. Dr. P.W.C. Akkermans MA

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Da steh ich nun, ich armer Tor!
Und bin so klug als wie zuvor.

(FAUST, JW Goethe)

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Manuscripts based on the studies described in this thesis

Chapter II — Pleumeekers HJCM, Hoes AW, Does E van der, Urk H van, Grobbee DE. Epidemiology of abdominal aortic aneurysms. Eur J Vasc Surg 1994;8:119-28.

Chapter III — Reitsma JB, Pleumeekers HJCM, Hoes AW, Kleijnen J, Groot RM de, Jacobs MJHM, Grobbee DE, Tijssen JGP. Increasing incidence of aneurysms of the abdominal aorta.(Submitted)

Chapter IV — Pleumeekers HJCM, Hoes AW, Mulder PGH, Does E van der, Hofman A, Laméris JS, Grobbee DE. Observer variability of ultrasound measurements of the abdominal aorta: the Rotterdam Study. (Submitted)

Chapter V — Pleumeekers HJCM, Hoes AW, Does E van der, Urk H van, Hofman A, Jong PTVM de, Grobbee DE. Aneurysms of the abdominal aorta in older adults: the Rotterdam Study. (Am J Epidemiol 1995;00:000-000)

Chapter VI — Pleumeekers HJCM, Hoes AW, Hofman A, Urk H van, Does E van der, Grobbee DE. Are aneurysms of the abdominal aorta of arteriosclerotic origin? Evidence from a population-based study. (Submitted)

Chapter VII — Pleumeekers HJCM, Hoes AW, Hofman A, Urk H van, Jong PTVM de, Does E van der, Grobbee DE. Selecting subjects for ultrasonographic screening of the abdominal aorta: Four different risk functions. (Submitted)

CHAPTER I

Introduction

Introduction

Case history.

A general practitioner is urgently called at 8.00 am in the morning because one of his male patients, 68 years of age, has collapsed with acute severe back pain, associated with vomiting. His medical record includes a history of high blood pressure since 10 years and increased serum cholesterol levels since 3 years. He uses atenolol 100 mg once daily and a cholesterol lowering diet. His last visit to the general practitioners' surgery was 6 weeks ago for his three monthly blood pressure check. There were no complaints at that moment and his blood pressure was 160/95 mm Hg.

On the morning of his urgent call the pain started three hours before in his back and radiated to his upper belly. The general practitioner visits his patient at home and finds him lying in bed, his skin is grey and moisturized. His pulse is weak and fast, 110 beats/min, and his blood pressure is 90/60 mm Hg. The abdomen is tender on palpation, and no abnormal masses are palpated. He is transported to the hospital by ambulance for his bad condition and for further diagnostic procedures. The electrocardiogram shows no signs of recent infarction, but ultrasound examination of the abdomen reveals a ruptured abdominal aortic aneurysm of 6 cm in anterior-posterior diameter. At 9.00 am an emergency operation is performed. The aneurysm is opened and a Dacron graft is inserted. After surgery, however, the patient does not regain consciousness and requires artificial respiration. Three days later he dies because of multiple organ failure. Permission for obduction is not given.

Once or twice a year a general practitioner is confronted with a patient with an abdominal aortic aneurysm. Sometimes presenting as dramatic as described above, sometimes as a chance finding in a patient seen for other reasons. When a patient dies as a result of a ruptured abdominal aortic aneurysm the question may be raised whether this death could have been prevented if the aneurysm was diagnosed earlier.

About 1% of all deaths in men of 55 years or older are caused by rupturing of an aneurysm of the abdominal aorta. Although the occurrence of this disease seems to be increasing, in both men and women, knowledge about the prevalence, incidence, etiology and risk factors of abdominal aortic aneurysms is incomplete. Such knowledge is, however, of importance in the discussion whether early detection can improve the prognosis of the disease.

In this thesis, the results of studies into the clinical epidemiology of

abdominal aortic aneurysms will be given. Most studies are part of the Rotterdam Study, a prospective cohort study among all inhabitants aged 55 years or older living in Ommoord, a suburb of Rotterdam. The primary aim of the Rotterdam Study is to investigate determinants of occurrence and progression of chronic disabling disease in elderly subjects.

This thesis is the result of close collaboration between the departments of Epidemiology & Biostatistics, General Practice and Vascular Surgery from Erasmus University. The advantage of a collaboration between general practitioners and epidemiologist in solving questions raised by day-to-day clinical practice has been recognized from the start of the scientific programme of the department of General Practice at Erasmus University and the results of the first project was laid down in 1979 in a combined thesis (1). We hope our work further illustrates the potential of incorporating the epidemiological approach in applied research in primary care.

In chapter II, the epidemiology of aneurysms of the abdominal aorta is described. The literature from the last three decades is reviewed with emphasis on prevalence, incidence, risk factors and prognosis.

The contribution of abdominal aortic aneurysms to mortality and morbidity in the Netherlands in the time period between 1972 to 1992 is described in chapter III. In addition, the in-hospital mortality for abdominal aortic aneurysms is studied.

In chapter IV, data on the accuracy of ultrasound measurements of the diameter of the abdominal aorta are presented.

Age- and gender specific prevalence of abdominal aortic aneurysms among 5,283 participants (3,066 women and 2,217 men), aged 55 years and older participating in the Rotterdam Study are given in chapter V.

In chapter VI, risk factors for abdominal aortic aneurysms are studied. Notably, the extent to which arteriosclerosis plays a part in the etiology of abdominal aortic aneurysms is addressed. In addition, the potential role of connective tissue weakness in promoting the formation of abdominal aortic aneurysms is investigated.

In chapter VII, four risk functions are described that may be applied in clinical practice to identify subjects with an increased risk of abdominal aortic

aneurysms and to select candidates for further ultrasonographic measurements.

Chapter VIII contains the main conclusions drawn from foregoing chapters. Further attention is paid to the implications for daily clinical practice and for screening programmes for abdominal aortic aneurysms in general. Finally, suggestions for further research are given.

References

1. Does E van der, Lubsen J. Acute coronary events in general practice: The Imminent Myocardial Infarction Rotterdam Study. Thesis. Rotterdam Erasmus University, 1979.

CHAPTER II

Epidemiology of abdominal aortic aneurysms

Introduction

Aneurysms of the abdominal aorta are a common cause of death. Ruptured abdominal aneurysms account for 1.3% of the deaths in men over 65 years of age (1). In principle, most of these deaths are preventable because asymptomatic aneurysms can be treated surgically. In 1952, Dubost (2) was the first to replace an aneurysmatically dilated abdominal aorta with graft material. Since then the prognosis of aneurysms of the abdominal aorta has changed dramatically. Nowadays the elective peri-operative mortality is less than 5% (3) and a patient surviving aortic grafting has a life expectancy similar to that of men and women in the same age category (4). In case of rupture of an abdominal aortic aneurysm only one out of three patients reaches the hospital alive. The reported mortality rates for emergency surgery for ruptured aneurysms vary from 30 to 63% (4-7).

Despite the importance of aneurysms of the abdominal aorta, little is known about its prevalence, incidence, risk indicators and prognostic factors. Only in recent years several studies dealing with the epidemiology of abdominal aortic aneurysms have been performed. This may be related to the development of ultrasound diagnosis in the mid-seventies, a technique which provides an easy, inexpensive and accurate method to detect aneurysms.

In this article the available literature on etiology, diagnosis, prevalence, incidence, risk indicators, and prognosis of abdominal aneurysms is reviewed. The objective of this review is to detect lacunas in the knowledge on the epidemiology of aneurysms of the abdominal aorta and to provide suggestions for future research in the light of the question whether population screening for aneurysms of the abdominal aorta should be advocated or not.

Etiology

Regarding the etiology of aneurysms, three theories have emerged: the genetic theory, the proteolytic enzyme theory and the trace metal theory (12). Aneurysms of the abdominal aorta were first thought to be of arteriosclerotic origin (8-10,43). Martin (11) was the first to question this concept, suggesting

that arteriosclerosis may not be the cause but rather the consequence of aortic degeneration. Sterpetti and co-workers (12) proposed the existence of two types of abdominal aneurysms. The first type is associated with arteriosclerotic occlusive disease and the other is not. In their study of 526 patients undergoing aneurysmal resection, 25% of the aneurysms was believed to be non-arteriosclerotic. There were significantly more ruptures in this group, compared to the arteriosclerotic group. Also, a positive family history of abdominal aortic aneurysms was reported more frequently in the group of the non-arteriosclerotic patients. Other differences between arteriosclerotic and non-arteriosclerotic patients with aneurysms suggest a generalized weakness of the aorta wall in non-arteriosclerotic aneurysms. This may explain the higher risk of rupture and the increased incidence of false aneurysms after the operation of aneurysms in these patients. They also appear to have a higher risk of aneurysms at other sites of the arterial tree.

The finding that men with a first degree relative with an abdominal aortic aneurysm experience a 10 fold increased risk of developing an abdominal aneurysm (13-19), provides a strong argument for a genetic component. Genetic variation on chromosome 16 in patients with an abdominal aneurysm has been reported (20). This has been related to an increased activity of alpha-2 haptoglobuline leading to an acceleration of the hydrolysis of elastin fibres by elastase. Probably because of the polymorphism between haptoglobuline and cholesterol ester transfer protein, haptoglobuline may affect lipid metabolism in the arterial wall in the same way as the cholesterol ester transfer protein does, and may ultimately lead to arteriosclerotic changes.

Other studies focus on structural defects of the aortic wall caused by increased proteolysis (9,21-24). Busuttil and co-workers (25) demonstrated a high collagenase activity in the aortic wall of patients with an abdominal aortic aneurysm, which was even higher in patients with a ruptured aneurysm. Cannon and co-workers (26,27) performed a case-control study comparing smoking patients with an aneurysm with a control group of smoking patients with occlusive disease of the abdominal aorta (Leriche syndrome). The study population was restricted to smokers to adjust for smoking induced proteolysis. There was an increase in serum proteolytic enzyme in smokers with an aneurysm

and not in smokers with Leriche Syndrome suggesting a role of, possibly smoking-induced, protease-antiprotease imbalance in the etiology of aneurysms. Cohen and co-workers (28) demonstrated a genetic predisposition of subjects with an abdominal aneurysm to have the monozygote phenotype for alpha-1 antitrypsin. This may link the proteolytic enzyme theory to the theory of a genetic involvement in the development of aneurysms of the abdominal aorta.

A third theory, the trace metal theory, is based on the observation that in the blotchy mouse aneurysm formation is related to an X-linked chromosome defect leading to an abnormality of the copper metabolism (29-31). In patients with aneurysms of the abdominal aorta, Tilson and Davis (91) demonstrated copper deficiency in liver and skin biopsies. Copper is thought to play a role in the cross linkages of collagen and elastin, which forms the extracellular matrix of the aortic wall. A deficiency of the copper metalloenzyme lysyl oxidase could result in a deficiency of collagen and elastin and weaken the aortic wall, thus making it prone to aneurysm formation.

Diagnosis

In general, physical examination is considered to be inadequate to detect asymptomatic aneurysms because only very large aneurysms may be palpated (32-34). A plain X-ray of the abdomen may give an adequate estimate of the diameter of the aorta but calcification of the aorta wall is needed to make measurement of the aortic diameter possible. These calcification are present in about 75% of the patients with an aneurysm of the abdominal aorta (35,36). Aortography is invasive and it underestimates the aneurysm diameter when a thrombus is present. Therefore it is unsuitable for screening purposes. Ultrasonography and computer tomography of the abdomen have an accuracy varying from 97% to 100% (35,37). Of these two, ultrasonography is relatively less expensive en more easy to perform, which makes it the method of choice for screening (38).

The criteria on which the diagnosis aortic aneurysm is based differ among studies. Both diameters of 30 mm (34,39,40,41) or over and 40 mm (33) or over

are frequently used. The diameter of the human abdominal aorta in non-aneurysmatic subjects varies according to gender. In studies of subjects older than 50 years the mean ultrasound diameter of the infrarenal abdominal aorta ranges from 12 to 19 mm in women and from 14 to 21 mm in men (33,42,43). Some studies take this variance of the normal aorta diameter into account and several cut-off points are used. Lindholm et al. (44) consider an aneurysm to be present if the diameter of the abdominal aorta is larger than the diameter of the aorta at the renal bifurcation. Collin (33) takes an increase of 5 mm of the abdominal aorta compared with the suprarenal segment of the aorta as the cut-off point and others argue that an aneurysm is present when there is a localized dilatation with at least a 50% increase in diameter compared to the aorta diameter at the bifurcation of the renal artery (45).

Prevalence

Estimates of the prevalence of abdominal aortic aneurysms may be obtained from population screening surveys, autopsy studies, or "epidemiological necropsy" studies.

In table 2.1. the results of nine screening surveys are given. These studies were restricted to caucasians. Data on other racial groups are not available. The reported prevalence in subjects of 50 years or older varies between 1.4% and 8.2%. Scott (40) observed a prevalence in men of 7.8% and in women of 1.4%. In a Dutch study, 4026 patient who had been referred to a hospital for ultrasound examination of the abdomen, ultrasound examination of the abdominal aorta was performed routinely (46). None of these patients were referred because of a suspected aneurysm. In 7.7% of the men and in 2.9% of the women an abdominal aneurysm of 30 mm or larger, or an increase of the distal aorta of at least 50% compared to the proximal part, was present. All the other screening surveys were restricted to men.

In table 2.2. prevalence estimates based on autopsy records are given. The prevalence in men varies from 1.4 to 4.3% and in women from 0.5% to 2.1%. Autopsy surveys comparing black and white subjects report a 3 times higher

prevalence among whites (47). Obviously, figures based on autopsy reports may be biased because patients who have autopsy are selected by cause of death. It seems reasonable to assume that sudden unexpected deaths are more likely to have autopsy than for example a patient dying of cancer. This could lead to an overestimate of the prevalence of abdominal aortic aneurysms, since death as a result of a ruptured aneurysm usually occurs suddenly. This is demonstrated by the results of Bengtsson and co-workers (48). They found a prevalence of abdominal aneurysms in 1986 of almost 8% in men over 50 years of age. This is rather high compared to the figures in table 2.1.

To reduce this selection bias the method of epidemiological necropsy has been developed. In these studies all necropsies in patients which a suspected

Table 2.1. Prevalence of aneurysms of the abdominal aorta in screening surveys.

First Author	Age	Gender	Number	Response rate (%)	Criterium (mm)	Prevalence (%)
Collin (33)	65-74	m	824	51.7	>30	5.4
O'Kelly (58)	65-74	m	1195	76.0	>25	7.8
					>40	1.5
Loh (75)	≥55	m	1293	50.8	>30	2.9
Scott (40)	65-80	m/w	7200	58.8	>29	4.3
Akkersdijk (46)	≥50	m/w	4026		>29	4.9
Smith (18)	65-75	m	2669	76	>29	8.2
					>40	3.0
Krohn (41)	≥60	m	500	46.6	>29	8.2
Lacarotti (89)	≥65	m	1748		>40	1.5
Bengtsson (90)	≥74	m	375		>40	3.3

m = men; w = women; All screening surveys used general practitioner records to identify subjects for screening. Akkersdijk et al. (46) used a population referred for abdominal ultrasound examination. Two studies (33,41) also used the change in diameter of the abdominal aorta compared to the normal aorta diameter, besides the absolute diameter of the abdominal aorta to define aneurysms.

Table 2.2. Prevalence of aneurysms of the abdominal aorta based on autopsy records.

First Author	Age	Number	Period	Prevalence (%) M	W
Bengtsson (48)	≥ 50	45,838	1958-86	4.3	2.1
McFarlane (49)	≥ 50	5,244	1950-84	2.6	1.3
Turk (76)	≥ 50	1,544	1963-64	2.3	1.6
Darling (64)	all ages	24,000	1952-75	1.4	0.5

≥ 50 = the denominator includes all post-mortem examinations in patients older than 50 years, in the given period; All ages = the denominator includes all post-mortem examinations in the given period; M = Men; W = Women.
NB No criteria for abdominal aneurysm are mentioned. The prevalence is the mean prevalence over the total study period.

diagnosis of an abdominal aortic aneurysm are excluded. Analogously, all deaths occurring outside the hospital are excluded, since out-of-hospital sudden deaths are more likely to lead to an autopsy than other out-of-hospital deaths. In the remaining autopsies the prevalence of aneurysms is then calculated. Prevalence figures obtained by this technique of "epidemiological necropsy" are similar to the results of screening surveys and vary in white males from 3.1% to 5.8% (49).

Incidence

The reported incidence of aneurysms of the abdominal aorta varies from 3.0 per 100,000 person years in women to 117.2 per 100,000 in men aged 55 years or over (table 2.3). The reported mortality from abdominal aneurysms varies between 0.91 per 100,000 person years in women and 47.1 per 100,000 person years in men (table 2.4). These results are based on hospital discharge and mortality statistics. The individual studies are difficult to compare because the age distribution varies across studies. In most studies an approximately fourfold incidence in men compared to women has been reported. In a study in Western

Australia (5) a relatively high incidence of abdominal aortic aneurysms was reported (117.2/100,000 person years). This may be attributed to fact that the study population was restricted to men older than 55 years of age. The other incidence estimates are based on studies in the general population. Almost all studies show a marked increase in the incidence of ruptured and non-ruptured abdominal aneurysms during the last decades. Only Lilienfield and co-workers (50) did not demonstrate an increasing incidence over the period from 1968 to 1981. This may be attributed to the use of death certificates only to calculate the population incidence, while other studies also used hospital records and autopsy reports. The increasing incidence of abdominal aortic aneurysms could reflect the influence of advancing diagnostic and surgical procedures in the last decades.

Risk indicators

Several risk indicators of aneurysms have been reported (table 2.5). Male sex is one of the most important risk indicators. For example, hospital admissions for abdominal aneurysms occur three times more often in men compared to women (51). In the United States death due to ruptured abdominal aortic aneurysms is about five times more common among white men than among white women (50). In England and Wales the age-standardized mortality rate for aneurysms is twice as high for men than for women (51). There is evidence, however, that these gender differences are decreasing. Since the late seventies an increased incidence of abdominal aneurysms among women has been reported in several countries (5,51,50). In a study from Australia (5) during the period 1971-81, a more than 100% increase of abdominal aortic aneurysms in men was found, while in women of the same age category a more than 200% increase in the incidence of aneurysms was reported. Scott and co-workers (40) reported a 1.4% prevalence for women between 65 and 80 years. The corresponding prevalence in men was 7.8%. After adjustment for differences in age the prevalence in men was 5.3 times higher than in women.

Age is clearly related to the risk of abdominal aneurysms. Death from a ruptured aneurysm is uncommon below the age of 55, but is more common with

advancing age. In men, a 10-fold increase in the incidence of abdominal aortic aneurysms from 55 up to 85 years of age has been reported (52,53). Scott and co-workers (40) found a more than sevenfold increase of deaths due to ruptured aneurysms with advancing age: 0.2% in those younger than 65 years of age died of a ruptured abdominal aortic aneurysm, compared to 1.5% in those above 81 years of age. In an autopsy study by Bengtsson and co-workers (48) a clear

Table 2.3. Incidence of aneurysms of the abdominal aorta and trends over time.

First Author	Period	Data source	Incidence @ /100,000 py			Trend # %/year
			Men	Women	Total	
Melton (77)	1951-80	1,2,3	NR	NR	31.9	+11
Castleden (5)	1971-82	1,3	117.2	33.9	NR	+4.2/6.3*
Fowkes (51)	1968-84	1	11.3	3.0	NR	+8/14 *
Ingoldby (74)	1974-83	1,2,3	NR	NR	17.0	+10
Naylor (78)	1971-1984	1	NR	NR	63.6	+6

1 = Hospital records; 2 = Death certificates; 3 = Autopsy reports; NR = not reported, py = person years; @ Incidence (per 100,000 person years) is calculated by taking the highest incidence reported in the study period. The denominator represents the total population, except in the studies by Castleden and Naylor, where the denominator consists of persons of 55 years or older.
# The trend is calculated by dividing the difference between the first and last year of study by the duration of the total study period. The incidence in the first year of the study is set at 100%
* Yearly trends for men and women are calculated separately.

increase of the prevalence of aneurysms in men from 55 years onwards was reported. The highest prevalence was found at the age of 80 years (5.9%). The prevalence in women increased from 70 years onwards and peaked at 90 years (4.5%).

The age-related prevalence of abdominal aneurysms in necropsies in the period 1970-84 (49) is given in Figure 1. An increase in the prevalence of aneurysms in men and women with advancing age is present. The difference in

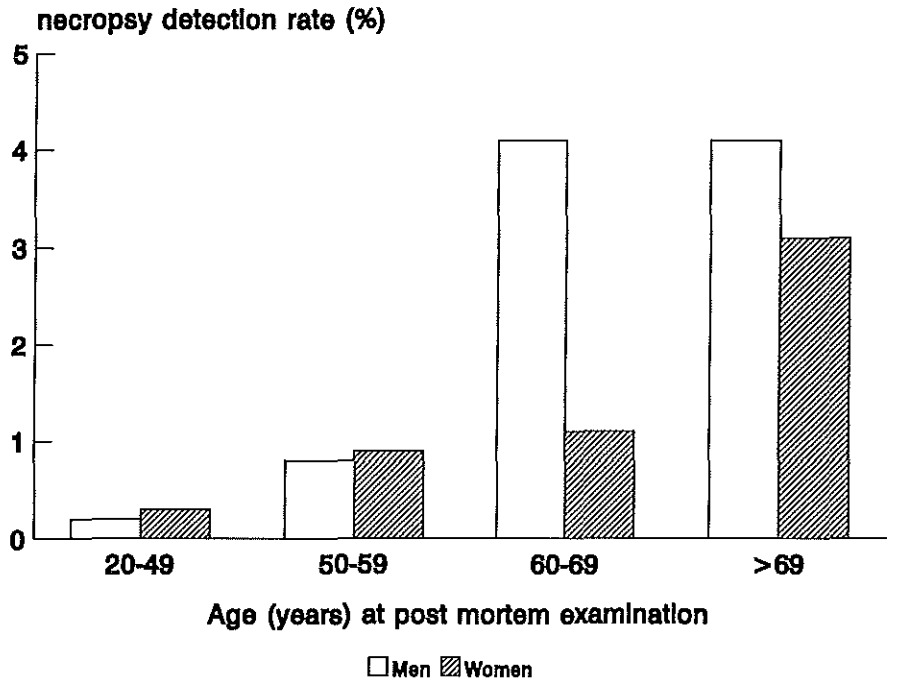

Figure 2.1. Necropsy detection rates (%), by age and gender, of aneurysms of the abdominal aorta in the United States in 1981 (49).

the necropsy detection rate between men and women seems to decrease with advancing age. This may partly result from selective survival of women with abdominal aortic aneurysms, or could be explained by assuming that aneurysm formation starts ten years later in women than it starts in men. Further, the possibility should be considered that the increased prevalence of abdominal aortic aneurysms demonstrated in these studies could be the result of the cumulation of a constant incidence over time, rather than an increased incidence with advancing age. This phenomenon is suggested by Bengtsson et al. (48) despite the fact that they conclude that a positive trend in incidence with advancing age exists.

Lillienfield (50) studied racial differences in mortality rates of aneurysms. In 1981 the annual rate of fatal aneurysms in white men was 5.0 per 100,000 patient years versus 1.5 per 100,000 patient years (relative risk of 3.3) in non-

white men. In women, this difference was less pronounced; 0.91 per 100,000 in white women per year versus 0.64 per 100,000 in non-white women per year (relative risk 1.4). In another study (47) the prevalence among white men was twice as high as in non-white men, whereas the prevalence in white and non-white women was similar. In an autopsy study Auerbach and Garfinkel (54) reported a prevalence of 2.4% in black subjects and 7.5% in whites. Although these studies show considerable racial differences in the prevalence of abdominal aortic aneurysms, this may at least partly be explained by differences in accessibility to medical care for white and non-white men and women.

Table 2.4. Mortality from aneurysms of the abdominal aorta and trends over time.

First Author	Period	Data Source	Incidence @ /100,000 py			Trend # %/year
			Men	Women	Total	
Mealy (79)	1979-86	1,3	23.1	6.2	17.6	+8.5
Lillienfield (50)	1968-81	2	5	1	NR	-0.3/-0.4*
Fowkes (51)	1950-84	1,2	47.1	22.2	NR	+16/28*
Johansson (6)	1980	1,2,3	8	3	6	

1 = Hospital records; 2 = Death certificates; 3 = Autopsy reports; NR = not reported, py = person years; @ Incidence (per 100,000 person years) is calculated by taking the highest incidence reported in the study period. The denominator represents the total population.
# The trend is calculated by dividing the difference between the first and last year of study by the duration of the total study period. The incidence in the first year of study is set at 100%
* Yearly trends for men and women are calculated separately.

The same difficulties arise when comparing different geographical areas. In England and Wales (51) a 9 times higher abdominal aortic aneurysm mortality rate compared to the United States (47.1 versus 4.9 per 100,000 person years) is reported. This could be the result of differences in medical practice and age- and gender differences between study populations.

To estimate the association between peripheral arterial disease and the

prevalence of abdominal aneurysms ultrasound screening of the abdominal aorta was performed in patients visiting out-patient clinics for peripheral vascular disease (55). The patients in the peripheral vascular disease group were compared to a control group with no signs of vascular disease. In male patients with peripheral vascular disease the prevalence of abdominal aortic aneurysms was 17% compared with 2.7% in the control group (relative risk 6.2). In a study of 201 patients with atherosclerosis (56), 9% appeared to have an unexpected abdominal aneurysm with a diameter of 35 mm or more. Collin (33) calculated the proportion of men with occlusive arterial disease who had an aneurysm, from

Table 2.5. Risk indicators for aneurysms of the abdominal aorta.

Risk indicator	References	Prevalence of AAA (%) in presence of risk indicator	Reported relative risk
Male gender	18,33,40,46, 45,48,75	3 to 8	2 to 4
Age >75	46,48,54,58 49,52	3 to 6	2 to 3
White race	50,54	2	1
Prior vascular disease	32,33,55,56, 80,81	5 to 20	2 to 10
Hypertension	8,33,34,40, 44,57,58	2 to 11	1 to 5
Cigarette smoking	8,26,33,54,56, 58,69,80	10 to 14	2 to 7
Family History	11,13-19,82 83,84	6 to 29	3 to 23
Hyper-cholesterolaemia	8,41	2 to 6	3

In case a proper control group was lacking, the relative risk range is estimated by dividing the highest reported prevalence to the expected prevalence in subjects of over 55 years of age: 2%.
AAA = Abdominal aortic aneurysm.

findings of a screening program in the population at large. In patients with ankle/brachial pressure indices of less than 0.8 and/or intermittent claudication, the prevalence of aneurysms was 15.2%. In the group without signs of peripheral vascular disease, the prevalence was 4.7% (relative risk 3.2).

The mechanic role of high blood pressure in the formation of aneurysms may seem obvious. Studies on this issue, however, have produced conflicting results. Allan (34) found 5.3% prevalence of abdominal aortic aneurysms among 168 hypertensive men and women. Twomey (57) screened 84 male patients visiting a hypertension clinic. Nine patients (10.7%) had an aneurysm of the abdominal aorta. However, these reports did not include a control group and were of limited size. Lindholm (44) screened 245 patients visiting a hypertension clinic and observed a prevalence in this group of 0.4%. Again, no control group was included. In two other studies comprising a control group, the prevalence of abdominal aneurysms in non-hypertensives was similar to that in hypertensive patients (33,40). O'Kelley and co-workers demonstrated a significantly higher risk of abdominal aneurysms in patients with a systolic blood pressure of 180 mm Hg or over compared with subjects with a lower systolic blood pressure (4.1 versus 1.2%) (58). No increased risk in patients with diastolic hypertension was found.

Smoking habits have been related to the occurrence of aneurysms (56). In a group of patients with peripheral vascular disease or coronary artery disease, aneurysms of the abdominal aorta were more prevalent among smokers compared to non-smokers. O'Kelley and co-workers (58) calculated a 4-fold risk of aneurysms for smokers compared to non-smokers (3.5 versus 0.9%).

Cholesterol is another cardiovascular risk factor believed to be associated with the occurrence of abdominal aneurysms. In an autopsy study of 8000 men (8), those with the highest cholesterol levels (6.3-13.9 mmol/L) were found to have a 2.3 times higher prevalence of abdominal aortic aneurysms than those with a low level of cholesterol (1.3-4.9 mmol/L). The authors concluded that the same factors associated with arteriosclerotic diseases were also associated with abdominal aortic aneurysms. It must be kept in mind, however, that these data are based on autopsy reports and that selection of patients may have influenced the results. This is illustrated by the results of a recent screening survey of

abdominal aortic aneurysms (41) in which no relation of serum cholesterol levels with the prevalence of aneurysms could be demonstrated.

A familial occurrence of aneurysms has often been demonstrated. In several studies a tendency of aneurysms to cluster in families was found. Darling and co-workers (13) compared 542 patients undergoing surgery for an abdominal aortic aneurysm with 500 patients without an aneurysm. In 15.1% of patients with an abdominal aneurysm one or more first degree relatives with an abdominal aneurysm were reported, compared to 1.8% in the control group. If two or more relatives in one family were affected, significantly more women were affected in these families. In a study of Webster and co-workers (17) a relative risk of having an abdominal aortic aneurysm for sisters of aneurysm patients compared to sisters of non-affected subjects of 22.9 was found (95% CI 8.4-49.9). The corresponding relative risk for brothers was 9.9 (95% CI 4.3-19.5). Parents of patients with an abdominal aneurysm and parents of those without an aneurysm were at similar risk of having an abdominal aortic aneurysm. Other studies also reported a high prevalence among siblings of aneurysm patients (15,16,18). In all but one study male siblings were more often affected than female siblings (approximately 29% versus 6%).

Finally, several other factors have been related to the occurrence of abdominal aortic aneurysms. These factors include body habitus (59), connective tissue abnormalities like inguinal hernia (26) and chronic obstructive lung disease, malignancies, number of pregnancies, immunologic impairment and alcoholic pancreatitis (45).

Prognosis

Determinants of rupture of aneurysms of the abdominal aorta are shown in table 2.6. Aneurysms tend to grow and with an increasing diameter the risk of rupture increases. In a population-based study (60) of patients with relatively small aneurysms a growth of 2 to 4 mm per year of abdominal aneurysms was estimated. Others (61-63) reported rates of growth for small aneurysms varying from 4 to 8 mm per year. The decision to perform elective surgical treatment of

abdominal aortic aneurysms is usually based on the fact that aneurysms larger than 50 mm are at increased risk of rupture. Nevertheless the absolute diameter is only weakly correlated with the risk of rupture of aortic aneurysms (60,64,66).

Darling and co-workers (64) studied 473 autopsies of patients with an abdominal aneurysm. In patients with an aneurysm of 40 to 70 mm, 25% of the aneurysms were ruptured and as much as 10% of the aneurysms with a diameter less than 40 mm was ruptured and led to the patient's death. On the other hand, follow-up studies (60,86-88) show that the rupture risk of patients with abdominal aortic aneurysms of less than 50 mm is very low. Ouriel and co-workers (65) standardized the aneurysm diameter to the supracoeliac aorta diameter, the predicted normal aorta size and the transverse diameter of the third lumbar vertebra. Only the latter correlated with the risk of rupture. None of the 36 patients with a ruptured aneurysm had a ratio between the transverse diameter

Table 2.6. Prognostic indicators of rupture of aneurysms of the abdominal aorta.

Prognostic indicator	Importance
Cigarette smoking (67-70)	++
Diastolic blood pressure (42,67)	+
Absence of peripheral vascular disease (12)	+
Ratio diameter vertebra L3/ AAA diameter > 1.0 (65)	++
Ratio normal aorta diameter/ AAA diameter > 2.7 (66)	+/-
AAA size > 50 mm (42,60,64,65)	+/-
Surgery unrelated to AAA (72)	+
Chronic obstructive pulmonary disease (42)	++
Pain and tenderness of AAA (73,42)	++
Sudden increase in size > 5 mm/ 6 months (63)	++
Fusiform shape of AAA (65)	+
Aortic blebs (71)	++

AAA = abdominal aortic aneurysm; + minor importance, +/- contrasting results, ++ major importance; Reference numbers are given in parentheses.

of L3 and the diameter of the aneurysm of less than 1. Based on another study (66) surgery is recommended in patients with a ratio of the diameter of the aneurysm and the aorta at the level of the superior mesenteric artery greater than 2.7, irrespective of the diameter of the aneurysm.

Besides the diameter of the aneurysm, other indicators of rupture risk have been investigated. Cronenwett an co-workers (42) followed 76 patients with an abdominal aneurysm. Aneurysmal diameters varied from 40 to 60 mm. They calculated a mortality risk from rupture of 5% per year. Diastolic blood pressure, initial anterior-posterior diameter of the aneurysm and the degree of coexisting pulmonary disease were independent predictors of rupture. Strachan (67), in a case-control study, compared smoking habits and diastolic blood pressure of patients with and without ruptured aneurysms of the abdominal aorta. An increase in the diastolic blood pressure of 10 mm Hg was associated with a 50% increased risk of rupture. He also reported a 15-times higher risk for smokers compared with lifelong non-smokers of death from a ruptured aneurysm, which was in accordance with other studies (68-70).

The anatomic structure of abdominal aneurysms seems to be of importance for the risk of rupture. Longer, fusiform aneurysms have a poorer prognosis than saccular ones (65). Aortic blebs, consisting of protrusions in the aortic wall and filled with thrombus en debris, are an indication of impending rupture (71). Also the risk of rupture of aneurysms seems to be higher when there is no evidence of peripheral vascular disease (12).

There have been some case reports about postoperative rupture of an aneurysm in patients operated for other reasons than aneurysm grafting (92,93). Durham and co-workers (72) followed 27 patients who underwent surgery unrelated to the aneurysm. One patient died of rupture 20 days after operation.

Prognosis after rupture is very poor (74,85). In a study of Johansson and co-workers (6) an overall mortality of 94% in patients with a ruptured abdominal aneurysm was reported. Although 67% of the patients reached hospital alive, only 15% were operated upon. The operation mortality was 62%.

Discussion

Aneurysms of the abdominal aorta are of increasing importance. Almost all studies have shown a marked increase in the incidence and prevalence of abdominal aortic aneurysms during the last decades. Although men are more often affected than women, women seem to be catching up rapidly with men (5,51). The increasing prevalence and incidence of abdominal aneurysms can not be explained by changes in diagnostic procedures or surgical practice alone, since these changes are likely to influence the occurrence of aneurysm in men and women equally. A true increase in incidence and prevalence probably exists.

The available prevalence estimates are often limited to men between 65 and 75 years of age. These figures are unlikely to be generalisable. Prevalence estimates in other age and gender categories are urgently needed. Also, more information about risk indicators of aneurysms is needed, in order to identify patients with a relatively high risk of having an abdominal aneurysm and to identify risk factors modifiable by preventive measures. Until now, only few risk indicators have been studied. Furthermore, in the majority of these studies a proper control group was lacking and thus no valid estimates of the relative risk are available. Most established cardiovascular risk factors such as smoking, cholesterol and hypertension, are associated with an increased risk of the occurrence of abdominal aortic aneurysms. Since these risk factors are also associated with the presence of atherosclerotic disease, further studies are warranted to asses whether these cardiovascular risk factors are etiologically related to aneurysm formation, or whether they are merely indicators of atherosclerosis, which often coincides with the presence of abdominal aortic aneurysms.

Randomized trials in patients with relatively small aneurysms are needed to provide estimates of rupture risk and efficacy of treatment in these patients. Special attention should be payed to risk indicators of aneurysm rupture. Their contribution to rupture risk should be quantified as such, that the decision to operate can be weighted more carefully and will not be based on diameter criteria alone, as is the case in most hospitals. When more patients with small aneurysms are diagnosed in large screening surveys the question how to handle

these patients becomes more urgent. Information on factors related to the prognosis of abdominal aneurysms will be essential in the development of screening strategies. Ideally, surgery should only be offered to those patients in whom rupture risk well exceeds the risk of surgery.

References

1. Collin J. Screening for abdominal aortic aneurysms. Br J Surg 1985;71:851-2.
2. Dubost C, Allery M, Oeconomos N. Resection of an aneurysm of the abdominal aorta. Arch Surg 1952;64:405-8.
3. Crawford ES, Saleh SA, Babb JW, Glaeser DH, Vaccaro PS, Silver A. Infrarenal abdominal aortic aneurysms. Factors influencing survival after operation. Ann Surg 1991;193:1699-708.
4. Fielding JWL, Black J, Ashton F, Slaney G, Campbell DJ. Diagnosis and management of 528 abdominal aortic aneurysms. Br Med J 1981;283:355-9.
5. Castleden WH, Mercer JC. Abdominal aortic aneurysms in western Australia: descriptive epidemiology and patterns of rupture. Br J Surg 1980;72:109-12.
6. Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. Br J Surg 1986;73:101-3.
7. Rantakokko V, Havia T, Igberg MV, Vänttinen E. Abdominal aortic aneurysms: a clinical and autopsy study of 408 patients. Acta Chir Scand 1983;149:151-5.
8. Reed D, Reed C, Stemmerman G, Hayashi T. Are aortic aneurysms caused by atherosclerosis? Circulation 1992;85:205-11.
9. Dobrin P. Pathophysiology and pathogenesis of aortic aneurysms. Surg Clin North Am 1989;69:687-703.
10. Zarins CK, Xu CP, Glagov S. Aneurysmal enlargement of the aorta during regression of experimental atherosclerosis. J Vasc Surg 1992;15:90-8.
11. Martin P. On abdominal aortic aneurysms. J Cardiovasc Surg 1978;19:597-8.
12. Sterpetti AV, Feldhaus RJ, Schultz RD, Blair EA. Identification of abdominal aortic aneurysms in patients with different clinical features and clinical outcomes. Am J Surg 1988;156:466-9.
13. Darling RC, Brewster DC, LaMuraglia GM, Moncure AC, Cambria RP, Abbot WM. Are familial abdominal aortic aneurysms different? J Vasc Surg 1989;10:39-43.
14. Norgard Ö, Rais O, Ängquist KA. Familial occurrence of abdominal aortic aneurysms. Surgery 1984;95:650-6.
15. Bengtsson H, Norrgård Ö, Ängquist KA, Ekberg O, Öberg L, Bergqvist D. Ultrasonografic screening of the abdominal aorta among siblings of patients with abdominal aortic aneurysms. Br J Surg 1989;76:589-91.
16. Webster MW, Ferrel RE, Jean PLS, Majumder PP, Fogel SR, Steed DL. Ultrasound screening

of first-degree relatives of patients with an abdominal aortic aneurysm. J vasc Surg 1991;13:9-14.

17. Webster MW, Jean PLS, Steed DL, Ferrel RE, Majumder PP. Abdominal aortic aneurysms: results of a family study. J Vasc Surg 1991;13:366-72.
18. Smith FCT, Grimshaw GM, Paterson IS, Tsang GMK, Shearman CP, Hamer JD. Community-based aortic aneurysm screening. Br J Surg 1992;79.
19. Johanson K, Koepsell T. Familial tendency for abdominal aortic aneurysms. JAMA 1986;156:1934-6.
20. Powell JT, Bashir A, Dawson S, Vine N, Henney AM, Humphries SE, Greenhalgh RM. Genetic variation on chromosome 16 is associated with abdominal aortic aneurysm. Clin Science 1990;78:13-6.
21. Reilly J, Tilson D. Incidence and etiology of abdominal aortic aneurysms. Surg Clin North Am 1989;69:705-11.
22. Summer D, Hokanson D, Strandness D. Stress-strain characteristics and collagen-elastin content of abdominal aortic aneurysms. Surg Gynecol Obstet 1970;130:459-66.
23. Dobrin P, Baker W, Gley W. Elastolytic and collagenolytic studies of arteries. Arch Surg 1984;119:405-9.
24. Powell J, Greenhalgh R. Cellular, enzymatic and genetic factors in the pathogenesis of abdominal aortic aneurysms. J Vasc Surg 1989;9:297-304.
25. Bussutil RW, Abou-Zamzam AM, Machleder HI. Collagenase activity of human aorta. A comparison of patients with and without abdominal aortic aneurysms. Arch Surg 1980;115:1373-8.
26. Cannon DJ, Casteel L, Read RC. Abdominal aortic aneurysm, Leriche's syndrome, inguinal herniation and smoking. Arch Surg 1984;119:387-9.
27. Cannon DJ, Read RC. Blood elastolytic activity in patients with aortic aneurysms. Ann Thorac Surg 1982;34:10-5.
28. Cohen JR, Sarfatti I, Ratner L , et al. Alpha-1 antitrypsin phenotypes in patients with abdominal aortic aneurysms. J Surg Res 1990;49:319-21.
29. Hollier LH, Stanson AW, Gloviczki P, et al. Arteriomegaly: classification and morbid implications of diffuse aneurysmal disease. Surgery 1983;93:700-8.
30. Rowe DH, McGoodwin EB, Martin GR, et al. A sex-linked defect in the crosslinking of collagen and elastin associated with the mottled locus in mice. J Exp Med 1974;139:180-92.
31. Hunt DM. Primairy defect in copper transport underlies mottled mutant in the mouse. Nature 1974;249:852-4.
32. Cabellon S, Moncrief CL, Pierre DR, Cavaugh DG. Incidence of abdominal aortic aneurysms in patients with atheromatous disease. Am J Surg 1983;146:575-6.
33. Collin J, Walton J, Araujo L, Lindsell D. Oxford screening programme for abdominal aortic aneurysms in men aged 65 to 74 years. Lancet 1988:613-5.
34. Allen PIM, Gourevitch D, McKinley J, Tudway D, Goldman M. Population screening for aortic aneurysms (Letter). Lancet 1987:736-7.

35. Lee KR, Walls WJ, Martin NL, Templeton AW. A practical approach to the diagnosis of abdominal aortic aneurysms. Surgery 1975;78:195-201.
36. Brewster DC, Darling RC, Raines JK, et al. Assessment of abdominal aortic aneurysm size. Circulation 1977;56:164-9.
37. Gomes M, Hakkal HG, Schellinger D. Ultrasonography and CT-scanning: a comparative study of abdominal aortic aneurysms. Comput Tomogr 1977;1:51-61.
38. Leopold GR. Ultrasonic abdominal aortagraphy. Radiology 1970;96:9-14.
39. Scott RAP, Ashton HA, Kay DN. Routine ultrasound screening in management of abdominal aortic aneurysm. Br Med J 1988;297:1709-10.
40. Scott RAP, Ashton HA, Kay DN. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. Br J Surg 1991;78:1122-5.
41. Krohn KD, Kullmann G, Kvernebo K, Rosen L, Kroese A. Ultrasonographic screening for abdominal aortic aneurysms. Eur J Surg 1992;158:527-30.
42. Cronenwett JL, Murphy TF, Zelenock GB, et al. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery 1985;98:472-83.
43. Zarin CK, Glagov S, Vesselinovitch D, Wissler RW. Aneurysm formation in experimental atherosclerosis: relationship to plaque evolution. J Vasc Surg 1990;12:246-56.
44. Lindholm L, Ejlertsson G, Forsberg R, Norgren L. Low prevalence of abdominal aortic aneurysms in hypertensive patients. Acta Med Scan 1985;218:305-10.
45. Anonymous. Suggested standards for reporting on arterial aneurysms. J Vasc Surg 1991;13:444-50.
46. Akkersdijk GJM, Puylaert JBC, Vries AC de. Het aneurysma aortae abdominalis als neven-bevinding bij echografisch onderzoek van het abdomen. Ned Tijdschr Geneeskd 1992;136:1907-13.
47. Johnson G, Avery A, McDougal G, Burnham SJ, Keagy BA. Aneurysms of the abdominal aorta in blacks and whites in North Carolina. Arch Surg 1980;120:1138-40.
48. Bengtsson H, Bergqvist D, Sternby NH. Increasing prevalence of abdominal aortic aneurysms. A necropsy study. Eur J Surg 1992;158:19-23.
49. McFarlane MJ. The epidemiologic necropsy for abdominal aortic aneurysms. JAMA 1991;265:2085-8.
50. Lillienfield DE, Gunderson PD, Sprafka JM, Vargas C. Epidemiology of aortic aneurysms: 1. Mortality trends in the United states, 1951 to 1981. Arteriosclerosis 1987;7:637-43.
51. Fowkes FGR, MacIntyre CCA, Ruckley CV. Increasing incidence of aortic aneurysms in England and Wales. Br Med J 1989;298:33-5.
52. Greenhalgh RM, Mannick JA. The cause and management of aneurysms. London, W.B. Saunders Company, 1991.
53. Bickerstaff LK, Hollier LH, Peenen HJ van, et al. Abdominal aortic aneurysms: the changing natural history. J Vasc Surg 1984;1:6-11.
54. Auerbach O, Garfinkel L. Atherosclerosis and aneurysms of the aorta in relation to smoking habits and age. Chest 1980;78:805-9.

55. Allardice JT, Allwright GJ, Wafula JMC, Wyatt AP. High prevalence of abdominal aortic aneurysms in men with peripheral vascular disease: screening by ultrasonography. Br J Surg 1988;75:240-2.
56. Lederle FA, Walker JM, Reinke DB. Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. Arch Intern Med 1988;148:1753-6.
57. Twomey A, Twomey EM, Wilkis RA, Lewis JD. Unrecognised aneurysmal disease in male hypertensive patients. Br J Surg 1984;71:307-8.
58. O'Kelly J, Heather P. General practice-based population screening for abdominal aortic aneurysms: a pilot study. Br J Surg 1989;76:479-80.
59. Liddington MI, Heather BP. The relationship between aortic diameter and body habitus. Eur J Vasc Surg 1992;6:89-92.
60. Nevitt MP, Ballard DJ, Hallett JW. Prognosis of abdominal aortic aneurysms. A population-based study. New Eng J Med 1989;321:1009-14.
61. Collin J, Aroujo L, Walton J. How fast do very small abdominal aortic aneurysms grow? Eur J Vasc Surg 1989;3:15-7.
62. Sterpetti AV, Schultz RD, Feldhaus RJ, Cheng SE, Peetz DJ. Factors influencing enlargement rate of small abdominal aortic aneurysms. J Surg Res 1987;43:211-9.
63. Delin A, Olsén H, Swedenborg J. Growth rate of abdominal aortic aneurysms as measured by CT. Br J Surg 1985;72:530-2.
64. Darling RC, Messina CR, Brewster DC, Ottinger LW. Autopsy study of unoperated abdominal aortic aneurysms. The case for early resection. Circulation 1977;56:161-4.
65. Ouriel K, Green RM, Donayre C, Shortell CK, Elliot J, DeWeese JA. An evaluation of new methods of expressing aortic aneurysm size: relationship to rupture. J Vasc Surg 1989;15:12-20.
66. Louridas G, Reilly K, Perry MO. The role of the aortic aneurysm diameter aortic diameter ratio in predicting the risk of rupture. S Afr Med J 1990;78:642-3.
67. Strachan DP. Predictors of death from aortic aneurysms among middle-aged men: the Whitehall study. Br J Surg 1991;78:410-4.
68. Khan H. The Dorn study of smoking and mortality among US veterans: report on 8 1/2 years of observation. Natl Cancer Inst Monogr 1966;19:1-125.
69. Hammond EC, Garfinkel L. Coronary heart disease, stroke and aortic aneurysms. Factors in the etiology. Arch Enverionm Health 1969;19:167-82.
70. Doll R, Peto R. Mortality in relation to smoking: 20 years of observation on male Britisch doctors. Br Med J 1976;ii:1525-36.
71. Hunter GC, Long SC, Yu GSM, McIntyre KE, Bernhard VW. Aortic blebs: possible site of aneurysm rupture. J Vasc Surg 1989;10:93-9.
72. Durham SJ, Steed DL, Moosa HH, Makaroun MS, Webster MW. Probability of rupture of an abdominal aortic aneurysm after an unrelated operative procedure: a prospective study. J Vasc Surg 1991;13:248-52.
73. Schatz IJ, Fairbairn JF, Juergens JL. Abdominal aortic aneurysms. Circulation 1962;26:200-5.

74. Ingoldby CJH, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. Br J Surg 1986;73:551-3.
75. Loh CS, Stevenson IM, Wu AVO, Eyes B. Ultrasound scan for abdominal aortic aneurysms. Br J Surg 1989;76:417.
76. Turk KAD. The post-mortem incidence of abdominal aortic aneurysms. Proc Royal Soc Med 1965;869-70.
77. Melton LJ, Bickerstaff LK, Hollier LH, et al. Changing incidence of abdominal aortic aneurysms: a population based study. Am J Epidemiol 1984;120:379-86.
78. Naylor AR, Webb J, Fowkes FGR, Ruckley CV. Trends in abdominal aortic aneurysm surgery in Scotland (1971-1984). Eur J Vasc Surg 1988;2217-21.
79. Mealy K, Salman A. The true incidence of ruptured abdominal aortic aneurysms. Eur J Surg 1988;2:405-8.
80. Thurmond AS, Semler HJ. Abdominal aortic aneurysm incidence in a population at risk. J Cardiovasc Surg 1986;27:457-60.
81. Sakalihasan N, Janssen N, Ries E, Creemers E, Limet R. Ultrasonographic screening for abdominal aortic aneurysms in patients with peripheral vascular disease. Br J Surg 1992;79,152.
82. Adams DCR, Tulloh BR, Poskitt KR. Screening for familial aneurysms. Br J Surg 1992;79.
83. Bengtsson H, Sonesson B, Lanne T, et al. Prevalence of abdominal aortic aneurysms in the offspring of patients dying from aneurysm rupture. Br J Surg 1992;79:1142-3.
84. Collin J, Walton J. Abdominal aortic aneurysms (AAAs): a familial disease. Br J Surg 1989;76:418.
85. Jenkins Mcl A, Ruckley CV, Nolan B. Ruptured abdominal aortic aneurysms. Br J Surg 1986;73:395-8.
86. Scott RAP, Ashton HA, Kay DN, Bowyer RC. Results of ultrasound follow-up of 102 abdominal aortic aneurysms. Br J Surg 1989;76:417-8.
87. Zoller WG, Schweke CK, Schweikhart HP, Spengel F Zöllner N. 15-jähriger Verlaufsbeobachtungen kleiner Bauchaortenaneurysmen. Klin Wochenschr 1992;69:147.
88. Brown PM, Pattenden R, Gutelius JR. The selective management of small abdominal aortic aneurysms: the Kingston study. J Vasc Surg 1992;15:21-7.
89. Bengtsson H, Bergqvist D, Ekberg O, Janzon L. A population based screening of abdominal aortic aneurysms (AAA). Eur J Vasc Surg 1991;5:53-7.
90. Lucarotti ME, Shaw E, Heather BP. Distribution of aortic diameter in a screened male population. Br J Surg 1992;79:641-2.
91. Tilson MD, Davis G. Deficiencies of copper and a compound with ion-exchange characteristics of pyridinoline in skin from patients with abdominal aortic aneurysms. Surgery 1983;94:134-41.
92. Swanson RJ, Littooy FN, Hunt TK, et al. Laparotomy as a precipitating factor in the rupture of intra-abdominal aneurysms. Arch Surg 1980;115:229-304.
93. Trueblood HW, Williams DK, Gustafson JR. Aneurysmal rupture following resection of abdominal malignancy. Am Surg 1976;42:535-7.

CHAPTER III

Increasing incidence of aneurysms of the abdominal aorta

Introduction

Recent reports from England and Wales, the United States and Australia have suggested an increase in mortality from aneurysms of the abdominal aorta during the last decades (1-3). Simultaneously, a marked increase in the number of hospital admissions and operations for these aneurysms was observed. The annual increase in the incidence of abdominal aortic aneurysms was estimated to be 4.2% in men and 14% in women (4).

Despite improvements in acute medical care, the prognosis for a patient with a ruptured aneurysm remains poor, with a mortality rate as high as 80% to 90% (5-8). After the first resection of an aneurysm of the abdominal aorta by Dubost in 1951, surgical treatment has become the standard treatment for aneurysms of a certain size (9). Mortality after elective surgery varies between 1.4% and 5% (3,10-18).

We studied the trends in the incidence of aneurysms of the abdominal aorta in The Netherlands by age, sex and calendar year from 1972 through 1992. In addition, changes in-hospital mortality after surgical treatment of abdominal aortic aneurysms were assessed.

Methods

Population data and the number of deaths due to aortic aneurysms in the Netherlands from 1972-1992 were obtained from Statistics Netherlands, Voorburg, The Netherlands. The number of deaths was grouped by 5-year age categories, sex and underlying cause of death. Causes of death were coded according to the International Classification of Disease (ICD). We used ICD-8 rubric aneurysm of the abdominal aorta (441.2) for the period 1972-1978, and we combined ICD-9 rubrics aneurysm of the abdominal aorta, ruptured (441.3) and without mentioning of rupture (441.4) for the period 1979-1992.

Data on hospital admissions for abdominal aortic aneurysms were obtained from the National Medical Register of SIG Health Care Information. In 1972, the starting point of this analysis, about 70% of all hospital admissions in The

Netherlands were recorded in this database, in 1978 this was 94%, and from 1986 onwards all admissions (100%) have been recorded. On the basis of these figures appropriate multiplying factors were used to estimate the total number of admissions in The Netherlands. Records include diagnoses at discharge, age and sex of the patient, duration of hospital stay, type of operations performed, and type of discharge (death or alive). The International Classification of Diseases Clinical Modification (ICD-CM) was used to classify diagnoses at discharge. For the period 1972-1979 we used ICD-CM-8 rubrics aneurysm of the abdominal aorta without (441.3) and with rupture (441.4). For the period 1980-1992 we used ICD-CM-9 rubrics aneurysm of the abdominal aorta with (441.3) and without rupture (441.4). Only first-listed discharge diagnosis were considered in this study.

For all admissions with a first-listed discharge diagnosis of abdominal aortic aneurysm it was determined whether an operation upon the aneurysm was performed. During the study period three different coding systems for operations were used. In the first two coding systems (1972-1989) operations on an abdominal aortic aneurysm were coded among a broader group of operations on abdominal arteries. The combination of a first-listed discharge diagnosis of abdominal aortic aneurysm and an operation from this group could result in a slight overestimation of the actual number of operations upon abdominal aortic aneurysms for that period.

In-hospital mortality (as a percentage) after surgery for non-ruptured or ruptured aneurysms of the abdominal aorta was calculated by dividing the number of patients who died in hospital after their operation by the total number of operations for aneurysms of the abdominal aorta.

Mid-year population figures were calculated by averaging the number of inhabitants in The Netherlands at the start and end of each year. Age adjusted rates were calculated by direct standardisation using the "new European standard population" as a standard (19). Age-specific rates were calculated using 10 year age-groups (45-54, 55-64, 65-74, 75-84, 85+).

Results

From 1972 through 1992 the population of The Netherlands increased from 13.3 million to 15.2 million. The number of inhabitants of 55 years or over increased from 2.6 million (19%) in 1972 to 3.4 million (22%) in 1992.

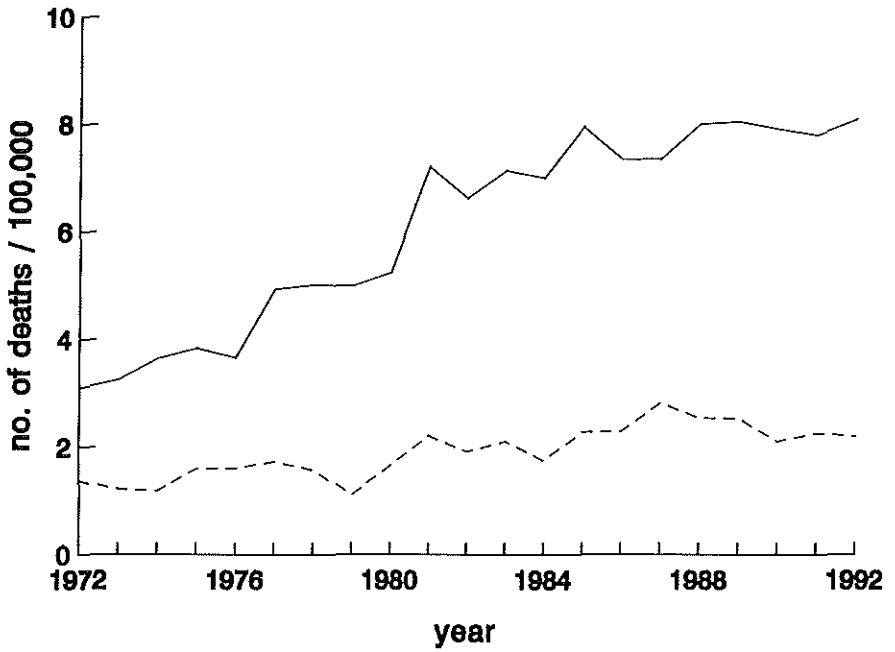

Figure 3.1. Age adjusted death rates for abdominal aortic aneurysms in men (solid line) and women (broken line)in the Netherlands from 1972-1992. Source: Statistics Netherlands. Standardized using the 'new' European Standard Population.

Mortality

The absolute number of deaths due to abdominal aortic aneurysms in The Netherlands rose from 231 in 1972 to 756 in 1992. For men, there was a 3.5-fold increase from 171 deaths in 1972 to 590 in 1992.

Table 3.1. Number of hospital admissions and in parentheses the percentage of admissions in which an operation was performed for ruptured and non-ruptured aneurysms of the abdominal aorta in the Netherlands from 1972 to 1992.

Year	Men		Women	
	ruptured	non-ruptured	ruptured	non-ruptured
1972	136 (44%)	204 (41%)	31 (23%)	62 (23%)
1977	329 (59%)	517 (58%)	43 (31%)	124 (34%)
1982	419 (63%)	1 034 (59%)	69 (36%)	171 (53%)
1987	655 (74%)	1 817 (65%)	114 (51%)	262 (52%)
1992	755 (67%)	2 724 (53%)	125 (59%)	398 (51%)

For women the number of deaths increase 2.8-fold from 60 to 166. Of all male deaths in 1992 above the age of 55 years 1.0% was attributed to aneurysms of the abdominal aorta. In women this proportion was 0.3%.

The age adjusted death rates for abdominal aortic aneurysms are shown in figure 3.1. In the 20-year period, the death rates for males increased 2.6-fold from 3.1 to 8.1 per 100,000 and for women 1.6-fold from 1.4 to 2.2 per 100,000. Analyses of age specific death rates for males showed that this rise was most pronounced in the higher age groups, especially in those above 75 years of age. In females, death due to abdominal aortic aneurysms was rare below the age of 75. The moderate rise in the age adjusted death rate for abdominal aortic aneurysms among women mainly resulted from a rise in those above the age of 85 years.

Hospital discharges

The total number of admissions with a first-listed discharge diagnosis of an abdominal aortic aneurysm increased from 433 (39% ruptured) in 1972 to 4,002

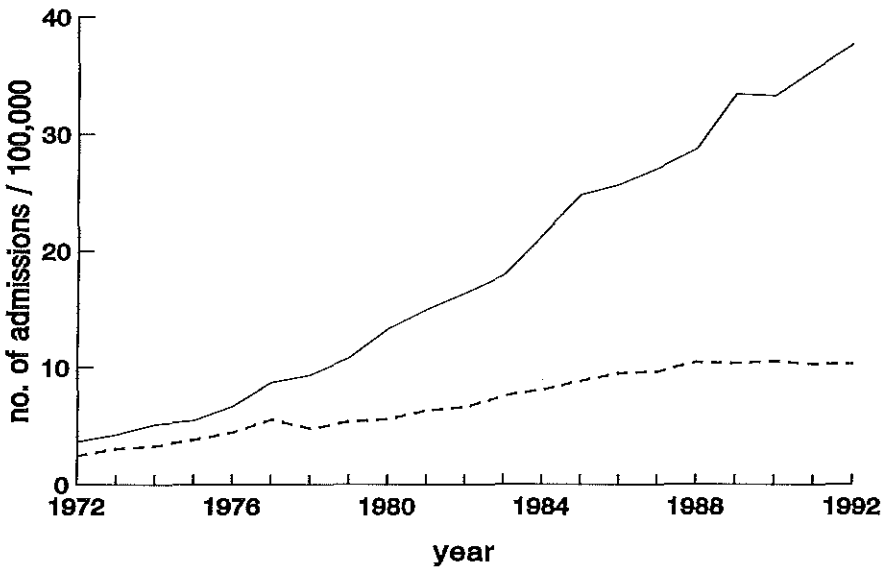

Figure 3.2. Age adjusted discharge rates for abdominal aortic aneurysms without rupture (solid line) and with rupture (broken line) in men in the Netherlands from 1972-1992. Source: SIG Health Care Information.

(22% ruptured) in 1992. In both men and women there was a marked increase in ruptured and non-ruptured cases, but the increase in non-ruptured aneurysms was more pronounced (table 3.1.). The contribution of ruptured cases of abdominal aortic aneurysms to the total number of admissions for ruptured aneurysms and for surgery upon non-ruptured aneurysms decreased from 63% in 1972 to 35% in 1992. The percentage of admissions for non-ruptured abdominal aortic aneurysms in which an operation was performed increased from 37% in 1972 to 53% in 1992, for ruptured aneurysms from 40% to 66%.

The age adjusted discharge rates for ruptured and non-ruptured aneurysms are shown in figure 3.2 (men) and figure 3.3 (women). In men, the age adjusted discharge rates for non ruptured abdominal aortic aneurysms increased 10-fold from 3.7 to 37.6 per 100,000. In women the increase was 4.6-fold from 1.2 to 5.5 per 100,000. For ruptured abdominal aneurysms these figures were less

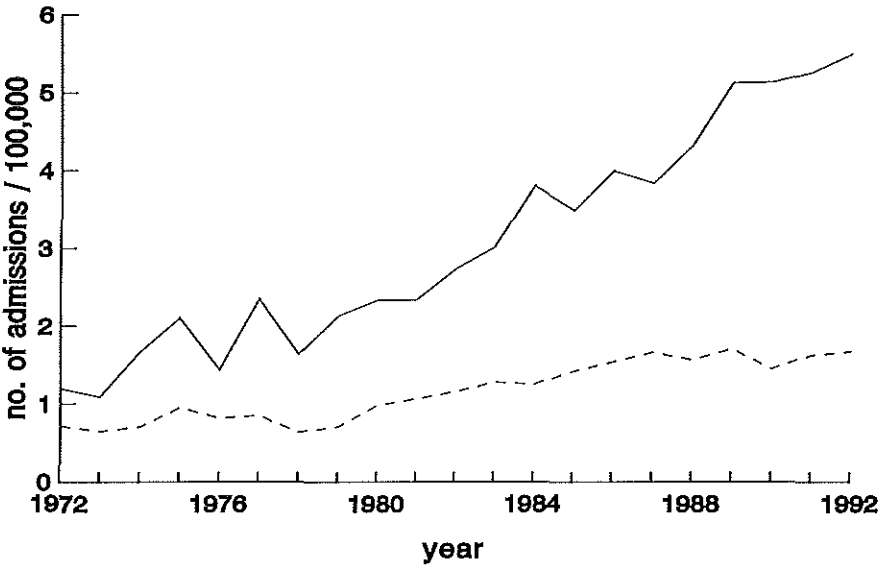

Figure 3.3. Age adjusted discharge rates for abdominal aortic aneurysms without rupture (solid line) and with rupture (broken line) in women in the Netherlands from 1972-1992. Source: SIG Health Care Information.

dramatic. In men there was a more than 4-fold increase from 2.4 to 10.3 per 100,000 and for women a 2.4-fold increase from 0.7 to 1.7 per 100,000.
For men, the age-specific discharge rates for non-ruptured abdominal aneurysms rose in all relevant age groups, but the increases were relatively higher in the age groups over 65 years of age (figure 3.4). In women, all age groups over 55 years of age contributed to the rise in hospital admissions for non-ruptured aneurysms of the abdominal aorta, although the largest increases were seen in the age groups between 65-84 years of age (figure 3.5).

In-hospital mortality

Age adjusted in-hospital mortality after surgery upon abdominal aortic aneurysms is presented in figure 3.6. In-hospital mortality after surgery upon non-ruptured aneurysms halved from 13% in 1972 to 7% in 1992 (men and women combined). In-hospital mortality in 1992 increased sharply with age from 4% in

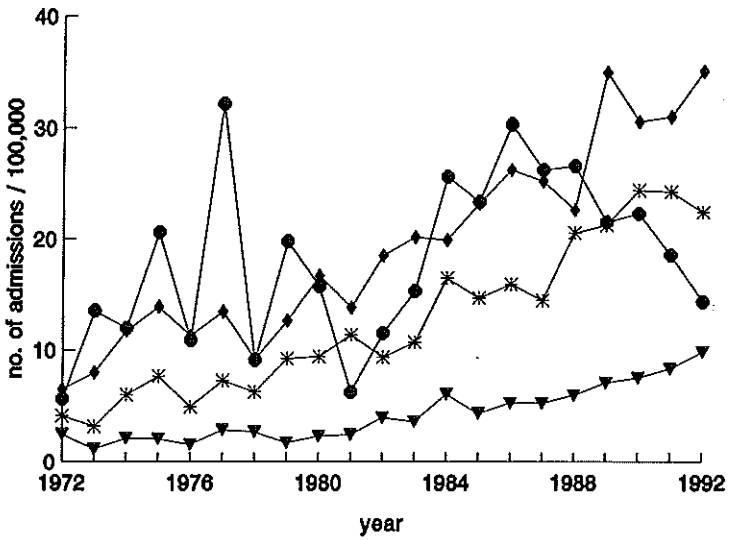

Figure 3.4. Age specific discharge rates for non-ruptured abdominal aortic aneurysms in men in The Netherlands from 1972-1992 (▼=55-64, ✻ =65-74, ♦=75-84, ●=85 and over). Source: SIG Health Care Information.

those aged 55-64 to 25% in those aged 85 years or over.

Age adjusted in-hospital mortality after an operation for a ruptured aneurysm of the abdominal aorta decreased also, from 52% in 1972 to 36% in 1992. Post-operative in-hospital mortality in 1992 for ruptured aneurysms increased with age from 28% in those aged 45-54 years to 71% in those aged 85 years or older.

Discussion

This study shows a pronounced increase in both mortality from and hospital discharge rates for aneurysms of the abdominal aorta in The Netherlands during the last two decades. This increase remained after adjustment for age and was more prominent in men than in women. During the same period, surgical outcome after surgery for ruptured abdominal aneurysms reduced gradually but

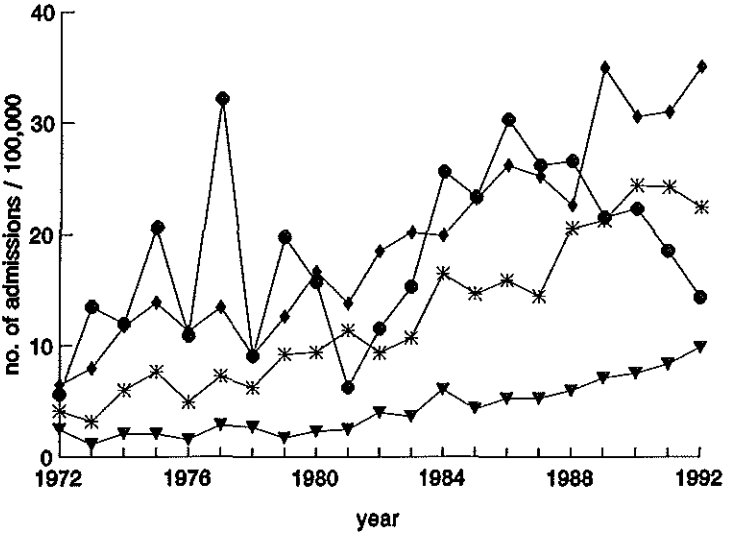

Figure 3.5. Age-specific discharge rates for non-ruptured abdominal aortic aneurysms in women in The Netherlands from 1972-1992 (▼=55-64, ✻ =65-74, ♦=75-84, ●=85 and over). Source: SIG Health Care Information.

remained high, while in-hospital mortality after elective surgery of abdominal aortic aneurysms halved to 7%.

Although the age adjusted death rates observed in The Netherlands are lower than those reported by Fowkes et al. in England & Wales (2), their relative increase in men from 1960 and 1984 was comparable with our estimate (2.6-fold in The Netherlands versus 2.5-fold in England and Wales). The higher death rate from aneurysms of the abdominal aorta in Fowkes' study could originate from their restriction to those aged 40 years or over, and from differences in the composition of the standard population. Lilienfeld (1) et al. observed death rates and trends similar to ours among whites in the United States, during the period 1951-1981.

Several factors have to be considered when interpreting an upward trend in data obtained from routine statistics. A first explanation for the observed increase in occurrence of aneurysms of the abdominal aorta could be an increase in detection rate. The widespread use of ultrasound in hospitals since the mid

seventies will have lead to the detection of many aneurysms previously unknown. In 1989 the board of radiologists in The Netherlands recommended that during all sonographic examinations of the abdomen an attempt should be made to visualize the abdominal aorta. With the introduction of a new diagnostic method, however, one would expect an accelerated increase in the number of cases, followed by a stabilization at a higher level, instead of the steady, continuous increase we observed in our study. It seems unlikely, therefore, that the increased use of "routine" ultrasound can fully explain the observed trends.

Changes in coding practice could be a second explanation for the observed increase. The introduction of a new, promising diagnostic method and the improvement in surgical techniques will have increased the medical awareness for aneurysms of the abdominal aorta. This might result in improved case finding and more deaths attributed to aneurysms and can explain part of the observed increase in mortality from abdominal aortic aneurysms. However, results from autopsy studies still suggest that many aneurysms remain undetected during life (20-23).

The number of hospital admissions can be influenced by changes in referral practice. The national hospital registry is based on admissions, not on individuals. Therefore, hospital statistics overestimate the incidence of new cases, as admissions for diagnostic work-up and referrals to other hospitals for operation can not be recognized. With the introduction of ultrasound and computerized tomographic examination techniques, that are often performed on an outpatient basis, the number of re-admissions might have decreased over time. This view is supported by the increase in the percentage of discharges for non-ruptured abdominal aortic aneurysms in which an operation was performed (37% in 1972 versus 53% in 1992).

Apart from the, undisputed, improvement in diagnostic capabilities and perhaps a change in coding practice, the rise in mortality and morbidity from aneurysms of the abdominal aorta could reflect a true increase in incidence. Although this type of research does not allow for a valid estimate of the incidence of aneurysms of the abdominal aorta there is evidence in favour for such a true increase. First of all, the increase was not the same in men and women. Both for mortality and for the number of hospital admissions men showed a

stronger increase than women. If the increase was solely caused by an improved detection rate one would expect similar effects in both sexes, unless of course, women had fewer sonograms then men. This seems unlikely. Secondly, there is a marked increase in the number of ruptured aneurysms where ultrasonographic detection does not play a major role. In former days, these emergencies would have been presented to the hospital anyway, irrespective of the availability of ultrasound. Thirdly, data from autopsy and epidemiologic necropsy studies indicate that an increase in the prevalence of aneurysms of the abdominal aorta exists, although no studies from The Netherlands are available (20-23).

Is a possible true increase in incidence of aneurysms of the abdominal aorta supported by other evidence? The etiology of aneurysms of the abdominal aorta remains a topic of debate (16,24-26). Smoking and a genetic predisposition are well recognised, while the role of atherosclerosis remains controversial (24). In contrast to the rise in mortality from abdominal aortic aneurysms there was a 40% decline in coronary heart disease mortality in The Netherlands during the same time period (27). This indicates that other etiologic factors than atherosclerosis are likely to contribute to the development of abdominal aortic aneurysms. On the other hand, the decline in mortality for coronary heart disease, as a competing cause of death, could have contributed to the increase in mortality and incidence of aneurysms of the abdominal aorta.

Survival after surgery upon both non-ruptured and ruptured aneurysms of the abdominal aorta improved. This probably reflects improvements in surgical and anaesthetic techniques. It should be stressed that hospital mortality is not cause-specific, and may arise from co-morbid conditions. The availability of ultrasound may have led to a disproportional increase in the detection of smaller aneurysms, thereby improving operation mortality. On the other hand, there is a trend to operate upon older patients and upon patients with more co-morbidity.

In conclusion, a clear increase in age-adjusted discharge rates of and mortality from abdominal aortic aneurysms occurred in The Netherlands between 1972 and 1992, notably in men. Undoubtedly, the introduction of ultrasound contributed to the observed trends, but a true increase in incidence of aneurysms of the abdominal aorta is a likely additional explanation.

References

1. Lilienfeld DE, Gunderson PD, Sprafka JM, Vargas C. Epidemiology of aortic aneurysms: I. Mortality trends in the United states, 1951 to 1981. Arteriosclerosis 1987;7:637-43.
2. Fowkes FGR, MacIntyre CCA, Ruckley CV. Increasing incidence of aortic aneurysms in England and Wales. Br Med J 1989;298:33-5.
3. Castleden WM, Mercer JC. Abdominal aortic aneurysms in Western Australia: descriptive epidemiology and patterns of rupture. Br J Surg 1985;72:109-12.
4. Pleumeekers HJCM, Hoes AW, Does E van der, Urk H van, Grobbee DE. Epidemiology of abdominal aortic aneurysms. Eur J Vasc Surg 1994;8:119-28.
5. Ingoldby CJH, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. Br J Surg 1986;73:551-3.
6. Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. Br J Surg 1986;73:101-3.
7. Mealy K, Salman A. The true incidence of ruptured abdominal aortic aneurysms. Eur J Vasc Surg 1988;2:405-8.
8. Jenkins AMcL, Ruckley CV, Nolan B. Ruptured abdominal aortic aneurysms. Br J Surg 1986;73:395-8.
9. Dubost C, Allary M, Oeconomos N. Resection of an aneurysm of the abdominal aorta: reestablishment of the continuity by a preserved human arterial graft, with result after five months. Arch Surg 1952;64:405-8.
10. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysms. II. Variables predicting morbidity and mortality. J Vasc Surg 1989;9:437-47.
11. AbuRahma AF, Robinson PA, Boland JP, et al. Elective resection of 332 abdominal aortic aneurysms in a southern West Virginia community during a recent five-year period. Surgery 1991;109:244-51.
12. Akkersdijk GJM, Graaf van der Y, Bockel van JH, Vries de AC, Eikelboom BC. Mortality rates associated with operative treatment of infrarenal abdominal aortic aneurysm in The Netherlands. Br J Surg 1994;81:706-9.
13. Johnston KW, Scobie TK. Multicenter prospective study of nonruptured abdominal aortic aneurysms. I. Population and operative management. J Vasc Surg 1988;7:69-81.
14. Mutirangura P, Stonebridge PA, Clason AE, et al. Ten-year review of non-ruptured aortic aneurysms. Br J Surg 1989;76:1251-54.
15. Greenhalgh RM. Prognosis of abdominal aortic aneurysm. Operate on tender aneurysms, but get better data on small asymptomatic aneurysms. Br Med J 1990;301:136.
16. Ernst CB. Abdominal aortic aneurysms. N Engl J Med 1993;328:1167-72.
17. Golden MA, Whittemore AD, Donaldson MC, Mannick JA. Selective evaluation and management of coronary artery disease in patients undergoing repair of abdominal aortic

aneurysms: a 16-year experience. Ann Surg 1990;212:415-23.

18. Naylor AR, Webb J, Fowkes FGR, Ruckley CV. Trends in abdominal aortic aneurysm surgery in Scotland (1971-1984). Eur J Vasc Surg 1988;2:217-21.
19. World Health Organization. World Health Statistics Annual 1992. Geneva: World Health Organization, 1993: XXII.
20. McFarlane MJ. The epidemiologic necropsy for abdominal aortic aneurysm. JAMA 1991;265:2085-88.
21. Johnson G Jr, Avery A, McDougal G, Burnham SJ, Keagy BA. Aneurysms of the abdominal aorta. Incidence in blacks and whites in North Carolina. Arch Surg 1985;120:1138-40.
22. Bengtsson H, Bergqvist D, Sternby NH. Increasing prevalence of abdominal aortic aneurysms: a necropsy study. Eur J Surg 1992;158:19-23.
23. Darling RC, Messina CR, Brewster DC, Ottinger LW. Autopsy study of unoperated abdominal aortic aneurysms. The case for early resection. Circulation 1977;56:161-4.
24. Reed D, Reed C, Stemmermann G, Hayashi T. Are aortic aneurysms caused by atherosclerosis? Circulation 1992;85:205-11.
25. Johansen K, Koepsell T. Familial tendency for abdominal aortic aneurysms. JAMA 1986;256:1934-36.
26. Martin P. On abdominal aortic aneurysms. J Cardiovasc Surg 1978;19:597-8.
27. Bots MC, Grobbee DE. Cardiovascular disease in The Netherlands over the past 25 years. Prevalence, incidence, trends in morbidity and mortality. Neth J Cardiol 1991;4:141-5.

CHAPTER IV

Observer variability of ultrasound measurements of the abdominal aorta: the Rotterdam Study

Introduction

Rupture of an aneurysm of the abdominal aorta is almost always fatal (1-3). It is the cause of death in about 1% of men over 65 years of age in Westernized societies (4). To prevent death from aneurysm rupture, early detection and subsequent surgical repair is necessary (5-7).

To assess the size of the diameter of the abdominal aorta several methods are available. Palpation, X-ray, aortography, CT-scanning and ultrasound are most often used (8-10). Ultrasonography is accepted as the most practical and reliable method (4) and large scale ultrasonographic screening for aneurysms of the abdominal aorta has been advocated by several researchers (4-7).

Although abdominal aortic aneurysms are located in the distal part of the aorta, the use of the distal aortic diameter as a single criterium in the decision to operate or to follow-up patients with an aneurysm has been challenged (11,12). However, the diameter of the distal aorta continues to play an important role in daily clinical practice (13). Because of the importance of the absolute distal diameter of the abdominal aorta (3,14-16) and the importance of an increase in diameter over time on the decision to intervene or to monitor patients, knowledge of the interobserver variability of ultrasound measurements of the aorta is essential.

Few studies on this issue are available and their results are conflicting (17-19). In none of these studies the observer variability of the proximal measurement of the abdominal aorta was evaluated although the ratio of the proximal and distal diameter is becoming increasingly important in the decision to intervene surgically (11,20). Furthermore, from an epidemiological point of view it is important to assess whether interobserver variability in the ultrasound measurement is different in subgroups of patients, notably in patients with risk indicators, thought to be related to the prevalence of abdominal aortic aneurysms, such as old age, male gender, high blood pressure and smoking. If interobserver variability is associated with these risk indicators, the study of the etiology and prognosis of abdominal aortic aneurysms will be hampered.

In the Rotterdam Study (21), a follow-up study among men and women aged 55 years or older, an ultrasound screening of the abdominal aorta is

performed. This enabled us to assess the interobserver variation of ultrasound measurements of the distal and proximal abdominal aorta. In addition, we studied whether interobserver variability was related to the presence of cardiovascular risk indicators.

Methods

A total of 135 consecutive participants of the Rotterdam Study was included in our study. The Rotterdam Study is a prospective follow-up study of 7983 subjects aged 55 years or over living in Ommoord, a suburb of Rotterdam. Rationale and design of this study are described in detail elsewhere (21). As part of the Rotterdam Study all participants are screened for aneurysms of the abdominal aorta by means of standardized ultrasonography to study the prevalence and risk indicators of aneurysms of the abdominal aorta. Presently, ultrasound data of 3,351 participants are available. The overall response rate of the study is 78%.

Following the Rotterdam Study scanning protocol, B-mode ultrasound recordings were made using a 3.5 MHz linear array probe (Toshiba SSH 60A). Subjects were not restricted in prior food intake and ultrasound recordings were made with the patient in supine position. No adjustments for blood pressure variations were made. Diameters were measured between the two most outer wall echoes in the anterior-posterior plane. First, a longitudinal scan of the abdominal aorta was made and the diameter of the widest part of the most distant section of the abdominal aorta was recorded (distal diameter). The diameter of the aorta was also measured at the level of the superior mesenteric artery (proximal diameter). An aneurysm was considered present if the distal aortic diameter was 35 mm or more or if the distal aortic diameter increased with more than 50% compared to the proximal diameter. For the present analysis, recordings and measurements were made by three technical assistants, who were trained especially for the project.

Of all possible sources of measurement imprecision, interobserver variability may constitute a large contribution to the variability in

ultrasonographic measurements of the abdominal aorta. Since we focused on interobserver variability as an important cause of variability in ultrasound measurements of the abdominal aorta, the time between two measurements was kept as short as possible to minimize the influence of biological variation over time. To assess the interobserver variability of measurements of the proximal and distal diameter of the abdominal aorta, duplicate measurements were performed in 135 participants of the Rotterdam Study. The second measurement was made within a few minutes after the first measurement by one of the other trained technical assistants, who was not aware of the results of the first measurement. Thus, three groups of paired measurements were formed by the three sonographers (SS, IH and IB). Because of technical reasons two of the three sonographers pairs could not complete the number of 50 measurements that were initially planned. At the end of the study, observer pair I had performed 50 paired measurements, while the corresponding numbers for pair II and pair III were 38 and 47, respectively.

Several cardiovascular risk indicators were measured to determine whether the levels of these cardiovascular risk indicators influenced interobserver variability. Blood pressure was measured in sitting position with a random-zero sphygmomanometer. The average of two consecutive measurements was used to calculate the diastolic and systolic blood pressure. Non-fasting blood samples were collected to determine serum total cholesterol using an automated enzymatic procedure (22). High density lipoprotein was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. Waist circumference was measured to detect a possible interference of bowel gas and fat between the transducer and the aorta with the diameter measurements.

The consecutive measurements were plotted against each other and intraclass correlation coefficients were calculated (23). Because a high level of correlation does not necessarily imply a clinically acceptable level of agreement between two measurements (24-26), we also calculated the mean differences, with standard errors and 95% confidence intervals between measurements. The limits of agreement were calculated according to Bland and Altman (20) as the mean difference between two observers $\pm$ 2 standard deviations.

Further, we estimated the correlation of the absolute difference between

consecutive measurements and the "true" aortic diameter (estimated as the mean of the two consecutive measurements in one subject) to assess whether interobserver variability increased with increasing aortic diameter. The Spearman rank correlation coefficient was calculated.

To determine the influence of the level of several cardiovascular risk indicators on measurement imprecision, Spearman rank correlations of the absolute difference between the two consecutive measurements and the level of cardiovascular risk indicators of each participant were calculated. Statistical analyses were performed using BMDP software.

Results

In table 4.1. selected characteristics of the 135 participants in our study and the first 3,351 participants in the Rotterdam Study are shown. The 135 participants were somewhat older (mean age 71 years) than those in the Rotterdam Study as a whole (mean age 68 years). The mean distal aorta diameter in the patients taking part in the interobserver variability study (19.6 mm 95% CI 17.9-21.2) was larger than in the total group (17.6 mm; 95% CI 17.4-17.8). No clear differences in other characteristics were present.

In figure 4.1 the distribution of the distal aorta diameter in the 135 subjects and in the 3,351 participants of the Rotterdam Study is shown. Despite the difference between the mean distal diameters in both groups, a similar distribution of the diameters over the whole range seems present.

In the figures 4.2. and 4.3. the first and second measurements of the distal (figure 4.2) and proximal (figure 4.3) aorta diameters are plotted against each other for the 135 participants. The intraclass correlation coefficients for two consecutive measurements of the distal aorta diameter was 0.998 and varied from 0.994 to 0.999 for the different observer pairs (table II). For the proximal aorta diameter, the correlation coefficient was 0.995 and varied from 0.993 to 0.999 between the observer pairs.

The maximum difference between two consecutive measurements by two different observers was 4 mm with a mean difference of 0.06 mm (95% CI -

0.15;0.27) for the distal aorta. The maximum difference for the proximal aorta was also 4 mm, but the mean difference between these measurements was 0.32 mm (95% CI 0.09;0.55). The mean differences between the different observers were small, ranging from 0.06 to 0.08 mm in distal readings and from 0.21 to 0.42 mm in the proximal readings. In the distal measurements the mean difference between two different observers did not statistically differ from zero in all the three observer pairs. In the proximal measurement, however, a statistically significant difference ($P<0.05$) between the first and second observer was present.

Table 4.1. Selected characteristics of the 135 participants in the interobserver variability study and of the first 3351 participants of the Rotterdam Study.

	Observer variability study	Rotterdam Study main cohort	p-value
Number	135	3,351	
Age (years)	71	68	< 0.01
Female sex	61%	64%	0.18
Weight (kg)	72 (1.12)	73 (0.21)	0.41
Height (cm)	166 (0.95)	167 (0.16)	0.62
Waist circumference (cm)	92 (0.95)	90 (0.19)	0.50
Diastolic BP (mm Hg)	73 (0.95)	74 (0.16)	0.50
Systolic BP (mm Hg)	141 (1.98)	138 (0.38)	0.26
Pulse (beats/minute)	74 (0.95)	73 (0.21)	0.68
Smoking (pack years)	34 (1.64)	33 (0.29)	0.56
Serum chol (mmol/L)	6.4 (0.10)	6.7 (0.02)	0.01
Serum HDL chol (mmol/L)	1.33 (0.03)	1.3 (0.01)	0.80
Distal aorta diameter (mm)	19.6 (0.08)	17.6 (0.08)	< 0.01
Proximal aorta diameter (mm)	19.9 (0.77)	20.0 (0.08)	0.62

Values are means with standard deviations in parentheses; BP = blood pressure; Chol = cholesterol.

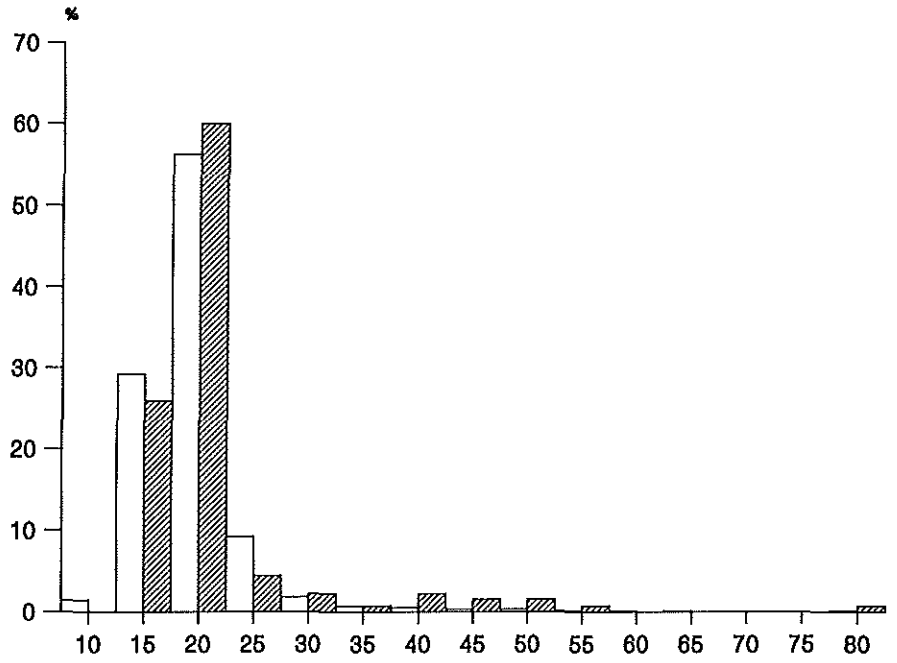

Figure 4.1. The distribution of the distal aortic diameter (mm) in the 135 subjects included in the interobserver variability study (shaded bars) and the distribution in the first 3,351 participants of the Rotterdam Study (white bars).

The limits of agreement between two observers varied from -2.78 to 2.90 mm for the distal measurement and from -2.48 to 3.32 mm for the proximal measurement.

In figure 4.4. and 4.5. the association between the absolute mean differences between the first and second measurement and the estimated "true" distal and proximal aorta diameters are given. An increase in measurement imprecision with increasing "true" aorta diameter seemed to be present for the proximal measurement of the aorta (Spearman rank correlation coefficient r= 0.20; p-value 0.02). Exclusion of one participant with an extremely large diameter of 80 mm did not change these findings.

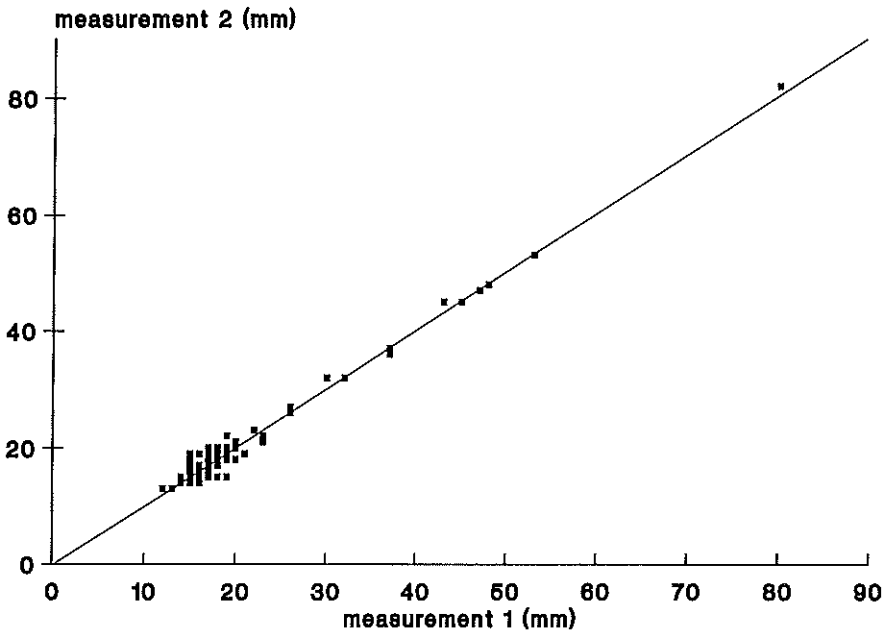

Figure 4.2. Correlation between two consecutive measurements by two different observers of the distal aorta diameter in 135 participants of the Rotterdam Study. (Intraclass correlation coefficients = 0.998)

No influence of the "true" diameter on measurement imprecision in the distal aorta was demonstrated (Spearman r=0.01; p=0.90).

The influence of selected cardiovascular risk indicators on measurement imprecision is shown in table 4.3. The absolute difference between two consecutive measurements appeared not to be influenced by age, gender, smoking habits, systolic and diastolic blood pressure, serum total and HDL cholesterol. However, a larger waist circumference was associated with an increase in measurement imprecision of the ultrasound measurement of the proximal diameter of the abdominal aorta (Spearman r= 0.24; p< 0.01).

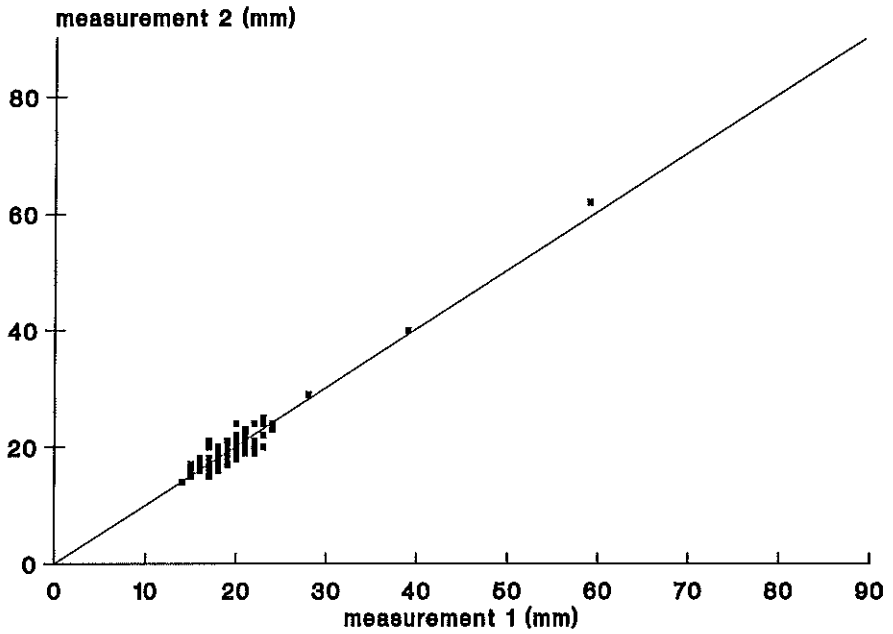

Figure 4.3. Correlation between two consecutive measurements by two different observers of the proximal aorta diameter in 135 participants of the Rotterdam Study. (Intraclass correlation coefficients = 0.995).

Discussion

In our population-based study among 135 subjects aged 55 years or older, the interobserver variability of ultrasound measurements of the distal part of the abdominal aorta, measured as the comparability of consecutive measurements by two different observers, was low. The interobserver variability of ultrasonographic measurements of the proximal aorta was higher and increased with an increase in the diameter of the aorta and with increasing waist circumference.

Three other studies on interobserver variability of ultrasound measurements of the abdominal aorta are available (17-19). All studies were relatively small and their results were conflicting. Ellis and co-workers (18) in a study among 10 patients reported an interobserver variability in the distal measurements of 8 mm. They could not demonstrate a relation between interobserver variability and

the true aortic diameter. Yucel and co-workers (17) concluded, from a study among 28 patients, that less than 5 mm could be the result of interobserver variability. Thomas and co-workers (19) studied interobserver variability in ultrasound measurements of the distal aorta in a two period crossover design to eliminate the change in aorta diameter over time, in 30 patients. They demonstrated a difference between two consecutive anterior-posterior aortic measurements of -1.04 mm (95% CI -2.84;0.23) which was not statistically significant.

Table 4.2. Results of consecutive measurements by two different observers of the proximal and distal diameter of the abdominal aorta.

Observer pair	N	Abs mean diff (mm)	SD	r	95% CI of the mean	Maximal absolute difference (mm)
Distal diameter.						
I	50	0.06	1.42	0.99	-0.34;0.46	4.0
II	38	0.08	1.02	0.99	-0.26;0.41	2.0
III	47	0.06	1.02	0.99	-0.24;0.36	4.0
Total	135	0.06	1.24	0.99	-0.15;0.27	4.0
Proximal diameter.						
I	50	0.42	1.45	0.99	0.01;0.83	4.0
II	38	0.32	1.16	0.99	-0.06;0.70	4.0
III	47	0.21	1.31	0.99	-0.17;0.60	3.0
Total	135	0.32	1.35	0.99	0.09;0.55	4.0

I (Observer 1 versus observer 2); II (Observer 1 versus observer 3); III (Observer 2 versus observer 3); N = number of participants; Abs mean diff = Absolute mean difference between the two observers (mm); SD = standard deviation; r = Intraclass correlation coefficient; Maximal abs diff = Maximal absolute difference between the two observers (mm).

Our finding that interobserver variability of distal measurement of the abdominal aorta is low, corresponds with the findings of Thomas and co-workers (19).

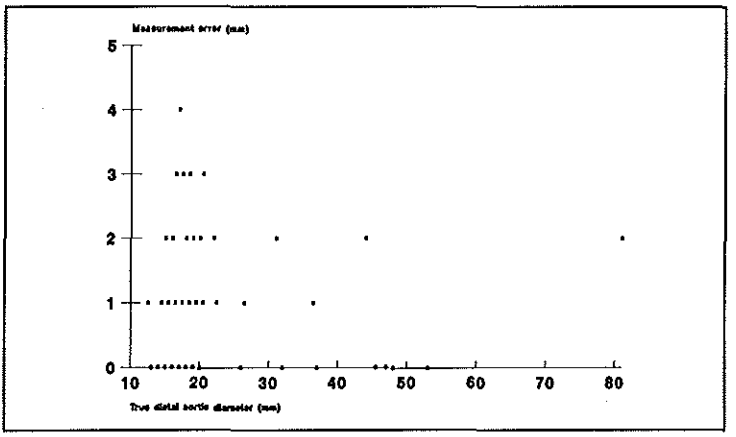

Figure 4.4. Correlation of the absolute difference between two consecutive measurements of the distal aorta diameter by two different observers (measurement error) and the "true" proximal aorta diameter, in 135 participants.

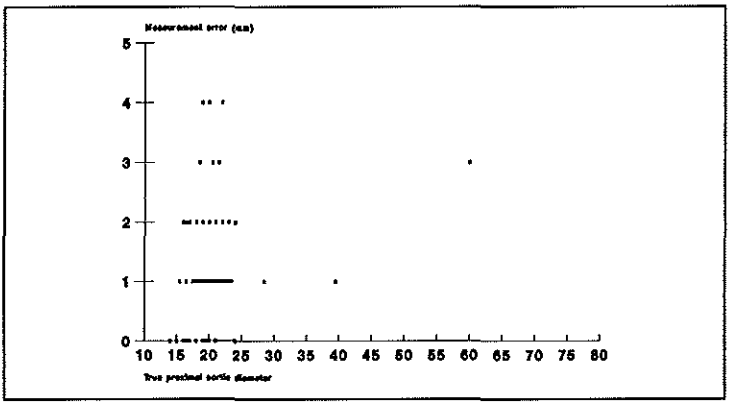

Figure 4.5. Correlation of the absolute difference between two consecutive measurements of the proximal aorta diameter by two different observers (measurement error) and the "true" proximal aorta diameter, in 135 participants.

In view of our estimated limits of agreement of ultrasound measurements of the distal aorta, differences between measurements of two observers of 3 mm or less can be the result of interobserver variability.

None of the earlier studies assessed interobserver variability in the proximal measurements. Since the biological variability in aorta diameters is correlated to body habitus, the proximal diameter of the abdominal aorta is used as a reference to calculate a relative increase in the size of the distal part of the abdominal aorta. In our study interobserver variability in the proximal measurement is relatively high.

Table 4.3. Correlation between the absolute difference between two consecutive measurements by two different observers of the proximal and distal aorta diameter and selected cardiovascular risk indicators.

Risk indicator	Proximal diameter r (p-value)	Distal diameter r (p-value)
Age	0.07 (0.44)	0.01 (0.94)
Gender	- 0.11 (0.22)	0.04 (0.65)
Height	0.01 (0.90)	-0.01 (0.26)
Weight	0.14 (0.11)	0.09 (0.31)
Waist circumference	0.24 (< 0.01)	0.13 (0.58)
Diastolic blood pressure	0.01 (0.91)	0.02 (0.83)
Systolic blood pressure	0.02 (0.80)	<0.01 (0.96)
Pulse rate	- 0.10 (0.27)	<0.01 (0.97)
Smoking (pack/years)	- 0.07 (0.44)	0.03 (0.71)
Serum total Cholesterol	- 0.05 (0.59)	0.06 (0.54)
Serum HDL cholesterol	- 0.13 (0.16)	-0.11 (0.23)

r = Spearman correlation coefficient

Our finding that waist circumference is correlated to interobserver variability in the proximal abdominal aorta only can be explained by the air and fat located between the transducer and the aorta in obese subjects. A better image of the abdominal aorta in slim subjects may be expected. The finding that with

increasing "true" proximal aorta diameter the interobserver variability of the proximal aorta increases, is another indication of the potential imprecision in ultrasonographic measurements of the proximal part of the abdominal aorta.

This impression can be explained by the difficulty of imaging the proximal part compared to the distal part of the abdominal aorta. Our sonographers were well trained and gained substantial experience in ultrasonographic techniques, but locating the mesenteric superior artery can be a problem, especially when the vision is blurred by gas in the stomach or colon.

We conclude that the interobserver variability of the distal aortic diameter is low. On the other hand interobserver variability in ultrasonographic measurements of the proximal aortic diameter is more pronounced, notably in obese subjects and in those with a large aortic diameter.

In the light of our findings and those of other studies (20,27), other measurements than the proximal aortic diameter may be more appropriate as a reference to the diameter of the distal abdominal aorta.

References

1. Richardson R, Norton LW, Eula J, et al. Accuracy of ultrasound in diagnosing abdominal masses. Arch Surg 1975;110:933-9.
2. Strachan DP. Predictors of death from aortic aneurysms among middle-aged men: the Whitehall study. Br J Surg 1991;78:410-4.
3. Szilagyi DE, Smith RF, DeRusso FJ, Elliot JP, Sherrin FW. Contribution of abdominal aortic aneurysmectomy to prolongation of life. Ann Surg 1966;164:678-99.
4. Collin J. Screening for abdominal aortic aneurysms. Br J Surg 1982;57:851-2.
5. Lederle FA, Walker JM, Reinke DB. Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. Arch Intern Med 1988;148:1753-6.
6. Anonymous. Periodic health examination, 1991 update: 5. Screening for abdominal aortic aneurysms. Can Med Assoc J 1991;145:783-9.
7. Harris PL. Reducing the mortality from abdominal aortic aneurysms: need for a national screening programme. Br Med J 1992;305:697-9.
8. Grave AH, Carpenter CM, Wicks JD, Edwards WS. Discordance in the sizing of abdominal aortic aneurysms and its significance. Am J Surg 1982;144:627-33.
9. Bluth EI, Ultrasound of the abdominal aorta. Arch Intern Med 1984;144:377-80.
10. Lindholm L, Ejlertsson G, Forsberg R, Norgren L. Low prevalence of abdominal aortic

aneurysms in hypertensive patients. Acta Med Scand 1985;218:305-10.

11. Anonymous. Suggested standards for reporting on arterial aneurysms. J Vasc Surg 1991;13:444-50.
12. Cronenwett JL, Murphy TF, Zelenock GB, et al. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery 1985;98:472-83.
13. Hollier LH, Taylor LM, Oschner J. Recommended indications for operative treatment of abdominal aortic aneurysms: report of a subcommittee of the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery. J Vasc Surg 1992;15:1046-56.
14. Cole CW. Highlights of an international workshop on abdominal aortic aneurysms. Can Med Assoc J 1989;141:393-5.
15. Crawford ES, Hess KR. Abdominal aortic aneurysms. N Eng J Med 1989;32:1040-2.
16. Jensen BS, Vestersgaard-Andersen T. The natural history of abdominal aortic aneurysms. Eur J Vasc Surg 1989;3:135-9.
17. Yucel KE, Fillmore DJ, Knox TA, Waltman AC. Sonographic measurement of abdominal aortic diameter: interobserver variability. J Ultrasound Med 1991;10:681-3.
18. Ellis M, Powell JT, Greenhalgh RM. Limitations of ultrasonography in surveillance of small abdominal aortic aneurysms. Br J Surg 1991;78:614-6.
19. Thomas PRS, Shaw JC, Ashton HA, Kay DN, Scott RAP. Accuracy of ultrasound in a screening programme for abdominal aortic aneurysms. J Med Screening 1994;1:3-6.
20. Louridas G, Reilly K, Perry MO. The role of the aortic aneurysm diameter aortic diameter ratio in predicting the risk of rupture. S Afr Med J 1990;78:642-3.
21. Hofman A, Grobbee DE, Jong PTVM de, Ouweland FA van den. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.
22. Gent CM van, Voort HA van der, Bruyn AM de, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.
23. Armitage P. Statistical methods in medical research. New York: Wiley & Sons, 1971.
24. Brennan P, Silman A. Statistical methods for assessing variability in clinical measures. Br Med J 1992;304:1491-4.
25. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;i:307-10.
26. Anonymous. Measurement imprecision: ignore or investigate. Lancet 1992;339:587-8.
27. Liddington MI, Heather BP. The relationship between aortic diameter and body habitus. Eur J Vasc Surg 1992;6:89-92.

CHAPTER V

Aneurysms of the abdominal aorta in older adults: the Rotterdam Study

Introduction

The question whether ultrasonographic screening for abdominal aortic aneurysms in asymptomatic subjects is justifiable, remains a subject of debate. In 1991 the Canadian Task force on Periodic Health Examination evaluated the literature to provide recommendations on this issue (1). The Task Force concluded that there is insufficient evidence to warrant screening programmes for abdominal aortic aneurysms using physical examination or ultrasonography. By contrast, based on the same literature, Harris (2) recently concluded that there is a need for a national screening programme to detect aneurysms of the abdominal aorta.

One of the reasons for this controversy is a lack of essential data. In particular, population-based data on the age- and gender specific distribution of distal and proximal aorta diameters are scarce (3). Several studies on the prevalence of aneurysms of the abdominal aorta are available. Most of these studies however, were performed in subgroups of patients, such as men (4-6), limited age groups (7-9), relatives of subjects with an aneurysm of the abdominal aorta (10-14), or subjects with peripheral arteriosclerosis (15-19) or hypertension (20). Furthermore, most of these studies were based on hospital-referred subjects.

To assess the age- and gender specific distribution of aortic diameters and the prevalence of aneurysms of the abdominal aorta, we conducted a population-based study in 5,419 subjects aged 55 years and older. In addition cardiovascular risk factors of abdominal aortic aneurysms were studied.

Methods

This study is part of the Rotterdam Study, a prospective follow-up study designed to investigate determinants of occurrence and progression of chronic disease in the elderly. Emphasis is on four areas of research, i.e. cardiovascular, neurogeriatric, locomotor and ophthalmologic diseases. The rationale and design of this study have been described previously (21).

All men and women of 55 years and older living in the same district, were

invited in co-operation with the general practitioners to take part in the study. Potential participants were identified with help from the municipality of Rotterdam.

10,215 subjects were invited to participate in the Rotterdam Study. Baseline measurements comprised a home interview and two visits to the research centre. For logistic reasons, ultrasound examination was included in the protocol 6 months after the start of the Rotterdam Study. Subjects living in nursing homes (n=1,056) were excluded because of technical limitations in the transport of the ultrasound equipment. The overall response rate was 78 percent, varying from 83 percent in those aged between 55 and 60 years to 50 percent in those of 80 years or over. Excluded from ultrasound examination were 37 (0.7 percent) subjects. In 27 subjects the abdominal aorta had already been replaced by a graft: in 4 of these an aneurysm was documented and in the other 23 grafting took place because of severe peripheral vascular disease. The 10 other subjects were known to have an aneurysm of the abdominal aorta and were under follow-up by surgeons elsewhere. Ultimately, 5,419 subjects underwent an ultrasound examination of the abdominal aorta. In 173 subjects (3.2 percent) it was impossible to visualise the distal part of the abdominal aorta and in 299 subjects (5.5 percent) the proximal diameter of the abdominal aorta could not be measured. The present results are based on 5,283 participants in whom at least a measurement of the distal aorta was available. Apart from a small number of subjects with an Asian background, all participants were Caucasian.

Three assistants were trained to perform ultrasonographic measurements of the abdominal aorta. Interobserver agreement between these assistants was high (Chapter IV) The abdominal aorta was visualised according to the Rotterdam Study scanning protocol. B-mode ultrasound recordings were made using a 3.5 MHz linear array probe (Toshiba SSH 60A) with the patient in supine position. Measurements were made throughout the day and no instructions about food intake prior to the ultrasound examination were given. First, a longitudinal scan of the abdominal aorta was made and the anterior-posterior diameter of the widest part of the most distant section of the abdominal aorta was recorded (distal diameter). Further, the anterior-posterior diameter of the aorta was measured at the level of the superior mesenteric artery (proximal diameter), to provide

an indication of the normal aortic diameter.

An aneurysm of the abdominal aorta was considered to be present when at least one of the two following criteria was met: [1] the distal diameter of the aorta was 35 mm or larger, or [2] the diameter of the distal aorta was at least 50 percent larger than the diameter of the proximal part of the abdominal aorta. Subjects with an aneurysm of the abdominal aorta according to these criteria were referred to the Department of Vascular Surgery, Academic Hospital Dijkzigt for further evaluation.An aneurysm was considered of the "saccular" type when the ratio between the distal and proximal aorta was 1.5 or more, indicating a local widening of the aorta. A "longitudinal" aneurysm was defined as a distal aortic diameter of 35 mm or larger and a ratio of the distal and proximal diameter of less then 1.5, indicating a widening beyond the mesenteric superior artery. Of all participants, several cardiovascular risk factors and the presence of cardiovascular disease were recorded. Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. Diastolic blood pressure was registered at Korotkoff V. Hypertension was defined as a systolic blood pressure of 160 or more or a diastolic blood pressure of 95 or more, or the use of antihypertensive drugs for the indication hypertension. Diabetes was defined as the current use of antidiabetic drugs or a blood glucose of 11.0 mmol/L or over, random or two hours after a 75 grams oral glucose load. Serum total cholesterol was determined by an automated enzymatic procedure in a non-fasting blood sample. Serum HDL-cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. Intermittent claudication and a history of angina were diagnosed using the Rose questionnaire (22). Myocardial infarction was defined as a history of myocardial infarction with hospital admission.

To study differences between the prevalence of aneurysms of the abdominal aorta reported in the other population-based screening surveys for abdominal aortic aneurysms, a comparison was made using the Rotterdam Study dataset as a reference. The criteria for defining aneurysms of the abdominal aorta used in these other studies were applied to those participants in the Rotterdam Study with the same age and gender characteristics. Prevalence rates were

calculated with exact 95 percent confidence limits.

The association between age and the aortic diameter was studied using a linear regression model. Analyses were performed using STATA software.

Results

In table 5.1. general characteristics of the study population are given for men and women separately. The distribution of the distal and proximal ultrasound diameter of the abdominal aorta and the distribution of the ratio between the distal and proximal aortic diameter are given in figures 5.1. and 5.2. The mean distal diameter was 19.7 mm (95% CI 19.4-19.9) in men and 16.2 (95% CI 16.1-16.3) in women.

Table 5.1. General characteristics of the 5,283 participants in the Rotterdam Study in whom ultrasound measurements of the abdominal aorta were obtained.

	Men (n=2,217)	Women (n=3,066)
Age (years)	67.2 (7.5)	68.1 (8.2)
Height (cm)	175.1 (6.9)	161.8 (6.5)
Weight (kg)	78.9 (10.7)	69.6 (10.8)
Systolic blood pressure (mm Hg)	138.7 (21.7)	139.4 (22.4)
Diastolic blood pressure (mm Hg)	74.7 (11.4)	73.4 (11.1)
Current smoking	24.5%	19.2%
Serum cholesterol (mmol/L)	6.3 (1.1)	6.9 (1.2)
Serum HDL-cholesterol (mmol/L)	1.2 (0.3)	1.5 (0.4)
Hypertension	26.6%	32.9%
Stroke	3.8%	2.4%
Diabetes	10.3%	9.3%
Intermittent claudication	2.0%	1.0%
History of angina pectoris	6.2%	6.8%
History of myocardial infarction	11.2%	3.4%

Numbers are proportions or means (SD).

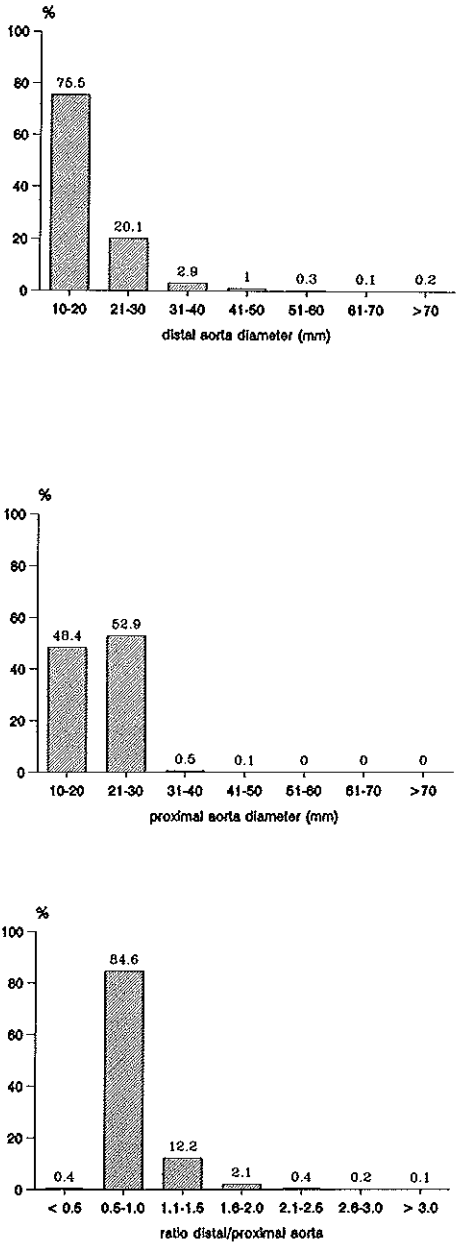

Figure 5.1. The distribution of the distal and proximal diameter of the abdominal aorta and the ratio between both measurements in 2,217 men.

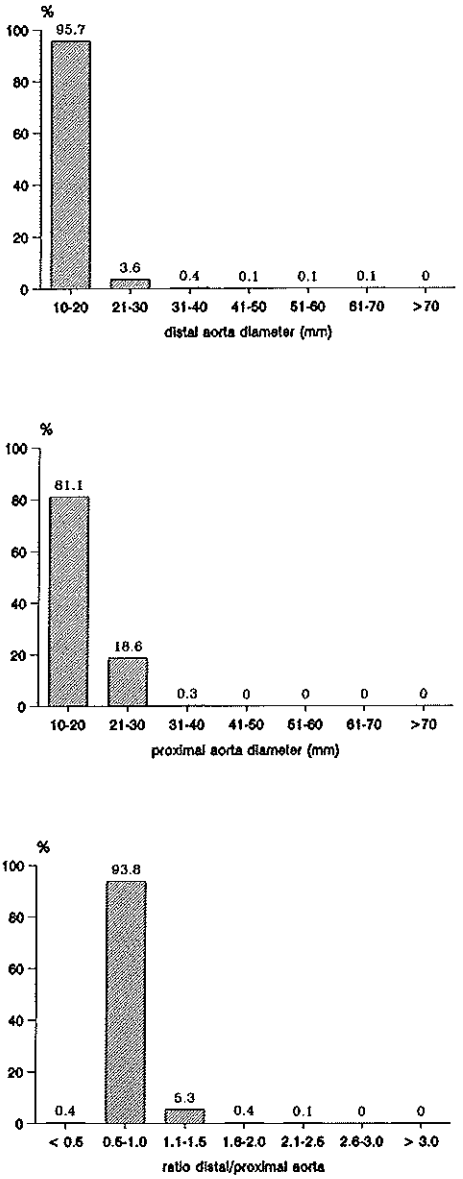

Figure 5.2. The distribution of the distal and proximal diameter of the abdominal aorta and the ratio between both measurements in 3,066 women.

The mean proximal diameter in men was 21.0 mm (95% CI 20.9-21.2) and 18.6 mm (95% CI 18.5-18.7) in women.

A clear increase in the distal and proximal diameter of the abdominal aorta with advancing age was present in both sexes (figure 7.3.). This trend was more pronounced in men. In men, the increase in the distal and proximal diameter per 10 years increase of age was 1.1 mm (95% CI 0.8-1.5) and 0.5 mm (95% CI 0.3-0.6), respectively. The corresponding figures in women were 0.5 mm (95% CI 0.4-0.6) and 0.3 mm (95% CI 0.2-0.4). The association between age and the aortic diameter did not materially change after exclusion of the subjects meeting the criteria for aortic aneurysms. The ratio of the distal and proximal diameter in men rose with 0.3 (95% CI 0.2-0.5) per 10 years increase of age. The ratio in women hardly increased with advancing age: 0.01 per 10 years of age (95% CI 0.01-0.02).

Table 5.2. Age- and gender specific prevalence of aneurysm of the abdominal aorta in subjects of 55 years and older.

Age (years)	Men		Women	
	#	% (95% CI)	#	% (95% CI)
55 - 59	4/426	0.9 (0.3-2.4)	1/573	0.2 (0.0-1.0)
60 - 64	17/540	3.1 (1.8-5.0)	3/690	0.4 (0.1-1.3)
65 - 69	19/483	3.8 (2.3-5.9)	1/593	0.2 (0.0-0.9)
70 - 74	17/387	4.4 (2.6-6.9)	6/551	1.1 (0.4-2.4)
75 - 79	22/265	8.3 (5.2-12.3)	4/373	1.1 (0.3-2.7)
≥ 80	12/116	10.3 (5.5-17.4)	6/286	2.1 (0.8-4.5)
Total	91/2217	4.1 (3.3-5.0)	21/3066	0.7 (0.4-1.1)

# number of aneurysms divided by the total number of subjects in the category.
CI = Confidence Interval.

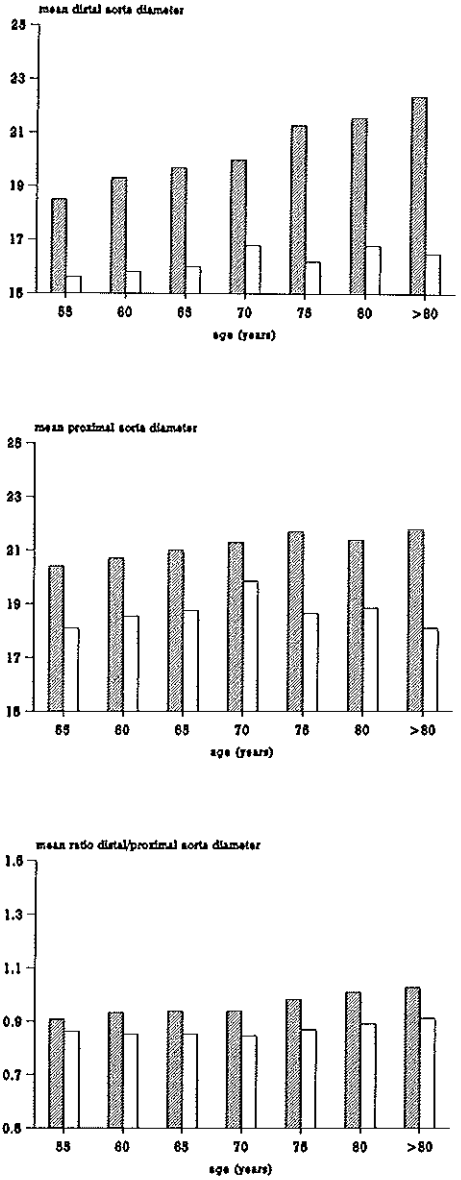

Figure 5.3. The mean aortic diameter (mm) in 5-years age categories for men (shaded bars) and women (white bars). The distribution of the distal, proximal and ratio between the mean distal and proximal aorta ultrasound diameters are given.

In 112 subjects (2.1 percent; 95% CI 1.7-2.5) an aneurysm of the abdominal aorta was present. The mean age in the subjects with an aneurysm of the abdominal aorta was 72.1 years (95% CI 70.6-73.6) compared to 67.5 years (95% CI 67.3-67.7) in non-aneurysmatic subjects. In 88 (78.6 percent) the maximal distal diameter exceeded 34 mm. 24 Subjects (21.4 percent) qualified solely because of an increase of more than 50 percent of the distal diameter compared to the proximal diameter. In this group the distal diameter lay between 25 and 35 mm. Two thirds of all aneurysms (n=79) were of the saccular type and were therefore limited to the distal part of the abdominal aorta.

Table 5.3. Potential cardiovascular risk factors in men and women with and without an aneurysm of the abdominal aorta, adjusted for differences in age.

	Men			Women		
Risk factor	AAA+ (n=91)	AAA- (n=2,126)	p-value	AAA+ (n=21)	AAA- (n=3,066)	p-value
Body mass index (kg/m2)	25.4	25.7	0.29	27.4	26.6	0.30
Systolic blood pressure (mm Hg)	142.0	138.6	0.14	142.8	139.5	0.48
Diastolic blood pressure (mm Hg)	76.5	74.7	0.14	75.5	73.5	0.41
Current smoking	37.6%	23.9%	<0.01	56.0%	19.1%	<0.01
Serum cholesterol (mmol/L)	6.6	6.3	0.04	7.3	6.9	0.11
Serum HDL-cholesterol (mmol/L)	1.2	1.2	0.53	1.4	1.5	0.32
Hypertension	29.2%	26.5%	0.59	42.1%	32.9%	0.37
Stroke	1.8%	3.9%	0.31	9.0%	2.3%	0.05
Diabetes	8.6%	10.4%	0.61	0.0%	9.4%	
Intermittent claudication	4.8%	1.8%	0.04	4.5%	1.0%	0.12
History of angina pectoris	8.3%	6.1%	0.39	13.4%	6.8%	0.24
History of myocardial infarction	15.7%	11.0%	0.17	8.7%	3.3%	0.37

Numbers are proportions or means; AAA+ = aneurysm of the abdominal aorta present; AAA- = aneurysm of the abdominal aorta absent.

Table 5.4. Reported prevalence of aneurysms of the abdominal aorta in eight population-based screening surveys, compared to the 5,283 participants of the Rotterdam Study.

First Author	Age	Gender	Number	Definition (mm)	Prevalence (%) (95% CI)	Adjusted Prevalence Rotterdam Study % (95% CI)
Rotterdam Study	≥55	men	2217	>34[$]	4.1 (3.3-5.0)	
		women	3066	>34[$]	0.7 (0.4-1.1)	
Collin (7)	65-74	men	426	>39[*]	5.4 (3.5-8.0)	5.2 (3.8-7.0)
				>39	2.3 (1.1-4.3)	1.8 (1.0-2.9)
O'Kelly (4)	65-74	men	906	>25	7.8 (6.2-9.8)	7.4 (5.7-9.4)
				>40	1.5 (0.8-2.6)	1.4 (0.7-2.5)
Loh (5)	≥55	men	657	>30	2.9 (1.7-4.5)	4.4 (3.5-5.3)
Scott (23)	65-80	men	1947	>29	7.8 (6.5-8.9)	5.9 (4.6-7.4)
		women	2290	>29	1.4 (0.9-1.9)	0.8 (0.4-1.4)
Akkersdijk (33)	≥50	men	1717	>29[$]	7.7 (6.5-9.1)	8.3 (7.2-9.5)
		women	2309	>29[$]	2.9 (2.2-3.6)	2.0 (1.5-2.5)
Smith (9)	65-75	men	2669	>29	8.2 (7.2-9.3)	4.8 (3.5-6.4)
				>40	3.0 (2.4-3.7)	1.5 (0.8-2.5)
Krohn (25)	≥60	men	500	>29[$]	8.2 (5.7-10.7)	9.4 (8.1-10.8)
Lucarotti (24)	65	men	4232	>39	1.3 (0.9-1.6)	1.5 (0.2-5.4)

CI = Confidence Interval; All but one of the screening surveys used records of general practitioners to identify subjects for screening. Akkersdijk et al. (33) used a population referred for abdominal ultrasound measurements; $ = Besides an absolute criterium for abdominal aortic aneurysms an aneurysm was considered to be present when the distal diameter was at least 150% of the proximal aortic diameter. * = Besides an absolute criterium for abdominal aortic aneurysms an abdominal aneurysm was also considered to be present when the distal aortic diameter exceeded the proximal aortic diameter with 5 mm or more.

In 33 subjects the aneurysm was of the longitudinal type. In those aged between 55 and 70 years more than 80 percent of the aneurysm was of the saccular type, whereas in those older than 70 years this was only the case in about 55 percent of the aneurysms.

The prevalence of aneurysms of the abdominal aorta in different age- and sex categories is given in table 5.2. The prevalence in men was 5.9 (95% CI 3.7-9.5) times higher than in women. In both men and women there was a ten-fold increase in the prevalence of abdominal aortic aneurysm from the youngest to the oldest age groups. The prevalence of large aneurysms with a distal diameter of 50 mm or more, commonly accepted as an indication for surgery, was 0.8 percent (95% CI 0.3-1.2) in men and 0.13 percent (95% CI 0.0-0.2) in women, showing a similar relative risk of 5.8 (95% CI 2.0-17.2).

In table 5.3. several potential risk factors for abdominal aortic aneurysms in subjects with and without an abdominal aortic aneurysm are compared for men and women separately. Subjects with an abdominal aneurysm had a more unfavourable cardiovascular risk profile than those without an aneurysm. In both men and women, current cigarette smoking was significantly more frequent among subjects with an abdominal aortic aneurysm. In addition, the mean serum cholesterol level was higher and intermittent claudication was more prevalent in those with an aneurysm, especially in men. In a comparison between 21 subjects with a large aneurysm (distal diameter 50 mm or more) and those with smaller aneurysms no clear differences in age (mean age 72 years in both groups) or in other risk factors could be demonstrated.

Discussion

In 5,283 participants in the Rotterdam Study the prevalence of aneurysms of the abdominal aorta was 2.1 percent, varying from 0.2 percent in women between 55 and 60 years of age to 10.3 percent in men of 80 years and older. Men are almost six times more often affected than women. A clear increase in the prevalence of aneurysms of the abdominal aorta and of the proximal and distal diameter of the abdominal aorta with advancing age is demonstrated.

The response rate in the Rotterdam Study of about 78 percent is relatively high, compared to similar surveys with response rates varying from 46.6 to 76% (4,5,7,9,23,24,25). Because of a lower response rate in the very old and the exclusion of subjects living in nursing homes, the prevalence may have been underestimated for this age group. Although, for logistical reasons, measurements of the abdominal aorta started six months after the start of the Rotterdam Study, this is unlikely to have influenced the accuracy of the prevalence estimates, because scheduling of the ultrasound examinations was based on ZIP-codes. This is illustrated by the similar prevalence estimates of abdominal aortic aneurysms observed in the different six-months periods of the study.

In about 97 percent of the measurements we succeeded to visualize the abdominal aorta. According to the Rotterdam Study scanning protocol, the time available for ultrasound measurements of the abdominal aorta was ten minutes. Compared to other studies, where the abdominal aorta was visualized in 82 to 99.9 percent (9,16,23,26), our success rate is good.

A significant increase of both aortic diameters with advancing age is present. This increase is more pronounced in men than in women and is larger in the distal than the proximal diameter of the abdominal aorta. It must be stressed, however, that these data are derived from a cross-sectional study and that our findings do not represent estimates of growth of the aortic diameter with advancing age. Follow-up studies are needed to obtain such estimates. Findings from previous studies on the relationship between the aortic diameters and age are conflicting. Liddington and et al. (27), in a cross-sectional study in men of 65 to 74 years of age, reported a significant association between age and the aortic diameter. O'Kelly and et al. (4) could not demonstrate a significant difference in the prevalence of large aortas between older and younger subjects. Further studies in this area are needed.

In our study, subjects with an abdominal aortic aneurysm had a more unfavourable cardiovascular risk profile, compared to those without an abdominal aneurysm, even after adjustment for differences in age. This indicates that cardiovascular risk factors are important in identifying subjects at higher risk of an abdominal aortic aneurysm. A question that remains to be answered is the

extent to which aortic aneurysms reflect severe arteriosclerotic vessel disease or may also be determined by factors other than those related to arteriosclerosis.

A comparison between the results of eight large screening surveys for abdominal aortic aneurysms and the findings from the Rotterdam Study is shown in table 4. When criteria for abdominal aneurysms and population characteristics of these other studies are applied to our own dataset, no major differences in the prevalence estimates are found. Only in the study of Smith and co-workers (9) the prevalence is 8.2 percent (95% CI 7.2-9.3) whereas the adjusted estimate in the Rotterdam Study dataset is 4.8 percent (95% CI 3.5-6.4). Little is known about geographical differences in the occurrence of abdominal aneurysms. Thus, it remains unclear whether this can explain the difference between the results reported by Smith and our findings. Geographical differences in smoking habits or other risk factors for abdominal aneurysms could play a role. Besides that, differences in the use of ultrasound equipment for routine examination of the abdomen in the period proceeding a screening survey can have been of influence on the number of subjects who had surgery for an abdominal aneurysm and this can explain differences in the reported prevalence of abdominal aortic aneurysms between survey.

The prevalence of abdominal aneurysms is six times lower in women than in men for both small and large aneurysms. This difference is often used as an argument to exclude women from screening surveys (7). However, in several studies based on population mortality statistics, the incidence of ruptured abdominal aneurysms was only 2 to 3.5 times higher in men compared to women (28,29). Also, in necropsy studies (30,31) a ruptured abdominal aorta is only two times more prevalent in men compared to women. Furthermore, several studies (8,12,31) have indicated that women are at higher risk of having the familial type of abdominal aneurysm. This type of aneurysm is considered to confer a greater risk of rupture (32). Although differences in the design of these studies make it difficult to draw definite conclusions, they provide some evidence that aneurysms in women are at greater risk of rupture than in men.

We conclude that an aneurysmatic dilatation of the abdominal aorta is not uncommon in older adults, especially in men. Age- and gender specific prevalence estimates of abdominal aortic aneurysms can be of use in selecting

subjects for ultrasound evaluation of the abdominal aorta. Before the decision to screen or not to screen for abdominal aneurysms can be made, additional data are needed. In particular, more should be known about factors influencing aneurysm formation, growth and rupture.

References

1. Anonymous. Periodic health examination, 1991 update: 5. Screening for abdominal aortic aneurysms. Can Med Assoc J 1991;145:783-9.
2. Harris PL. Reducing the mortality from abdominal aortic aneurysms: need for a national screening programme. Br Med J 1992;305:697-9.
3. Anonymous. Suggested standards for reporting on arterial aneurysms. J Vasc Surg 1991;13:444-50.
4. O'Kelly J, Heather P. General practice-based population screening for abdominal aortic aneurysms: a pilot study. Br J Surg 1989;76:479-80.
5. Loh CS, Stevenson IM, Wu AVO, Eyes B. Ultrasound scan for abdominal aortic aneurysms. Br J Surg 1989;76:417.
6. Lucarotti M, Shaw E, Poskitt K, Heather B. The Gloucestershire Aneurysm Screening Programme: the first 2 years experience. Eur J Vasc Surg 1993;7:397-401.
7. Collin J, Walton J, Araujo L, Lindsell D. Oxford screening programme for abdominal aortic aneurysms in men aged 65 to 74 years. Lancet 1988;613-5.
8. Darling RC, Brewster DC, LaMuraglia GM, Moncure AC, Cambria RP, Abbot WM. Are familial abdominal aortic aneurysms different? J Vasc Surg 1989;10:39-43.
9. Smith FCT, Grimshaw GM, Paterson IS, Tsang GMK, Shearman CP, Hamer JD. Community-based aortic aneurysm screening. Br J Surg 1992;79:152.
10. Norgard Ö, Rais O, Ängquist KA. Familial occurrence of abdominal aortic aneurysms. Surgery 1984;95:650-6.
11. Webster MW, Ferrel RE, Jean PLS, Majumder PP, Fogel SR, Steed DL. Ultrasound screening of first-degree relatives of patients with an abdominal aortic aneurysm. J Vasc Surg 1991;13:9-14.
12. Webster MW, Jean PLS, Steed DL, Ferrel RE, Majumder PP. Abdominal aortic aneurysm: results of a family study. J Vasc Surg 1991;13:366-72.
13. Johanson K, Koepsell T. Familial tendency for abdominal aortic aneurysms. JAMA 1986;256:1934-6.
14. Adams DCR, Tulloh BR, Poskitt KR. Screening for familial aneurysms. Br J surg 1992;79:152.

15. Thurmond AS, Semler HJ. Abdominal aortic aneurysm incidence in a population at risk. J Cardiovasc Surg 1986;27:457-60.
16. Allardice JT, Allwright GJ, Wafula JMC, Wyatt AP. High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography. Br J Surg 1988;75:240-2.
17. Cabellon S, Moncrief CL, Pierre DR, Cavaugh DG. Incidence of abdominal aortic aneurysms in patients with atheromatous disease. Am J Surg 1983;146:575-6.
18. Lederle FA, Walker JM, Reinke DB. Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. Arch Intern Med 1988;148:1753-6.
19. Sakalihasan N, Janssen N, Ries E, Creemers E, Limet R. Ultrasonographic screening for abdominal aortic aneurysms in patients with peripheral vascular disease. Br J Surg 1992;79:152.
20. Lindholm L, Ejlertsson G, Forsberg R, Norgren L. Low prevalence of abdominal aortic aneurysms in hypertensive patients. Acta Med Scand 1985;218:305-10.
21. Hofman A, Grobbee DE, Jong PTVM de, Ouweland FA van den. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.
22. Rose GA, Blackburn H. Cardiovascular survey methods. Geneva: World Health Organisation, 1968.
23. Scott RAP, Ashton HA, Kay DN. Abdominal aortic aneurysms in 4237 screened patients: prevalence, development and management over 6 years. Br J Surg 1991;78:1122-5.
24. Lucarotti ME, Shaw E, Heather BP. Distribution of aortic diameter in a screened male population. Br J Surg 1992;79:641-2.
25. Krohn KD, Kullmann G, Kvernebo K, Rosen L, Kroese A. Ultrasonographic screening for abdominal aortic aneurysm. Eur J Surg 1992;158:527-30.
26. Scott RAP, Ashton H, Sutton GLJ. Ultrasound screening of a general practice population for aortic aneurysms. Br J Surg 1986;73:318.
27. Liddington MI, Heather BP. The relationship between aortic diameter and body habitus. Eur J Vasc Surg 1992;6:89-92.
28. Fowkes FGR, Macintyre CCA, Ruckley CV. Increasing incidence of aortic aneurysms in England and Wales. Br Med J 1989;298:33-5.
29. McFarlane MJ. The epidemiologic necropsy for abdominal aortic aneurysm. JAMA 1991;265:2085-8.
30. Bengtsson H, Bergqvist D, Sternby NH. Increasing prevalence of abdominal aortic aneurysms. A necropsy study. Eur J Surg 1992;158:19-23.
31. Bengstsson H, Norrgård Ö, Ängquist KA, Ekberg O, Öberg L, Bergqvist D. Ultrasonographic screening of the abdominal aorta among siblings of the patients with abdominal aortic aneurysms. Br J Surg 1989;76:589-91.
32. Sterpetti AV, Feldhaus RJ, Schultz RD, Blair EA. Identification of abdominal aortic aneurysm patients with different clinical features and clinical outcomes. Am J Surg 1988;156:466-9.

33. Akkersdijk GJM, Puylaert JBC, Vries AC de. Het aneurysma aortae abdominalis als nevenbevinding bij echografisch onderzoek van het abdomen. Ned Tijdschr Geneeskd 1992;136:1907-13.

CHAPTER VI

Are aneurysms of the abdominal aorta of arteriosclerotic origin? Evidence from a population-based study

Introduction

Aneurysms of the abdominal aorta account for about 1.0% of all deaths in men of 55 years or older in The Netherlands (1). Little is known about the etiology of aneurysms of the abdominal aorta, although both arteriosclerosis (2-5) and connective tissue abnormalities of the aortic wall (6-8) have been suggested to play a role in abdominal aneurysm formation.

Arteriosclerotic changes in the intimal layers of the abdominal aorta are thought to affect the diffusion of oxygen and nutrients to the outer layers of the abdominal aorta. This may lead to changes in the aortic wall structure, making the aorta susceptible to dilatation (3).

In addition, abnormalities in connective tissue components such as type III collagen or elastin have been observed in patients with abdominal aortic aneurysms, suggesting an alternative etiology of abdominal aortic aneurysms (9-11). An increased proteolytic activity, potentially resulting from a genetic predisposition, may induce aneurysm formation by destruction of collagen and elastin (12,13).

Although both mechanisms may be involved in the formation of abdominal aortic aneurysms, their relative importance has not been established yet. Some studies suggest that two etiologically different types of abdominal aortic aneurysms can be distinguished. Other studies support the idea of a multifactorial disease (11).

The objective of our study was to examine possible etiological factors of abdominal aortic aneurysms. Both risk indicators related to arteriosclerosis and those indicative of connective tissue disorders were studied, in order to assess whether arteriosclerosis and connective tissue disorders are involved in the etiology of abdominal aortic aneurysms.

Methods

The Rotterdam study is a population-based, prospective follow-up study, aimed to investigate determinants of disease occurrence and progression in elderly

subjects (14). 7,983 subjects aged 55 years and older living in Ommoord, a suburb of Rotterdam, take part in the study. The overall response rate is 78%. Participants were interviewed at home and visited the research centre twice.

Ultrasound examination of the abdominal aorta was introduced in the protocol six months after the start of the study. Subjects living in nursing homes (n=1,056) were excluded from the ultrasound examination. Ultimately, 5,456 subjects had an ultrasound examination of the abdominal aorta. In 173 subjects (3.2%) it was impossible to visualise the distal part of the abdominal aorta. The present results are based on 5,283 participants in whom a measurement of the distal aorta was available.

Three trained assistants performed the ultrasonographic measurements. Interobserver agreement between these assistants was high, as has been described previously (Chapter IV). A 3.5 MHz linear-array transducer was used (Toshiba SSH 60A). First, a longitudinal scan of the abdominal aorta was made. Measurements were taken from the most anterior to the most posterior wall echo. The diameter of the widest part of the abdominal aorta (distal aorta) and the diameter at the level of the superior mesenteric artery (proximal aorta) were recorded. An aneurysm was considered present when the distal aortic diameter was 35 mm or more or when the ratio between the distal and proximal aorta was 1.5 or more (15-17).

Risk indicators

Two sets of risk indicators potentially related to the development of abdominal aortic aneurysms, were studied: some known to be related to arteriosclerosis and others indicative of connective tissue weakness.

A family history of cardiovascular disease was considered positive if a first degree relative had a myocardial infarction or stroke before the age of 65. Smoking was coded as "never", "former" and "current". Height and weight were measured and body mass index was calculated in kilograms per square meter. Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. Diastolic blood pressure was registered at Korotkoff V. Diabetes was

defined as the current use of antidiabetic drugs or a blood glucose level of 11.0 mmol/L or over, random or two hours after a 75 grams oral glucose load. Serum total cholesterol was determined by an automated enzymatic procedure (18) in a non-fasting blood sample. Serum HDL-cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium.

As markers of collagen weakness, information on a history of inguinal hernia surgery (19,20) and the use of pulmonary medication (i.e. corticosteroids, beta-agonists or theophylline) as an indication of obstructive lung disease (21-23) were used. Data on the number of operations for inguinal hernia and the age at which surgery was performed, were collected.

Data analysis.

First, (multiple) linear regression analysis was used to assess the relation between potential etiologic factors and the distal diameter of the abdominal aorta. Second, odds ratios (as an approximation of the relative risk), were calculated using logistic regression analyses with the presence of an abdominal aortic aneurysm as the dependent variable. Separate multivariate analyses were performed for risk factors related to arteriosclerosis (also including age and gender) and indicators related to connective tissue weakness (also including age, gender and smoking).

To assess the proportion of abdominal aortic aneurysms in the population that may be attributed to a certain risk indicator, the etiological fraction (EF) was calculated according to Miettinen (24) using the formula EF = CF * (RR-1)/RR, where the relative risk (RR) represents the odds ratio of the risk indicator resulting from the multiple logistic regression analyses and the case fraction (CF) represents the prevalence of the risk indicator in those with an abdominal aortic aneurysm. The proportion of aneurysm attributable to arteriosclerosis or connective tissue weakness was estimated by adding the etiological fractions of indicators of arteriosclerosis and connective tissue weakness, respectively. Because the etiological fraction is calculated from the odds ratio from the logistic regression which may overestimate the relative risk, and as a result of imprecision in these estimates, the summation of the etiological fraction can exceed 100%.

Missing values for continuous risk factors were substituted by the mean value of that risk factor. Missing values for categorical variables were coded as a separate category.

Further, the association between the potential risk factors and two different types of aneurysms was examined, [1] saccular aneurysms i.e. aneurysms localized to the distal aorta with a distal/proximal ratio of 1.5 or more and

Table 6.1. Main characteristics of the study population.

	men (n=2,217)	women (n=3,066)
Age (years)	67.2 (7.5)	68.1 (8.2)
Body mass index (kg/m^2)	25.7 (2.9)	26.6 (3.9)
Serum cholesterol (mmol/L)	6.3 (1.1)	6.9 (1.2)
Serum HDL cholesterol (mmol/L)	1.2 (0.3)	1.5 (0.4)
Current smoker (%)	24.5	19.2
Former smoker (%)	59.5	28.4
Never smoker (%)	16.0	52.3
Diastolic blood pressure (mm Hg)	74.7 (11.4)	73.4 (11.1)
Systolic blood pressure (mm Hg)	138.7 (21.8)	139.4 (22.5)
Myocardial infarction (%)	11.2	3.4
Angina pectoris (%)	6.2	6.8
Stroke (%)	3.8	2.4
Intermittent claudication (%)	2.0	1.0
Ankle/arm index $\leq$ 90% (%)	13.7	15.2
Diabetes mellitus (%)	10.3	9.3
Inguinal hernia surgery (%)	18.2	3.2
Pulmonary medication (%)	6.3	3.8
Aortic aneurysm (%)	4.1	0.7
Distal aortic diameter (mm)	19.7 (6.1)	16.2 (3.1)
Proximal aortic diameter (mm)	21.0 (3.3)	18.6 (2.6)

Numbers are means with standard deviation, or percentages

[2] longitudinal aneurysms, i.e. those extending beyond the offspring of the mesenteric artery with a distal diameter of 35 mm or more and a distal/proximal ratio of less than 1.5).

Results

Characteristics of the 2,217 men and 3,066 women included in the study are given in table 6.1. An aneurysm of the abdominal aorta was present in 91 men (4.1%, 95% CI 3.3;5.0) and 21 women (0.7%, 95% CI 0.4;1.1).

Table 6.2. Potential risk factors and change (mm) in the distal diameter of the abdominal aorta. Results of multivariate analyses.

Risk indicator	Coefficient#	95%CI	p-value
Male gender	3.36	3.03;3.57	<0.01
Age (years)	0.09	0.07;0.11	<0.01
Body mass index (kg/m^2)	0.11	0.07;0.15	<0.01
Serum cholesterol (mmol/L)	-0.02	-0.12;0.08	0.70
Serum HDL-cholesterol (mmol/L)	-0.41	-0.05;-0.77	0.03
Current smoker@	0.97	0.62;1.32	<0.01
Former smoker@	0.43	0.14;0.71	<0.01
Diastolic blood pressure (mm Hg)	0.02	0.01;0.03	<0.01
Family history of CVD	0.07	-0.25;0.39	0.67
Diabetes mellitus	-0.68	-0.13;-0,23	<0.01
Inguinal hernia surgery	0.30	-0.14;1.74	0.18
Pulmonary medication	-0.21	-0.75;0.33	0.44

CVD = Cardiovascular disease; CI = confidence interval; @ = Never smokers served as a reference group; # = Coefficient indicates the increase (mm) of the distal diameter of the abdominal aorta, associated with an increase of one unit of a continuous risk factor or with the presence of a dichotomous risk factor, studied in the multivariate analyses.

In men, the mean aortic diameter was 19.7 mm (SD 6.0) and in women 16.2 mm (SD 3.0). The distal aortic diameter increased with increasing age, diastolic blood pressure, body mass index and was larger in smokers (table 6.2.). Subjects with diabetes mellitus and those with a high serum HDL-cholesterol level had a smaller aortic diameter.

Risk factors known to be related to arteriosclerosis were strongly associated with the presence of abdominal aortic aneurysms in our study were male gender, increasing age, higher levels of serum cholesterol and cigarette smoking. Increasing levels of serum HDL-cholesterol and the presence of diabetes were

Table 6.3. Relative risk for presence of an abdominal aortic aneurysm according to potential risk factors.

Risk indicator	Unadjusted RR	Age and gender adjusted RR	Mutually adjusted RR
Male gender	6.2 (3.9;10.0)	7.0 (4.3;11.3)	5.9 (3.4;10.3)
Age (per 5 years)	1.4 (1.3;1.6)	1.5 (1.3;1.7)	1.7 (1.5;1.9)
Body mass index (per 5 kg/m2)	0.8 (0.6;1.1)	1.0 (0.9;1.5)	0.9 (0.6;1.3)
Serum cholesterol (per 1 mmol/L)	1.0 (0.8;1.1)	1.2 (1.1;1.4)	1.2 (1.1;1.4)
Serum HDL-cholesterol (per 1 mmol/L)	0.3 (0.2;0.6)	0.7 (0.4;1.3)	0.7 (0.3;1.2)
Current smoker	4.2 (2.4;7.3)	3.6 (2.0;6.6)	3.8 (2.1;7.0)
Former smoker	2.6 (1.5;4.4)	1.6 (0.9;2.9)	1.7 (0.9;3.0)
Diastolic BP (per 5 mm Hg)	1.1 (1.0;1.2)	1.1 (1.0;1.2)	1.1 (1.0;1.2)
Systolic BP (per 10 mm Hg)	1.1 (1.0;1.2)	1.1 (1.0;1.2)	1.0 (0.9;1.2)
Family history of CVD (yes/no)	1.1 (0.7;1.7)	1.3 (0.8;2.2)	1.3 (0.8;2.1)
Diabetes mellitus	0.8 (0.4;1.7)	0.6 (0.3;1.3)	0.6 (0.3;1.3)
Inguinal hernia	2.8 (1.7;4.4)	1.3 (0.8;2.2)	1.4 (0.9;2.3)
Inguinal hernia (at < 25 years)	3.5 (1.5;8.1)	3.1 (1.3;7.5)	3.3 (1.4;8.0)
Inguinal hernia (at ≥ 25 years)	2.7 (1.6;4.5)	1.2 (0.7;2.0)	1.2 (0.7;2.1)
Pulmonary medication	1.3 (0.6;2.8)	1.0 (0.5;2.1)	0.9 (0.4;1.9)

CVD = Cardiovascular disease; BP = Blood pressure; RR = relative risk (95% confidence interval).

inversely related with the presence of abdominal aortic aneurysms (table 6.3.), although these associations did not reach conventional levels of statistical significance.

Of the potential indicators of connective tissue weakness the use of pulmonary medication showed no clear association with the aortic diameter or the prevalence of abdominal aneurysms (tables 6.2. and 6.3.). However, subjects with a history of hernia inguinal surgery had a relative risk of an abdominal aortic aneurysm of 1.4 (95% CI 0.9;2.3) compared to those without. Among these, those who had inguinal hernia surgery before the age of 25 years were at the highest risk of an abdominal aortic aneurysm. The estimated relative risk in this group compared to subjects without a history of inguinal hernia surgery was 3.3 (95% CI 1.4;8.0). Smoking appeared to modify the relationship between surgery for inguinal hernia and abdominal aortic aneurysms. The relative risk associated with surgery for inguinal hernia was 2.0 (95% CI 0.9;4.6) in current smokers compared to 1.0 (95% CI 0.2;4.0) in never smokers. Restriction of the study population to subjects without a history of cardiovascular disease did not change the risk estimates of the indicators of connective tissue weakness.

Separate analyses for men and women did not reveal differences in risk factors of abdominal aortic aneurysms, although the number of women with an abdominal aortic aneurysm was often to small to yield precise estimates of relative risks. Furthermore, no clear differences between risk factors for those aneurysms confined to the distal aorta (saccular type) compared to those extending beyond the offspring of the mesenteric superior (longitudinal type) artery could be demonstrated.

In table 6.4. the estimated proportion of abdominal aortic aneurysms that may be attributed to the risk indicators studied are given. 6% of the occurrence of abdominal aortic aneurysm can be explained by a history of inguinal hernia surgery as an indication of connective tissue abnormality. Risk factors of arteriosclerosis, such as a body mass index of 30 kg/m^2 or more, serum cholesterol levels exceeding 6.4 mmol/L, current and former smoking, diastolic blood pressure of 95 mm Hg or more, systolic blood pressure of 160 mm Hg or more and a family history of cardiovascular disease contribute to about 90% of all abdominal aortic aneurysms.

Discussion

Our findings demonstrate that risk factors for arteriosclerosis are also associated with the occurrence of abdominal aortic aneurysms. This suggests that arteriosclerosis plays a role in the etiology of abdominal aortic aneurysms. Further, the finding that a history of inguinal hernia surgery at a relative young age was related to the presence of abdominal aortic aneurysms indicates that

Table 6.4. Case fraction and etiological fraction of different risk indicators of abdominal aortic aneurysms.

Risk indicator	Case fraction[#](%)	Etiological fraction[$](%)
Indicators of arteriosclerosis		
Serum cholesterol ≥ 6.5 mmol/L	57.1	26.4
Current smoker	37.8	33.1
Former smoker	45.5	17.4
Diastolic blood pressure ≥95 mm Hg	6.3	2.5
Systolic blood pressure ≥ 160 mm Hg	21.4	2.3
Family history of cardiovascular disease	18.8	4.2
Indicators of connective tissue weakness		
Inguinal hernia surgery	21.8	6.2
Inguinal hernia surgery (at < 25 years)	5.4	3.8
Inguinal hernia surgery (at ≥ 25 yes/no)	16.4	2.7

= Case fraction is the prevalence of the risk indicator among subjects with an abdominal aortic aneurysm; $ = Etiological fraction is the proportion of abdominal aortic aneurysms that may be attributed to the risk factor.

congenital weakening of the collagen structure may predispose to aneurysm formation. The majority (approximately 90%) of abdominal aortic aneurysms, however, can be attributed to risk factors associated with arteriosclerosis. To appreciate the findings of our study some limitations must be discussed. In this cross-sectional study the prevalence of abdominal aortic aneurysms not only indicates the risk of subjects to have an aneurysm of the abdominal aorta but may also reflect the effect of risk factors on aneurysm growth and prognosis.Aneurysms that grow fast or have a high rupture risk will be underrepresented in this type of study. Sterpetti and coworkers (24) reported two different types of aneurysms. One type, represented by 75% of the aneurysms observed, is characterised by a high risk of rupture and showed less evidence of arteriosclerotic occlusive disease, while the second type is characterized by multiple signs of arteriosclerotic disease and a relatively low risk of rupture. The latter type may be overrepresented in our study.

Most previous studies about the association between arteriosclerosis and aneurysms of the abdominal aorta were based on clinical or autopsy data. Although selection of patients related to the severity of disease may have occurred in these studies, the same associations with risk factors of arteriosclerosis, in particular serum cholesterol level, hypertension and smoking habits, were observed in our population-based study (3,26,27).

The inverse relation between diabetes and the diameter of the abdominal aorta is difficult to explain and has, to our knowledge, not been reported by others. Kita and co-workers (27) found an increased risk of abdominal aortic aneurysms in subjects with familial hypercholesterolemia and diabetes. Hammond and Garfinkel (5) could not demonstrate a relation between diabetes and death from aortic aneurysms and others did not observe an association between serum glucose and the incidence of abdominal aortic aneurysms (4). Selective survival of subjects free of diabetes could underlie our observation in this cross-sectional study among relatively old subjects.

Our study suggests that the relationship between a history of inguinal hernia surgery and aneurysms of the abdominal aorta is modified by smoking status. This may be explained by an effect of smoking on the serum alpha-1-antitrypsin activity. A relative increase of the alpha-1-antitrypsin activity will lead to an

increase in serum elastase which may lead to aneurysm formation as has been demonstrated by Dobrin and co-workers (7).

The use of a history of inguinal hernia surgery or the use of pulmonary medication as a proxy of connective tissue weakness can be criticized. Since, however, no direct information on, for example, the genetic predisposition in collagen or elastin production or the serum alpha-1-antitrypsin concentration in the participants was available, an approximation for connective tissue quality had to be chosen. The use of pulmonary medication as an indication of emphysema of the lung has limitations because it is well possible that many patients included in this group have chronic obstructive lung disease without signs of emphysema. Such misclassification may dilute a possible relation. Because inguinal hernia as well as emphysema may be caused by other factors not related to connective tissue abnormalities, the relative risks are likely to be underestimated.

The results of our study give support to the view that arteriosclerosis plays a role in the formation of abdominal aortic aneurysms. Although general arteriosclerosis is probably the most important cause of aortic aneurysms, the relation between inguinal hernia surgery and the occurrence of abdominal aortic aneurysms suggests that connective tissue weakness, in a certain subgroup of patients, may also play a role in the formation of aneurysms.

References

1. Akkersdijk GJM, Graaf van der Y, Bockel van JH, Vries de AC, Eikelboom BC. Mortality rates associated with operative treatment of infrarenal abdominal aortic aneurysm in The Netherlands. Br J Surg 1994;81:706-9.
2. Cabellon S, Moncrief CL, Pierre DR, Cavaugh DG. Incidence of abdominal aortic aneurysms in patients with atheromateus disease. Am J Surg 1983;146:575-6.
3. Reed D, Reed C, Stemmerman G, Hayashi T. Are aortic aneurysms caused by atherosclerosis? Circulation 1992;85:205-11.
4. Tilson MD. Aortic aneurysms and atherosclerosis. Circulation 1992;85:378-9
5. Hammond EC, Garfinkel L. Coronairy heart disease, stroke and aortic aneurysms. Factores in the etiology. Arch Enverionm Health 1969;19:167-82.
6. Summer D, Hokanson D, Strandness D. Stress-strain characteristics and collagen-elastin

content of abdominal aortic aneurysms. Surg Gynecol Obstet 1970;130:459-66.

7. Dobrin P, Baker W, Gley W. Elastolytic and collagenolytic studies of arteries. Arch Surg 1984;119:405-9.
8. Powell J, Greenhalgh R. Cellular, enzymatic and genetic factors in the pathogenesis of abdominal aortic aneurysms. J Vasc Surg 1989;9:297-304.
9. Cohen JR, Sarfatti I, Ratner L , et al. Alpha-1 antitrypsin phenotypes in patients with abdominal aortic aneurysms. J Surg Res 1990;49:319-21.
10. Dobrin P. Pathophysiology and pathogenesis of aortic aneurysms. Surg Clin North Am 1989;69:687-703.
11. Reilly J, Tilson D. Incidence and etiology of abdominal aortic aneurysms. Surg Clin North Am 1989;69:705-11.
12. Menashi S, Campa J, Greenhalgh R, et al. Collagen in abdominal aortic aneurysms: typing, content and degradation. J Vasc Surg 1987;6:578-82.
13. Huebner K, Isobe M, Gasson J, et al. Localization of the gene encoding human erythroid potentiating factor to chromosome region Xp 11.1-11.4. Am J Genet 1986;38:819-826.
14. Hofman A, Grobbee DE, Jong PTVM de, Ouweland FA van den. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.
15. Collin J. Screening for abdominal aortic aneurysms. Br J Surg 1982;57:851-2.
16. Anonymus. Suggested standards for reporting on arterial aneurysms. J Vasc Surg 1991;13:444-50.
17. Harris PL. Reducing the mortality from abdominal aortic aneurysms: need for a national screening programme. Br Med J 1992;305:697-9.
18. Gent CM van, Voort HA van der, Bruyn AM de, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-251.
19. Cannon DJ, Casteel L, Read RC. Abdominal aortic aneurysm, Leriche's syndrome, inguinal herniation and smoking. Arch Surg 1984;119:387-9.
20. Wagh PV, Leverich AP, Sun CN, White HJ, Read RC. Direct inguinal herniation in men: a disease of collagen. J Surg Res 1974;17:425-33.
21. Cronenwett JL, Murphy TF, Zelenock GB, Whitehouse WM, Lindenauer SM, Graham LM, Quint LE, Silver TM, Stanley JC. Acturarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery 1985;98:472-83.
22. Cannon DJ, Read RC. Metastatic emphysema. A mechanism for acquiring inguinal herniation. Ann Surg 1981;194:270-8.
23. Laarhoven CJ van, Borstlap AC, Berge Henegouwen DP van, Palmen FM, Verpalen MC, Schoenmaker MC. Chronic obstructive pulmonary disease and abdominal aortic aneurysms. Eur J Vasc Surg 1993;7:386-90.
24. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol 1974;99:325-32.

25. Sterpetti AV, Feldhaus RJ, Schultz RD, Blair EA. Identification of abdominal aortic aneurysm patients with different clinical features and clinical outcomes. Am J Surg 1988;156:466-9.
26. Auerbach O, Garfinkel L. Atherosclerosis and aneurysms of aorta in relation to smoking habits and age. Chest 1980;78:805-9.
27. Kita Y, Shimizu M, Sugihara N, Shimizu K, Miura M, Koizumi J, Mabuchi H, Takeda R. Abdominal aortic aneurysms in familial hypercholesterolemia. Case reports. Angiology 1993;44:491-9.

CHAPTER VII

Selecting subjects for ultrasonographic screening of the abdominal aorta: Four different risk functions

Introduction

Early detection and surgical treatment of subjects with an abdominal aortic aneurysm is important to prevent death from rupture (1,2). Ultrasonographic assessment of the abdominal aortic diameter provides an accurate method to detect abdominal aortic aneurysms, but the effectiveness of population ultrasonographic screening for this condition is thought to be low (3). In particular, the question which patients will eventually benefit most from screening for abdominal aneurysms remains unsolved.

The effectiveness of ultrasound screening for abdominal aortic aneurysms can be increased by preselecting subjects based on risk factors for the disease (4). Ideally, such a high risk approach should decrease the number of subjects that require ultrasonographic assessment while still detecting most of the abdominal aortic aneurysms.

Several strategies to select subjects at increased risk of an abdominal aortic aneurysm have been advocated (5-9). Notably, preselection based on age and gender, information that can easily be obtained from population registries, has been suggested. For example, in the Oxford screening program (10), only men between 65 and 74 years of age were invited to take part and Scott and coworkers (11) selected men and women from 65 to 80 years of age.

Selection of subjects using information obtained from a medical questionnaire may be of additional value in reducing the number of subjects that have to be referred for ultrasound examination. Variables to be considered in such a questionnaire are a history of cardiovascular disease, a family history of abdominal aneurysms (12-14), smoking habits (15,16) and other potential risk indicators (17-19).

Selection based on information not obtainable by a questionnaire has also been advocated. For example using risk indicators such as high blood pressure (20), increased serum cholesterol levels (21,22) and signs of peripheral vascular disease (23), have been proposed for this purpose.

The most labour-intensive and expensive way to select subjects at increased risk of an abdominal aneurysm would be the inclusion of findings from physical examination. However, whether palpation or auscultation of the abdomen in

routine medical practice is of additional value to select patients at increased risk of an abdominal aortic aneurysm remains unclear. Although, obviously, larger aneurysms are more easily discovered by physical examination (24), it is estimated that only 30% to 50% of all abdominal aneurysms can be detected through abdominal palpation (9). Little is known about the value of auscultation.

The aim of the present study was to examine risk functions, reflecting the four strategies presented above, to identify subjects with an increased risk of having an abdominal aortic aneurysm in order to preselect subjects for ultrasonographic screening for abdominal aortic aneurysms.

Methods

This study is part of the Rotterdam Study, a population-based cohort study, aimed to investigate determinants of disease occurrence and progression in older subjects. The cohort includes 7,983 subjects aged 55 years or older living in Ommoord, a suburb of Rotterdam. The response rate for the baseline examinations of the Rotterdam Study was 78%.The rationale and design of the study have been described elsewhere (25). In short, all subjects were interviewed at home and invited to visit the research centre twice for extensive clinical measurements. A physical examination, including palpation of the abdomen and auscultation of the abdominal aorta, was performed at the research centre by a physician before ultrasound scanning of the abdominal aorta. At physical examination, a palpable dilatation of the abdominal aorta according to the physician was scored as a positive palpation. If the abdominal aorta could not be palpated because of obesity or if the investigating physician judged the diameter of the abdominal aorta to be normal, palpation was scored negative. All bruits registered over the abdominal aorta, irrespective of their possible origin, were scored as a positive auscultation.

After physical examination, ultrasound scanning of the abdominal aorta was performed using a 3.5 MHz linear-array transducer (Toshiba SSH 60A). The distance between the most anterior and the most posterior wall echo was measured. The diameter of the widest part of the abdominal aorta (distal aorta)

and the diameter at the level of the superior mesenteric artery (proximal aorta) were recorded. An aneurysm was considered present when the distal aortic diameter was 35 mm or more or when the ratio between the distal and proximal aorta was 1.5 or more (26). Subjects living in nursing homes (n=1056) were excluded from ultrasound examination because of technical limitations in the transport of the ultrasound equipment. Subjects with a history of abdominal aortic repair were also excluded (n=27). In 173 subjects (3.2%) it was technically impossible to visualise the abdominal aorta. In total, 5,283 subjects with available ultrasound measurements of the abdominal aorta were included in the analyses.

Several factors potentially associated with the occurrence of abdominal aortic aneurysms were studied. Smoking behaviour was coded as "never", "former" and "current". The presence of intermittent claudication and a history of angina was assessed using the "Rose" cardiovascular questionnaire (27). A history of myocardial infarction was considered positive if the subject reported to have been hospitalized for the condition. Questions were asked about a history of surgery for an inguinal hernia and about the use of blood pressure lowering drugs for the indication hypertension.

Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. Diastolic blood pressure was registered at Korotkoff V. The ankle systolic blood pressure was measured at the posterior tibial artery using a 8 MHz continuous wave Doppler probe (Huntleigh 500D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmanometer, and the ankle/arm blood pressure ratio of the systolic blood pressure at the ankle and the systolic blood pressure at the arm was calculated. The lowest ankle/arm index in either leg was used in the analysis. Peripheral vascular disease was considered present when the ankle/arm index was 0.9 or less (28). Serum total cholesterol was determined by an automated enzymatic procedure (29) in a non-fasting blood sample. Serum HDL-cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium.

Four risk functions to identify subjects at an increased risk of an abdominal aortic aneurysm were developed. The first risk function was based on the

information readily available in most population registries and included age and gender as independent predictors of abdominal aortic aneurysms. In a second risk function the added value of a structured medical questionnaire was determined. Besides age and gender, this risk function included smoking behaviour, the use of antihypertensive drugs for the indication hypertension, the presence of intermittent claudication, a history of angina, myocardial infarction, stroke and inguinal hernia surgery. In the third risk function the following variables were considered in addition to those already included in the second risk function: ankle/arm blood pressure index, serum cholesterol and HDL-cholesterol levels, and diastolic and systolic blood pressure. Finally, a fourth risk function was derived, considering all information potentially obtainable in a clinical or general practice setting: including the findings from physical examination (palpation and auscultation) as well as the variables examined in the previous three risk functions.

For all risk indicators considered for inclusion in the risk functions, univariate odds ratios, positive predictive values, sensitivity and specificity were calculated. Next, age- and gender-adjusted odds ratios with standard errors were calculated using a logistic regression model with the presence of an aneurysm as the dependent variable. Risk indicators with an age- and gender adjusted coefficient/standard error ratio of 1.4 or more or -1.4 or less were entered in a multivariate logistic regression model together with the other variables selected for that risk function.

The general formula of the risk function is: $p(\text{aneurysm}) = 1/[1+\exp(-(b_0+b_{1\ldots n}X_{1\ldots n}))]$ where P(aneurysm) is the probability of an individual to have an abdominal aortic aneurysm, b_0 is the intercept in the logistic equation, $b_{1\ldots n}$ stands for the logistic coefficients of the variables X1 to Xn. $X_{1\ldots n}$ represent the value of the variable $X_{1\ldots n}$ in a particular individual. In case of a dichotomous variable the value is 1 in the presence and 0 in the absence of the risk indicator.

In order to determine the capacity of the four risk functions to predict the occurrence of abdominal aortic aneurysms, areas under the receiver operator characteristic (ROC) curve were calculated and compared (30). To determine the effectiveness of either risk function in preselecting subjects with an increased risk of an abdominal aortic aneurysm for further ultrasound examination the overall

sensitivity, specificity, and the proportion of the total population selected for further ultrasonographic evaluation were estimated. These parameters were calculated for all four risk functions using a 1.5%, 2% and 3% estimated probability of an individual to have an abdominal aortic aneurysm as cut-off points above which ultrasonographic assessment of the abdominal aorta is necessary.

Since, in clinical practice, abdominal aortic aneurysms that have a distal diameter of 50 mm or more are considered indications for elective replacement by a graft (31), we further calculated the proportion of abdominal aortic aneurysms with an indication for surgery that would be detected by each risk function.

Table 7.1. General characteristics of the 5,283 participants of the Rotterdam Study in whom ultrasound measurements of the abdominal aorta were obtained.

	Mean or %	SD#
Women (%)	58.0	
Age (years)	67.7	7.9
Systolic blood pressure (mm Hg)	139.2	22.2
Diastolic blood pressure (mm Hg)	73.9	11.3
Hypertension (%)	30.3	
Serum cholesterol (mmol/L)	6.7	1.2
Serum HDL-cholesterol (mmol/L)	1.4	0.4
Current smoking (%)	23.5	
Intermittent claudication (%)	1.5	
Angina pectoris (%)	6.8	
History of stroke (%)	3.1	
History of myocardial infarction (%)	6.6	
History of inguinal hernia surgery (%)	9.6	
Distal aortic diameter (mm)	17.6	4.9
Proximal aortic diameter (mm)	19.6	3.2
Abdominal aortic aneurysm (%)	2.1	

SD = Standard deviation

Results

General characteristics of the study population are given in table 7.1. In 112 subjects (2.1%; 95% CI 1.7-2.5) an abdominal aortic aneurysm was diagnosed by ultrasound. The mean distal aortic diameter in subjects with an abdominal aortic aneurysm was 41.5 mm (SD 11.8) and ranged from 25 to 92 mm.

Table 7.2. Sensitivity, specificity, positive predictive value and odds ratio (Coefficient/Standard error) of risk indicators associated with the occurrence of abdominal aortic aneurysms in older adults.

Risk indicator	N	Sens %	Spec %	PPV %	Odds Ratio# (Coeff/SE)
Male gender	2217	81	59	4.1	6.5 (6.7)
Age 55-65 years	2455	22	43	1.1	1.0$
Age 66-75 years	1931	38	62	2.1	1.4 (2.3)
Age > 75 years	897	39	81	4.2	2.7 (4.6)
Current smoking	1108	38	79	3.7	3.1 (3.6)
Antihypertensive drug use	774	36	70	2.5	1.8 (2.2)
Cholesterol ≥ 6.5 mmol/L	2785	57	46	2.2	1.8 (2.8)
Angina pectoris	338	11	94	3.5	1.7 (1.6)
History of myocardial infarction	338	17	94	5.2	1.5 (1.4)
Ankle arm index ≤ 0.9	617	29	89	5.0	2.1 (3.2)
Intermittent claudication	74	5	99	8.1	1.9 (1.3)
History of inguinal hernia surgery	486	22	91	4.9	1.5 (1.6)
Enlarged aorta on palpation	148	19	97	13.4	7.0 (6.0)
Bruit over abdominal aorta	213	14	96	6.7	1.9 (1.8)

N = number of subjects positive for the risk indicator; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; # = Adjusted for all other determinants; $ = reference category; A coefficient/standard error of ≥ 1.96 indicates a p-value of ≤ 0.05.

In table 7.2. positive predictive value, sensitivity, specificity and odds ratios for diagnosing abdominal aortic aneurysms are presented for age, gender, selected patients characteristics and for palpation and auscultation of the abdomen. Although the prevalence of abdominal aortic aneurysms increased with age, about 60% of all aneurysms was detected in subjects aged between 55 and 75 years. In 13.4% of the subjects with an apparently enlarged aorta during palpation, an aneurysm was diagnosed by ultrasound. The mean distal aortic diameter of those aneurysms that were diagnosed by palpation, was 47 mm and ranged from 32 mm to 92 mm. The diagnostic accuracy of abdominal palpation was similar in those with a relatively high and a relatively low waist circumference.

Table 7.3. Indicators of abdominal aortic aneurysms with logistic coefficients included in four different risk functions.

Variable	Logistic Coefficient (SE)			
	RF_1	RF_2	RF_3	RF_4
Constant	- 10.67	-11.83	-14.86	-15.02
Male gender	1.95 (0.25)	1.70 (0.27)	1.88 (0.27)	1.94 (0.28)
Age (years)	0.08 (0.02)	0.09 (0.01)	0.09 (0.01)	0.09 (0.01)
Serum cholesterol level (mmol/L)			0.20 (0.08)	0.19 (0.08)
Diastolic blood pressure (mm Hg)			0.02 (0.01)	0.02 (0.01)
Antihypertensive drug use		0.69 (0.25)		
Former smoker (versus never smoker)	0.52 (0.30)	0.51 (0.30)	0.49 (0.31)	
Current smoker (versus never smoker)	1.33 (0.31)	1.26 (0.31)	1.16 (0.32)	
Intermittent claudication		0.89 (0.46)		
Ankle/arm index $\leq$ 0.90			0.56 (0.24)	0.46 (0.25)
Enlarged aorta on palpation				1.94 (0.32)
Bruit over abdominal aorta				0.61 (0.35)

Results of multivariate logistic regression; RF = risk function; SE = Standard error.

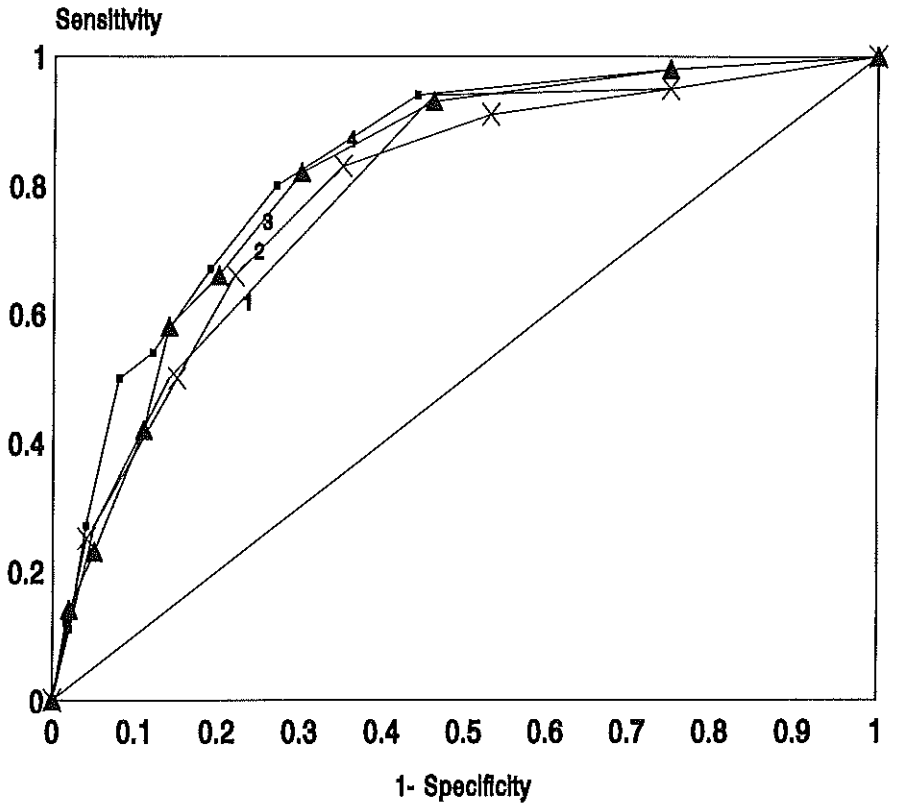

Figure 7.1. Receiver operator characteristic (ROC) curve of the four risk functions predicting the presence of an abdominal aortic aneurysm. Risk function 1 includes age and gender, risk function 2 includes age, gender and data from a structured medical questionnaire, risk function 3 also includes blood pressure and cholesterol levels and risk function 4 includes all variables of risk function 3 and the results of physical examination.

The variables eventually included in the four risk functions to preselect subjects with an increased risk for abdominal aortic aneurysms are given in table 7.3. In figure 7.1. the ROC curves for the risk functions are given. The area under the curve was 0.77 for the first risk function (age and gender), 0.80 for the second (including age, gender and variables assessable in a short medical questionnaire), 0.81 for the third (also including blood pressure and cholesterol

levels) and 0.83 for the fourth risk function, considering all the previous potential risk indicators plus the results of physical examination of the abdomen.

In table 7.4. the sensitivity, specificity and the proportion of subjects selected for further ultrasound measurements by using the four risk functions are given. When a
probability of 1.5% of having an aneurysm is chosen as the cut-off point above which referral for ultrasonographic screening of the abdominal aorta is indicated, a sensitivity ranging from 80% to 94% is achieved, depending which risk function is used, with only 36% to 49% of subjects referred for ultrasonography.

Table 7.4. Proportion of subjects selected for ultrasound assessment, sensitivity and specificity in the four risk functions to predict the presence of abdominal aortic aneurysms. Calculations were made by assuming different cut-off points for an individual's risk of an abdominal aortic aneurysm above which referral for ultrasonography is indicated, ranging from 1.5% to 3%.

Risk function	1	2	3	4
p(AAA) ≥ 1.5%				
Proportion selected	36%	49%	49%	46%
Sensitivity	80%	94%	93%	94%
Specificity	65%	52%	52%	55%
p(AAA) ≥ 2%				
Proportion selected	23%	21%	21%	19%
Sensitivity	63%	63%	64%	59%
Specificity	78%	80%	80%	82%
p(AAA) ≥ 3%				
Proportion selected	11%	10%	8%	5%
Sensitivity	38%	40%	38%	34%
Specificity	90%	91%	93%	95%

p(AAA) = probability that an aneurysm is present estimated by either risk function; Selected = proportion of subjects selected from the study population (n=5,283) for further ultrasound evaluation of the abdominal aorta.

At a lower cut-off level the sensitivity of the risk function increases to about 100% but 100% of all subjects would then be referred for ultrasonography. When a higher cut-off point for the estimated risk of an abdominal aortic aneurysm is used, the proportion of subjects that have to be referred for ultrasound assessment decreases at the expense of a sensitivity of 70% or lower.

If a cut-off point of 1.5% is used the results of risk functions two, three and four do not differ appreciably. The second risk function seems preferable over risk functions three and four because the information needed to estimate the probability of an abdominal aortic aneurysm is most easy to obtain. Still, although only 7 out of 112 aneurysms were not selected by risk function two at a cut-off point of 1.5%, 4 of those had a distal diameter exceeding 50 mm, and thus had an indication for surgery. The use of the risk function one, based on age and gender only will further reduces the number of subjects to be referred for ultrasound assessment of the abdominal aorta to 36%, but sensitivity would

Table 7.5. Proportion of the 21 abdominal aortic aneurysms with an indication for surgery (i.e. distal aortic diameter ≥ 50 mm), that would be detected by applying the risk functions using different cut-off points for the risk of an abdominal aortic aneurysm above which referral for ultrasonography is indicated, ranging from 1.5% to 3%.

	p(AAA)		
	≥ 1.5%	≥ 2%	≥ 3%
Risk function			
1	90%	81%	52%
2	81%	71%	62%
3	81%	76%	52%
4	86%	76%	48%

P(AAA) = The probability that an abdominal aortic aneurysm is present estimated by either risk function.

decrease to 80% compared to 94% in risk function two. In table 7.5. the proportion of all abdominal aortic aneurysms with an indication for surgery that would be detected by applying the risk functions is calculated, using the same three probability cut-off points mentioned earlier. With an increasing cut-off point from 1.5% to 3%, 50% to 90% of all abdominal aortic aneurysms with an indication for surgery will be detected. No major differences in the sensitivity of the four risk functions were observed. Risk function one, including only age and gender, seems most attractive to preselect subjects for screening of aneurysms with an indication for surgery as these variables can be easily obtained and the number of subjects that have to be referred for ultrasound examination is similar or even lower than for the other risk functions.

Discussion

The objective of this study was to examine the possibility of relatively simple preselection of subjects at increased risk of having an abdominal aortic aneurysm in order to increase the effectiveness of ultrasound screening. Four risk functions to predict the presence of an abdominal aortic aneurysm were compared. Our analyses suggest that preselection of high risk subjects is feasible using a simple structured medical questionnaire. If all subjects with a predicted probability of the presence of an aneurysm of 1.5% or more are selected for further ultrasound assessment, 49% of the population would be referred for ultrasonography and 94% of all abdominal aortic aneurysms would be detected. If the objective of screening would be to detect aneurysms with an indication for surgery, i.e. with a distal diameter of 50 mm or more, the risk function based on age and gender only would be preferable.

Several preselection criteria for ultrasound screening for abdominal aortic aneurysms have been proposed previously. Collin and coworkers (10) recommended selective screening of men aged 65 to 74 years and some have followed this suggestion (32-34). These criteria were based on the results of autopsy studies and on the appreciation that subjects in this age group will benefit most from surgery if an aneurysm is diagnosed. However, no information

about the sensitivity and specificity of such selection is available from population-based studies . Application of the criteria to our study population would select 15% of the participants for further ultrasound examination, but identify only 31% of all aneurysms (sensitivity). With a little more effort, by sending all subjects a questionnaire, the sensitivity could be increased to 52% with the same 15% referral rate. This sensitivity seems a relevant improvement of the age and gender criteria used by Collin and co-workers, but may still be considered too low.

It has also been suggested to identify high risk subjects by using a positive history of cardiovascular disease as the main criterium (8,17). Data to support such an approach have come from studies in men and women visiting clinics for peripheral artery disease or coronary artery disease with a reported prevalence of abdominal aortic aneurysms of up to 10%. In our study, the prevalence ranged from 3% to 8% in subjects with signs of cardiovascular disease. Still, by using this approach many cases would remain undetected. Based on our data the sensitivity of intermittent claudication was 5% and a history of myocardial infarction had a sensitivity of 17% (table 2).

In our study, no information was available on family history of abdominal aortic aneurysms. As results from recent studies support the presence of a familial tendency in the occurrence of abdominal aortic aneurysms (12,14,35,36) the use of this information could further improve the performance of a prescreening assessment.

Less than one out of five abdominal aneurysms was detected by physical examination in our study. This is low compared to the results in some other studies (7,10,18,24) where the sensitivity of abdominal palpation was estimated to be 30% to 65%, and may be explained by the limited experience our study physicians had with palpation and auscultation of the abdominal aorta. However, our approach may well reflect routine screening standards. Lederle and coworkers (9) concluded that, although palpation of the abdomen had a sensitivity of about 50% in experienced hands, all aneurysms palpated during screening were missed by a previous routine physical examination of the abdomen.

Our study was population-based and confined to men and women who were

healthy enough to take part in a demanding research programme. Importantly, this group of subjects may benefit most from screening because they are similarly healthy enough to undergo elective surgery when an aneurysm is diagnosed. Because the prevalence of abdominal aortic aneurysms differs according to race (37) and because in our study only caucasians were studied, the generalizability of our findings to other populations remains to be established.

We believe that the risk functions we developed can be useful in determining an individual's risks of an abdominal aortic aneurysm and may aid in selecting patients for further ultrasonographic assessment. In particular, the use of a structured medical questionnaire where, in addition to age and gender, cardiovascular risk factors are assessed, can be of value to increase effectiveness of screening for abdominal aneurysms in a primary care setting. However, application of our risk functions to other groups of individuals would require validation of the risk functions in these populations (38).

More generally, before screening programmes for abdominal aortic aneurysms can be initiated, the benefit of such programmes has to be weighted against the costs. Such analyses are not possible on the basis of our data. Also, further research may identify determinants of growth and rupture, to select those with an increased risk of rupture for immediate surgery and to select those with slowly growing aneurysms and a low tendency to rupture for regular ultrasonographic follow-up .

We conclude that a risk function, based on age, gender and data obtained from a medical questionnaire can markedly increase effectiveness of screening for abdominal aortic aneurysms by reducing the number of subjects referred for ultrasound examination, while detecting the vast majority of subjects with an abdominal aortic aneurysm.

References

1. Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. Br J Surg 1986;73:101-3.

2. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. J Vasc Surg 1989;9:437-47.
3. Anonymous. Periodic health examination, 1991 update: 5. Screening for abdominal aortic aneurysms. Can Med Assoc J 1991;145:783-9.
4. Hill GB. Selective screening. J Chron Dis 1986;39:251-2.
5. Collin J. Screening for abdominal aortic aneurysms. Br J Surg 1982;57:851-2.
6. Lee KR, Walls WJ, Martin NL, Templeton AW. A practical approach to the diagnosis of abdominal aortic aneurysms. Surgery 1975;78:195-201.
7. Twomey A, Twomey EM, Wilkis RA, Lewis JD. Unrecognised aneurysmal disease in male hypertensive patients. Br J Surg 1984;71:307-8.
8. Allardice JT, Allwright GJ, Wafula JMC, Wyatt AP. High prevalence of abdominal aortic aneurysms in men with peripheral vascular disease: screening by ultrasonography. Br J Surg 1988;75:240-2.
9. Lederle FA, Walker JM, Reinke DB. Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. Arch Intern Med 1988;148:1753-6.
10. Collin J, Walton J, Araujo L, Lindsell D. Oxford screening programme for abdominal aortic aneurysms in men aged 65 to 74 years. Lancet 1988;i:613-5.
11. Scott RAP, Ashton HA, Kay DN. Routine ultrasound screening in management of abdominal aortic aneurysms. Br Med J 1988;296:1709-10.
12. Johanson K, Koepsell T. Familial tendency for abdominal aortic aneurysms. JAMA 1986;256:1934-6.
13. Webster MW, Jean PLS, Steed DL, Ferrel RE, Majumder PP. Abdominal aortic aneurysms: results of a family study. J Vasc Surg 1991;13:366-72.
14. Adams DCR, Tulloh BR, Poskitt KR. Screening for familial aneurysms. Br J Surg 1992;79.
15. Auerbach O, Garfinkel L. Atherosclerosis and aneurysms of the aorta in relation to smoking habits and age. Chest 1980; 78:805-9.
16. Khan H. The Dorn study of smoking and mortality among US veterans: report on 8 1/2 years of observation. Natl Cancer Inst Monogr 1966;19:1-125.
17. Thurmond AS, Semler HJ. Abdominal aortic aneurysm incidence in a population at risk. J Cardiovasc Surg 1986;27:457-60.
18. Cabellon S, Moncrief CL, Pierre DR, Cavaugh DG. Incidence of abdominal aortic aneurysms in patients with atheromatous disease. Am J Surg 1983;146:575-6.
19. Liddington MI, Heather BP. The relationship between aortic diameter and body habitus. Eur J Vasc Surg 1992;6:89-92.
20. Grimshaw GM, Thompson JM, Hamer JD. Prevalence of abdominal aortic aneurysms associated with hypertension in an urban population. J Med Screening 1994;1:226-8.
21. Kita Y, Shimizu M, Sugihara N, Shimizu K, Miura M, Koizumi J, Mabuchi H, Takeda R. Abdominal aortic aneurysms in familial hypercholesterolemia. Case reports. Angiology 1993;44:491-9.

22. Hammond EC, Garfinkel L. Coronary heart disease, stroke and aortic aneurysms. Factors in the etiology. Arch Enverionm Health 1969;19:167-82.
23. Sakalihasan N, Janssen N, Ries E, Creemers E, Limet R. Ultrasonographic screening for abdominal aortic aneurysms in patients with peripheral vascular disease. Br J surg 1992;79:152.
24. Beede SD, Ballars DJ, James M, Ilstrup DM, Hallet JH. Positive predictive value of clinical suspicion of abdominal aortic aneurysms. Arch Int Med 1990;150:549-51.
25. Hofman A, Grobbee DE, Jong PTVM de, Ouweland FA van den. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.
26. Anonymous. Suggested standards for reporting on arterial aneurysms. J Vasc Surg 1991;13:444-50.
27. Rose GA, Blackburn H. Cardiovascular survey methods. Geneva: World Health Organisation, 1968.
28. Fowkes FGR, Houseley E, Cawood EHH et al. Edinburgh artery study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20:384-94.
29. Gent CM van, Voort HA van der, Bruyn AM de, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-251.
30. Hanley JA, McNeil BJ. A method of comparing the areas under the Receiver Operating Characteristic curves derived from the same cases. Radiology 1983;148:839-43.
31. Hollier LH, Taylor LM, Oschner J. Recommended indications for operative treatment of abdominal aortic aneurysms: report of a subcommittee of the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery. J Vasc Surg 1992;15:1046-56.
32. O'Kelly J, Heather P. General practice-based population screening for abdominal aortic aneurysms: a pilot study. Br J Surg 1989;76:479-80.
33. Harris PL. Reducing the mortality from abdominal aortic aneurysms: need for a national screening programme. Br Med J 1992;305:697-9.
34. Derbyshire NDJ, Lindsell DRM, Collin J, Creasy TS. Opportunistic screening for abdominal aortic aneurysms. J Med Screening 1994;1:220-2.
35. Darling RC, Brewster DC, LaMuraglia GM, Moncure AC, Cambria RP, Abbot WM. Are familial abdominal aortic aneurysms different? J Vasc Surg 1989;10:39-43.
36. Norgard Ö, Rais O, Ängquist KA. Familial occurrence of abdominal aortic aneurysms. Surgery 1984;95:650-6.
37. Johnson G, Avery A, McDougal G, Burnham SJ, Keagy BA. Aneurysms of the abdominal aorta in blacks and whites in North Carolina. Arch Surg 1980;120:1138-40.
38. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules applications and methodological standards. N Eng J Med 1984;310:573-7.

CHAPTER VIII

General discussion

In this chapter some general issues of the clinical epidemiology of abdominal aortic aneurysms will be addressed, with special emphasis on screening. Further, suggestions for future research are given.

The problem: frequent and increasing

Aneurysms of the abdominal aorta occur relatively frequent in older subjects, especially in men. In the Rotterdam Study the prevalence was 2.1% (95% CI 1.7;2.5), 4.1% in men and 0.7% in women.

In an analysis of data from the Netherlands we observed a clear increase in the number of hospital admissions for abdominal aortic aneurysms from 1972 to 1992. In men the age-adjusted hospital discharge rates for non-ruptured aneurysms increased from 3.7 to 37.6 per 100,000 and in women from 1.2 to 5.5 per 100,000. For ruptured aneurysms the figures increased from 2.4 to 10.3 per 100,000 in men and from 0.7 to 1.7 per 100,000 in women. Obviously, such an increase in the occurrence of abdominal aortic aneurysms when maintained will have an impact on the surgical workload resulting from the disease in the near future. In 1972, 371 subjects underwent acute or elective abdominal aortic aneurysm surgery in the Netherlands and this number increased to 2,226 in 1992. This represents a six-fold increase in hospital discharge rates for ruptured and non-ruptured abdominal aortic aneurysms in two decades and is comparable to the figures presented in other studies (1-5). Health care planners must be prepared for an increasing demand for surgical personnel and facilities to operate patients with an abdominal aortic aneurysm.

In the same time period death rates from abdominal aortic aneurysms increased also. In 1992, 1% of all deaths in men and 0.3% of all deaths in women of 55 years and older were attributed to the rupture of an abdominal aortic aneurysm.

The increase in hospital admissions and death rates can only partly be explained by better diagnostic and surgical facilities and are probably also due to a true increase in the incidence of abdominal aortic aneurysms as has been discussed in chapter III.

The etiology: arteriosclerosis only?

As we have demonstrated in our study, arteriosclerosis plays a dominant role in the formation of abdominal aortic aneurysms and may account for as much as 90% of the cases. By using a history of inguinal hernia surgery as a, far from ideal, proxy of connective tissue weakness, we concluded that connective tissue weakness is likely to contribute to the occurrence of abdominal aortic aneurysms also. While connective tissue weakness clearly plays a less prominent role than arteriosclerosis in the formation of the vast majority of abdominal aortic aneurysms, findings from studies from Sterpetti and coworkers (6) and Cronenwet (7) suggest that abdominal aortic aneurysms associated with collagen structural defects may have a worse prognosis than those associated with arteriosclerosis. In that respect, aneurysms that are related to connective tissue weakness, although less prevalent than arteriosclerotic aneurysms, could be of particular importance.

The relation between connective tissue weakness and the occurrence of abdominal aortic aneurysms should be investigated further. Few studies (8,9) have pointed to the possibility of using inguinal hernia surgery as a marker of weakening in the collagen structure. Furthermore, the occurrence of obstructive pulmonary disease, that is associated with an increased protease activity, has been related to an increased incidence of abdominal aortic aneurysms (10). Both markers may be of use in identifying subjects with aneurysms or with an increased risk of aneurysm rupture. Possibly, other indicators of collagen weakness (e.g. increased alpha-1-antitrypsin (11) or elastolytic activity (12)) are more useful to identify subgroups of high-risk patients. In addition, an influence of elastase on aneurysm formation and of collagenase on aneurysm growth and rupture have been described (13), and genetic variations on chromosome 16 (14) have been associated with abdominal aortic aneurysms. It would be of interest to know whether enzyme activity or genetic markers could be used in tracing subjects with an increased risk of abdominal aortic aneurysms or in determining the risk of rupture in subjects with an abdominal aortic aneurysm.

Screening: prospects and problems

The ultimate aim of screening subjects for abdominal aortic aneurysms is not to detect abdominal aneurysms but to reduce mortality from rupture. In this respect, the results of a recent randomized trial from Scott and co-workers (30) showing a 50% reduction in the incidence of aneurysm rupture in ultrasonographically screened men compared to non-screened men, are in favour of screening. However, the sample size of this study was too low to warrant definitive conclusions.

It is believed that 30% to 60% of abdominal aortic aneurysms rupture (16). Thus, about 50% of the aneurysms identified in a screening programme is detected unnecessarily because the patients will not die from aneurysm rupture. Factors predicting rupture have not been established yet and studies addressing this issue are urgently needed. So far, the diameter of the aneurysm and sudden growth or complaints are the main variables used in selecting subjects for surgical repair. The aneurysm diameter corresponds reasonable well with rupture risk but the use of the diameter in selecting subjects for surgery has been discussed (17). According to autopsy studies (18) the proportion of aneurysms that rupture increases from 13% in those with a diameter of less than 50 mm to 60% in those with a diameter of 100 mm or more. It is assumed that subjects with an aortic diameter of 50 mm or more have an annual risk of rupture of 5% (7) and will benefit from aneurysm surgery, which has an estimated operation mortality of 8%. However, as long as it is uncertain which patients are at increased risk of rupture, subjects with a relatively benign dilatation of the abdominal aorta run the risk of being submitted to unnecessary, and also potentially fatal, medical procedures. Since several variables such as increased diastolic blood pressure, cigarette smoking and the presence of lung emphysema are potentially associated with an increased risk of aneurysm rupture (7,15), detection and subsequential surgical repair of aneurysms in subgroups of patients with one of these characteristics may be useful strategy to reduce mortality from aneurysm rupture. Such mortality benefit using this approach, however, has not been assessed.

It is important to realise that an aneurysm is not just an extremely wide

aortic diameter but also reflects changes in the aortic wall, not present in normal aortas, that make the aorta susceptible to rupture (13). Because the aortic diameter is much easier to establish than these changes in the aorta wall, the former is used to define aortic aneurysms. The mean proximal aortic diameter (often considered as a proxy for an individual's normal aortic diameter) varies from 12 to 19 mm in women and from 14 to 21 mm in men. Therefore, the Subcommittee on Reporting Standards for Arterial Aneurysms (19) defined an aneurysm as a permanent localized dilation with at least a 50% increase in diameter compared to the expected normal diameter. Several cut-off points of the distal abdominal aortic diameter including 25, 30, 35 mm are used to select subjects for further ultrasound follow-up. Based on the definition of the Subcommittee for reporting standards for arterial aneurysms these definitions using absolute distal diameters are sometimes combined with a definition based on a relative increase of the distal diameter by 5 mm or 50% compared to the proximal aortic diameter.

In our research we decided to define abdominal aortic aneurysms using a combination of the absolute distal diameter and a relative increase of the distal compared to the proximal aortic diameter, thus accounting for the variability in the normal aortic diameter among the population. In subjects with a small "normal" aortic diameter, e.g. of 15 mm, an abdominal aortic diameter of 22 mm should be interpreted differently as a similar abdominal aortic diameter in a subject with a "normal" aortic diameter of 20 mm.

Whether a low cut-off point or a high cut-off point should be used in screening for abdominal aortic aneurysms depends on the importance of limiting the number of subjects incorrectly diagnosed as having either a normal aortic diameter (false negative) or a dilated aorta (false positive). A low cut-off of the distal aortic diameter should be used if small aortic aneurysms bear a considerable risk of rupture. However, small aneurysms are thought not to grow very fast and do have a low risk of rupture (20). For this reason, we decided to use a relatively high cut-off point of 35 mm. In addition, the anxiety the knowledge of having an abdominal aortic aneurysm, a potentially fatal condition, may bring about in a screened subject, should not be disregarded. If defining abdominal aneurysms at lower cut-off points is considered, for example with the

aim of closely monitoring growth, further research on the psychological consequences for the individual patient of the awareness that he or she has an abdominal aneurysm is important. In view of this, a cut-off point of 35 mm and an increase of 50% or more of the distal compared to the proximal aortic diameter seems most appropriate to select subjects with an abdominal aortic aneurysm for regular follow-up in screening programmes for abdominal aortic aneurysms.

To increase effectiveness of screening for abdominal aortic aneurysms methods to restrict screening to high-risk patients may be useful. For our purpose we developed four risk functions to identify those with a sufficiently increased risk of an abdominal aortic aneurysm.

Preselection based on age, gender, smoking behaviour, use of antihypertensive drugs and the presence of intermittent claudication can easily be assessed by a short self administered questionnaire and may reduce the number of subjects to be referred for ultrasound assessment of the abdominal aorta diameter from 100% to 50% with a minimal decrease in sensitivity from 100% to 94%. We did not obtain information about familial occurrence of abdominal aortic aneurysms in our study. This information may further increase the sensitivity of the risk function but its effect on the specificity remains to be established. Following this approach to preselect subjects for screening for abdominal aortic aneurysms offers several advantages. Firstly, women are not excluded from screening as has been the case in several previous screening surveys. This is especially important because women seem to have a higher risk of rupture then men (21), and because abdominal aortic aneurysms in women can indicate a genetic predisposition of abdominal aortic aneurysms in first degree relatives (22). Secondly, the risk function can easily be applied in general practice to identify subjects at increased risk of abdominal aortic aneurysms, given that the necessity of a screening programme for abdominal aortic aneurysms is acknowledged.

Before such a screening programme can be initiated with confidence the following questions need to be answered:

1. What are the determinants of aneurysm growth and rupture?
2. What is the effect of screening for abdominal aortic aneurysms on the mortality related to the disease?
3. What is the cost-effectiveness of screening and what is the effect on a subjects' quality of life of detecting an abdominal aneurysm that is too small for surgical repair?
4. Can operation mortality and morbidity further be improved by new surgical techniques and will it increase the benefits of screening?

Screening: consequences

The effect of a national screening program in the Netherlands on the surgical workload can be estimated from the prevalence of abdominal aortic aneurysms observed in our study. According to our criteria, 2.1% of all subjects of 55 years or older has an abdominal aortic aneurysm. Among the approximately 3400,000 inhabitants of 55 years or older in 1992, 71,400 abdominal aneurysms can be expected. 20% of the aneurysms detected in our screening survey had an anterior-posterior diameter of the aneurysm of 50 mm or more, which is generally considered an indication for surgery. Thus, after a screening survey of all subjects of 55 years and older, 14,280 subjects would be eligible for surgery for their aneurysm. If all subjects were screened at a 7-year interval as has been proposed earlier (23), about 2,000 subjects would need to be operated per year: the same number of subjects that presently has surgery for an aneurysm. Thus, a 7-year screening interval would lead to approximately a doubling of the numbers of aortic repairs in the first screening years, since a reasonable reduction in the number of aneurysms discovered accidentally or presenting as ruptured can only be expected when the majority of subjects has been screened, this would clearly demand extra surgical planning and facilities.

In determining the cost-effectiveness of screening for abdominal aortic aneurysms, operation mortality plays an important role. In-hospital mortality for elective surgery in the Netherlands in 1992 was 7% and increased with age from

4% in those aged 55-64 years to 25% in those of 85 years or older. In literature, mortality rates of less than 5% have been reported. Besides operation mortality, non-fatal complications should also be weighted if the benefits of screening and surgery are calculated. Important complications of aneurysm surgery are intestinal ischemia, renal damage requiring dialyses, leg ischemia, myocardial infarction or stroke (24).

The total costs of screening programmes are difficult to estimate. Collin (25) estimated an amount of US $13,500 for each life saved in a national screening programme for abdominal aortic aneurysms in men aged 65-74 years. However, neither the costs of ultrasound follow-up in about 80% of the aneurysms that are too small to have surgery, nor the costs related to complications following surgery such as ischaemic colitis or renal insufficiency, were accounted for. Moreover, not only the economics of a screening programme have to be considered but quality of life needs to be taken into account, both for those that will have surgery and for those with an aneurysm who need to have bi-annual ultrasound follow-up.

A new situation may emerge if other forms of treatment become available. New surgical techniques, with less complications, to replace aortic aneurysms may be of great importance in reducing operation mortality and morbidity. In addition, the results of treating aneurysm patients with beta-adrenergic blockade seems promising (26,27).

The first experience with treatment of abdominal aortic aneurysms with placement of a transfemoral aortic stent has been reported (28-30). Currently, however, only approximately 15% of the patients with an abdominal aortic aneurysm is eligible for endovascular grafting. Other problems, such as distal and proximal graft fixation and training of vascular surgeons need to be dealt with. If morbidity and mortality are reduced, as can be expected, with transfemoral endovascular techniques, and safety is established during long-term follow-up, this may increase the potential for screening.

Conclusion

Abdominal aortic aneurysms are relative common in the elderly, especially in men. Over the last decades death rates from and hospital admissions for abdominal aortic aneurysms have increased in part due to an increased incidence of the disease, resulting in an increased burden on medical facilities. Besides age and gender, risk factors associated with arteriosclerotic disease are also associated with the occurrence of abdominal aortic aneurysms. We examined various risk functions to identify subjects at an increased risk of an abdominal aortic aneurysm in general practice. The use of such a preselection would greatly reduce the number of subjects requiring ultrasound examination in a screening programme with minimal negative effects on the sensitivity.

The Rotterdam Study has shown that screening for abdominal aortic aneurysms is feasible and will lead to the detection of a considerable number of subjects with an abdominal aortic aneurysm. Still, as long as it is unclear which factors determine aneurysm growth an rupture and which patients with an abdominal aneurysm will benefit most from surgery, population screening should not be advocated. Nevertheless, because of the increasing prevalence of the disease and the high mortality rate in case of rupture, an abdominal aneurysm should be suspected and ultrasound examination of the abdominal aorta could be considered in older subjects with an unfavourable cardiovascular risk profile.

References

1. Ingoldby CJH, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. Br J Surg 1986;73:551-3.
2. Castleden WH, Mercer JC. Abdominal aortic aneurysms in western Australia: descriptive epidemiology and patterns of rupture. Br J Surg 1980;72:109-12.
3. Mc Jenkins A, Ruckley CV, Nolan B. Ruptured abdominal aortic aneurysms. Br J Surg 1986;73:395-8.
4. Fowkes FGR, Macintyre CCA, Ruckley CV. Increasing incidence of aortic aneurysms in England and Wales. Br Med J 1989;298:33-5.

5. Naylor AR, Webb J, Fowkes FGR, Ruckley CV. Trends in abdominal aortic aneurysm surgery in Scotland (1971-1984). Eur J Vasc Surg 1988;2217-21.
6. Sterpetti AV, Schultz RD, Feldhaus RJ, Cheng SE, Peetz DJ. Factors influencing enlargement rate of small abdominal aortic aneurysms. J Surg Res 1987;43(3):211-9.
7. Cronenwett JL, Murphy TF, Zelenock GB, Whitehouse WM, Lindenauer SM, Graham LM, Quint LE, Silver TM, Stanley JC. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery 1985;98:472-83.
8. Cannon DJ, Casteel L, Read RC. Abdominal aortic aneurysm, Leriche's syndrome, inguinal herniation and smoking. Arch Surg 1984;119:387-9.
9. Lehnert B, Wadouh F. High coincidence of inguinal hernias and abdominal aortic aneurysms. Ann Vasc Surg 1992;6(2):134-7.
10. Laarhoven CJHM, Borstlap ACW, Berge Henegouwen DP van, Plamen FMLHG, Verpalen MCPJ, Schoemaker MC. Chronic obstructive pulmonary disease and abdominal aortic aneurysms. Eur J Vasc Surg 1993;7:386-90.
11. Cohen JR, Sarfatti I, Ratner L , et al. Alpha-1 antitrypsin phenotypes in patients with abdominal aortic aneurysm. J Surg Res 1990;49:319-21.
12. Cannon DJ, Read RC. Blood elastolytic activity in patients with aortic aneurysm. Ann Thorac Surg 1982;34:10-5.
13. Summer D, Hokanson D, Strandness D. Stress-strain characteristics and collagen-elastin content of abdominal aortic aneurysms. Surg Gynecol Obstet 1970;130:459-66.
14. Powell JT, Bashir A, Dawson S, Vine N, Henney AM, Humphries SE, Greenhalgh RM. Genetic variation on chromosome 16 is associated with abdominal aortic aneurysms. Clin Science 1990;78:13-6.
15. Scott RAP, Wilson NM, Ashton HA, Kay DN. Influence of screening on the incidence of ruptured abdominal aortic aneurysms: 5-year results of a randomized controlled study. Br J Surg 1995;82:1066-70.
16. Szilagyi DE, Elliot JP. Clinical fate of patients with a-symptomatic abdominal aortic aneurysms and unfit for surgical treatment. Arch Surg 1972;104:600-6.
17. Louridas G, Reilly K, Perry MO. The role of the aortic aneurysm diameter aortic diameter ratio in predicting the risk of rupture. S Afr Med J 1990;78:642-3.
18. Darling RC, Messina CR, Brewster DC, Ottinger LW. Autopsy study of unoperated abdominal aortic aneurysms. The case for early resection. Circulation 1977;56:161-4.
19. Anonymous. Suggested standards for reporting on arterial aneurysms. J Vasc Surg 1991;13:444-50.
20. Nevitt MP, Ballard DJ, Hallett JW. Prognosis of abdominal aortic aneurysms. A population-based study. New Engl J Med 1989;321:1009-14.
21. Bengtsson H, Bergqvist D, Sternby NH. Increasing prevalence of abdominal aortic aneurysms. A necropsy study. Eur J Surg 1992;158:19-23.
22. Darling RC, Brewster DC, LaMuraglia GM, Moncure AC, Cambria RP, Abbot WM. Are familial abdominal aortic aneurysms different? J Vasc Surg 1989;10:39-43.

23. Bengtsson H, Bergqvist D, Jendteg S, Lindgren B, Persson U. Ultrasonographic screening for abdominal aortic aneurysm: analysis of surgical decisions for cost-effectiveness. World J Surg 1989;13:266-71.
24. Aburahma AF, Robinson PA, Boland JP, Lucente JP, Stuart SP, Neuman SS, Hall MD, Hoak BA. Elective resection of 332 abdominal aortic aneurysms in a southern West-Virginia community during a recent five-year period. Surgery 1991;109:244-51.
25. Collin J. Screening for abdominal aortic aneurysms. Br J Surg 1982;57:851-2.
26. Leach SD, Toole AL, Stern H, et al. Effect of beta-adrenergic blockade on the growth rate of abdominal aortic aneurysms. Arch Surg 1988;123:606-9.
27. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. New Engl J Med 1994;30:1335-85.
28. Balm R, Eikelboom BC, Smit AMGA de, Mali WPThM. Behandeling van een infrarenaal aorta-aneurysma door middel van een transfemoraal ingebrachte endoprothese: Eerste ervaring bij 9 patienten in Nederland. Ned Tijdschr Geneeskd 1995;139:717-21.
29. Mol BAJM de, Vroonhoven ThJMV van. Gecontroleerde verspreiding van nieuwe medische technologie: Transfemorale plaatsing van een endoprothese ter behandeling van een aneurysma van de abdominale aorta. Ned Tijdschr Geneeskd 1995;139:712-6.
30. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991;5:491-9.

Summary

The objective of the work presented in this thesis was to investigate the frequency of abdominal aneurysms in elderly subjects, to identify risk indicators of abdominal aneurysms and to evaluate the capacity of several diagnostic strategies to preselect subjects for ultrasound screening.

After a short introduction in chapter I, a review of the current literature on the etiology, diagnosis, prevalence and incidence of abdominal aortic aneurysms is given in chapter II. A clear increase in the incidence of abdominal aortic aneurysms in the last decades has been described. Despite improvement in diagnostic and surgical techniques, death rates for abdominal aortic aneurysms seemed not to have improved in parallel. Operation mortality decreased to about 5%, but the number of aneurysms that do not come to the attention of the surgeon is still relatively high. It is assumed that only 35% of patients with a ruptured aneurysms will reach a hospital alive and of those only 50% survives. Although several reports are available addressing the costs and benefits of screening asymptomatic persons for abdominal aneurysms, results are inconclusive and further research is necessary.

In chapter III the trend in the incidence of aneurysms of the abdominal aorta in the Netherlands during the past two decades is studied. We analyzed all hospital admissions for and deaths due to aneurysms of the abdominal aorta in the Netherlands from 1972 through 1992. From 1972 to 1992 age adjusted mortality from aneurysms of the abdominal aorta rose from 3.1 to 8.1 per 100,000 in men, and from 1.4 to 2.2 per 100,000 in women. Age adjusted discharge rates for non-ruptured abdominal aortic aneurysms increased from 3.7 to 37.6 per 100,000 in men and from 1.2 to 5.5 in women. For ruptured aneurysms, the age-adjusted discharge rates increased from 2.4 to 10.3 per 100,000 in men and from 0.7 to 1.7 per 100,000 in women. Age-adjusted in-hospital mortality after surgery upon non-ruptured aneurysms was halved during the study period, from 13% in 1972 to 7% in 1992. Age-adjusted in-hospital mortality after acute repair of ruptured abdominal aortic aneurysms decreased from 52% in 1972 to 36% in 1992. There has been an impressive increase in hospital-based incidence of, and mortality from aneurysms of the abdominal

aorta during the past two decades in the Netherlands. The improved detection capability through ultrasound examination is probably a major contributor to this increase, but gender differences and the rise in the number of ruptured aneurysms suggest that a real increase in incidence exists, especially in men.

In chapter IV, the variability in ultrasound measurements of the abdominal aorta is assessed. In addition, the extent to which observer variability is influenced by cardiovascular risk factors is examined. In 135 subjects taking part in a screening survey for abdominal aortic aneurysms, two observers measured the distal and proximal ultrasound diameter of the abdominal aorta, using B-mode ultrasound. The mean difference between two different observers was 0.06 mm (95% CI -0.15;0.27) for measurements of the distal aorta and 0.32 mm (95% CI 0.09;0.55) for measurements of the proximal aorta. Maximal differences between observers for measurements of both the distal and proximal aortic diameter were 4.0 mm. Interobserver variability in the proximal and distal measurements of the abdominal aorta was not related to the level of the major cardiovascular risk indicators. However, interobserver variability in ultrasound measurements of the proximal aorta increased with increasing waist circumference and increasing diameter of the proximal aorta. It is concluded that interobserver variability in ultrasound measurements of the distal abdominal aorta is low and that interobserver variability in the proximal measurements is higher, notably in obese subjects with large aortic diameters.

In chapters V an VI the age- and gender specific prevalence and risk factors of aneurysms of the abdominal aorta are presented and the question whether arteriosclerosis or connective tissue disorders are involved in the etiology of abdominal aortic aneurysms is addressed. In 5,419 subjects (42% men, 58% women) aged 55 years or older ultrasound measurement of the diameter of the abdominal aorta were performed. An aneurysm was defined as a distal aortic diameter of 35 mm or more or a dilatation of the distal compared to the proximal part of the abdominal aorta of 50% or more. Cardiovascular risk factors and variables indicative of connective tissue disorders were assessed to study whether they were related to the occurrence of abdominal aortic

aneurysms. As an indicator of connective tissue disorders a history of inguinal hernia surgery was recorded. After adjustment for potential confounders the mean distal aortic diameter in men was larger than in women (19.7 versus 16.2 mm), increased with age, diastolic blood pressure and body mass index, and was larger in smokers. In contrast, HDL-cholesterol levels and diabetes were inversely related to the distal diameter. The mean distal and proximal aortic diameter increased 0.7 mm and 0.3 mm, respectively, with every 10 years of age. In 2.1% (95% CI 1.7-2.5) of the study population an aneurysm was present; in 4.1% (95% CI 3.2-4.9) of the men and 0.7% (95% CI 0.4-1.0) of the women. Cardiovascular risk factors positively associated with the presence of aneurysms of the abdominal aorta were diastolic blood pressure, smoking and serum cholesterol level. Subjects with a history of inguinal hernia had a 1.4 fold (95% CI 0.9;2.3) increased risk of an abdominal aortic aneurysm. This relative risk was 3.3 (95% CI 1.4;8.0) in those who had inguinal surgery before the age of 25 years. Risk factors associated with arteriosclerosis were estimated to contribute to the occurrence of approximately 90% of all abdominal aortic aneurysms, while 6% could be attributed to risk indicators of connective tissue weakness. The strong relationship between risk factors of arteriosclerosis and aneurysms of the abdominal aorta supports the view that arteriosclerosis is implicated in the etiology of abdominal aortic aneurysms. In addition, there is some evidence that connective tissue disorders are involved.

In chapter VII, risk functions to predict the probability of a subject to have an abdominal aortic aneurysm, based on different ways of obtaining information about risk indicators, are described. These risk functions may be used to increase the effectiveness of screening. We developed four risk functions and estimated the performance to preselect subjects in a screening programme. The first risk function was based on age and gender, and the second on a short medical questionnaire (including questions on age, gender, smoking behaviour, the use of drugs for the indication hypertension, a history of intermittent claudication, angina, stroke or inguinal hernia surgery). A third risk function included, apart from age, gender and smoking habits, variables not obtainable by a questionnaire (ankle/arm blood pressure index, serum cholesterol and HDL-cholesterol levels,

diastolic and systolic blood pressure). In the fourth risk function palpation and auscultation of the abdominal aorta were added to the variables considered in the third risk function. The areas under the receiver operator curve for the four different risk functions were 0.77, 0.80, 0.81 and 0.83 respectively. If a cut-off point of a probability of having an abdominal aortic aneurysm of 1.5% or more was used to select subjects for ultrasonographic examination of the abdominal aorta, the sensitivity of identifying subjects with an abdominal aortic aneurysm varied from 80% for the first risk function to approximately 94% in the other risk functions. The proportion of subjects with a probability exceeding 1.5% of having an aneurysm, and thus selected for ultrasonographic screening, varied from 36% in risk function I to approximately 50% in the other risk functions. Our results show that the effectiveness of screening programmes for abdominal aortic aneurysms may be increased by selecting high risk subjects by means of a short medical questionnaire.

In chapter VIII, several important aspects of the clinical epidemiology of abdominal aortic aneurysms are discussed in more detail. The increasing incidence of abdominal aortic aneurysms will have an impact on the surgical workload in the near future. Although arteriosclerosis plays an important role in the formation of abdominal aortic aneurysms, the place of connective tissue weakness in aneurysm formation should be investigated further, with special emphasis on the role of collagen weakness as a potential indicator of the presence of and rupture risk of aneurysms. The pros and cons of screening for abdominal aortic aneurysms are discussed in view of the current scientific knowledge. Several topics related to the issue are elaborated, e.g. the identification of subjects at high risk, the assessment of a cut-off point of the aortic diameter to define aneurysms, the psychological consequences of a screening programme and cost-effectiveness of screening. It is concluded that at this point in time it is too early to advocate national screening programmes for abdominal aortic aneurysms.

Samenvatting

Het doel van de in dit proefschrift beschreven onderzoekingen was drieledig. Op de eerste plaats werd onderzocht hoe vaak het aneurysma van de abdominale aorta voorkomt bij ouderen. Ten tweede werd nagegaan welke factoren samenhangen met het vóórkomen van aneurysma's van de abdominale aorta en tot slot werd onderzocht wat de waarde is van verschillende diagnostische strategieën om vooraf personen te selecteren voor echografische screening op aneurysma's van de abdominale aorta.

Na een korte introductie in hoofdstuk I, wordt in hoofdstuk II een overzicht gegeven van de recente literatuur met betrekking tot de etiologie, diagnostiek, prevalentie en incidentie van aneurysma's van de abdominale aorta. In de literatuur wordt een duidelijke toename van de incidentie van aneurysma's in de laatste decennia beschreven. Ondanks uitbreiding van de diagnostische mogelijkheden om aneurysma's op te sporen en de verbetering van de chirurgische behandeling is de sterfte ten gevolge van aneurysma's niet evenredig gedaald. De post-operatieve sterfte voor electief geopereerde aneurysma's is gedaald tot minder dan 5%, maar een aanzienlijk gedeelte van de abdominale aneurysma's komt niet onder de aandacht van de chirurg. Men neemt aan dat slechts 35% van de patiënten met een geruptureerd aneurysma het ziekenhuis levend bereikt en dat hiervan ongeveer de helft alsnog overlijdt. Alhoewel er verschillende onderzoekingen zijn die de kosten-effectiviteit van screening van asymptomatische personen op het vóórkomen van het aneurysma van de abdominale aorta bestuderen, zijn de resultaten van deze studies niet eensluidend en is verder onderzoek noodzakelijk.

In hoofdstuk III wordt de trend beschreven in de incidentie van aneurysma's van de abdominale aorta gedurende de laatste twee decennia in Nederland. Hiertoe werden de gegevens van alle ziekenhuisopnamen in verband met een aneurysma van de buikaorta en de sterfte ten gevolge van een aneurysma in Nederland van 1972 tot 1992 geanalyseerd. Van 1972 tot 1992 steeg de voor de leeftijd gecorrigeerde sterfte aan aneurysma's van de abdominale aorta van 3,1 tot 8,1 per 100.000 bij mannen en van 1,4 tot 2,2 per 100.000 bij vrouwen. De voor leeftijd gecorrigeerde ziekenhuisopnamen in verband met een abdominaal

aneurysma steeg van 3,7 tot 37,6 per 100.000 bij mannen en van 1,2 tot 5,5 per 100.000 bij vrouwen. Het aantal voor leeftijd gecorrigeerde ziekenhuisopnamen voor geruptureerde aneurysma's steeg van 2,4 naar 10,3 per 100.000 bij mannen en van 0,7 naar 1,7 per 100.000 bij vrouwen. De voor leeftijd gecorrigeerde post- operatieve sterfte bij een niet geruptureerd abdominaal aneurysma halveerde in de bestudeerde periode, van 13% in 1972 naar 7% in 1992. De voor de leeftijd gecorrigeerde sterfte na een operatie in verband met een geruptureerd aneurysma daalde van 52% in 1972 naar 36% in 1992. er is een duidelijke toename van zowel de op ziekenhuisdiagnoses gebaseerde incidentie van het aneurysma van de abdominale aorta als de sterfte ten gevolge van abdominale aneurysma's gedurende de laatste twee decennia in nederland. De verbeterde diagnostiek van het abdominaal aneurysma door middel van echografie is waarschijnlijk voor een groot gedeelte verantwoordelijk voor de toenemende incidentie van deze aandoening. Gezien echter deze verschillen in toename tussen mannen en vrouwen en het feit dat er eveneens een toename te zien is van de incidentie van geruptureerde aneurysma's is een reële toename van de incidentie, vooral bij mannen, waarschijnlijk.

In hoofdstuk IV wordt de variabiliteit in echografische metingen van de diameter van de buikaorta bepaald. Daarnaast wordt onderzocht in hoeverre de variabiliteit in de echografisch vastgestelde aorta diameter afhankelijk is van cardiovasculaire risico factoren. Bij 135 personen, die deelnamen aan een screeningsonderzoek op het aneurysma van de abdominale aorta, werd door twee verschillende waarnemers de distale en proximale aorta diameter met behulp van B-mode echografie gemeten. Het gemiddelde gemeten verschil tussen twee echografische metingen van twee verschillende waarnemers was 0,06 mm (95% BI -0.15;0.27) bij de distale aorta en 0,32 mm (95% BI 0.09;0.55) bij meting van de proximale aorta. Het grootste verschil tussen twee waarnemers bij echografische metingen van zowel de distale als de proximale aorta diameter bedroeg 4.0 mm. De interobserver variabiliteit bij zowel de distale als de proximale metingen van de abdominale aorta was niet gerelateerd aan het al dan niet aanwezig zijn van cardiovasculaire risicofactoren. De interobserver variabiliteit van echografische metingen van de proximale aorta nam echter toe

met een toenemende proximale diameter van de aorta en met een toename van de omvang van de taille.

Wij concluderen dat de interobserver variabiliteit van echografische metingen van de distale aorta gering is. Interobserver variabiliteit van de echografische metingen van de proximale aorta is daarentegen hoger, vooral bij personen met een grote taille omvang en een relatief grote aorta diameter.

In hoofdstuk V en VI worden respectievelijk de leeftijds- en geslachts-specifieke prevalentie van het aneurysma van de abdominale aorta en risico - indicatoren van het aneurysma beschreven. Verder wordt er ingegaan op de vraag of arteriosclerose, dan wel bindweefselafwijkingen een rol spelen bij de etiologie van het aneurysma. Bij 5.419 personen (42% mannen en 58% vrouwen) van 55 jaar of ouder werden echografische metingen van de distale en proximale diameter van de abdominale aorta verricht. Een aneurysma werd als aanwezig beschouwd indien de distale aorta diameter groter, of gelijk aan 35 mm was of als de diameter van de distale aorta 50% of meer was toegenomen ten opzichte van de proximale diameter. Cardiovasculaire risicofactoren en indicatoren van bindweefselzwakte werden eveneens vastgesteld met als doel na te gaan of er een verband bestaat tussen het voorkomen van deze risicofactoren en het aneurysma van de abdominale aorta. Een liesbreukoperatie in de anamnese werd beschouwd als een indicator van bindweefselzwakte. De gemiddelde distale aorta diameter bij mannen was groter dan bij vrouwen (19,7 versus 16,2 mm) en nam toe met de leeftijd, diastolische bloeddruk, Quetelet index en was groter bij rokers ook na correctie voor potentiële confounders. De distale aorta diameter was kleiner bij personen met een verhoging van het HDL-cholesterol en bij personen met diabetes. De gemiddelde distale en proximale aorta diameter nam respectievelijk 0,7 mm en 0,3 mm toe met elke 10 jaar toename van de leeftijd. Een aneurysma werd gevonden bij 2,1% (95% BI 1,7;2,5) van de populatie; bij 4,1% (95% BI 3,2;4,9) van de mannen en 0,7% (95% BI 0,4;1,0) van de vrouwen. De cardiovasculaire risicofactoren die positief gecorreleerd waren met het voorkomen van aneurysma's van de abdominale aorta waren de diastolische bloeddruk, roken en het serum cholesterol gehalte. Personen die een liesbreukoperatie hadden ondergaan, hadden een 1,4 maal verhoogd risico op een

aneurysma (95% BI 0,9;2,3). Dit relatieve risico was 3.3 (95% BI 1,4;8,0) voor personen die een liesbreuk operatie hadden ondergaan voor het 25-ste levensjaar. Risicofactoren die geassocieerd worden met arteriosclerose spelen naar schatting een rol bij het ontstaan van abdominale aneurysma's voor ongeveer 90%. Ongeveer 6% van de aneurysma's kan worden toegeschreven aan risico indicatoren van bindweefselzwakte.

Het sterke verband tussen risicofactoren voor arteriosclerose en het voorkomen van aneurysma's van de abdominale aorta ondersteunen de gedachte dat arteriosclerose een rol speelt bij de etiologie van abdominale aneurysma's. Daarnaast bestaan er aanwijzingen dat bindweefselzwakte hierbij ook van belang is.

In hoofdstuk VII worden verschillende risicofuncties beschreven aan de hand waarvan de kans berekend kan worden van een individu op het hebben van een aneurysma van de abdominale aorta. De risicofuncties onderscheiden zich door de wijze waarop informatie wordt verzameld over de verschillende risico-indicatoren. Deze risicofuncties kunnen gebruikt worden om de effectiviteit van echografische screening op aneurysma's van de buikaorta te vergroten. Vier risicofuncties werden door ons ontwikkeld en nagegaan werd hoe goed zij in staat zijn om personen te selecteren voor een screeningsprogramma. De eerste risicofunctie ging uit van de risicofactoren leeftijd en geslacht. De tweede was gebaseerd op een korte medische vragenlijst omtrent leeftijd, geslacht, rookgedrag, het gebruik van medicatie in verband met hoge bloeddruk, een diagnose van claudicatio intermittens, angina pectoris, of CVA of een liesbreuk-operatie in het verleden. De derde risicofunctie bevatte naast leeftijd en geslacht, variabelen die niet met behulp van een vragenlijst te verkrijgen zijn zoals enkel/arm systolische bloeddruk index, serum cholesterol- en HDL-cholesterol-waarden en de diastolische- en systolische bloeddruk. Tenslotte werd een vierde risicofunctie afgeleid, waarbij aan de variabelen uit de derde risicofunctie de resultaten van palpatie en auscultatie van de buikaorta werden toegevoegd. De grootte van het gebied onder de reciever operator curve (ROC) van de vier verschillende functies was respectievelijk 0,77, 0,80, 0,81 en 0,83. Als alle personen die een kans van 1,5% of meer hebben op een aneurysma, berekend

door de verschillende risicofuncties, verwezen zouden worden voor echografisch onderzoek, dan zou de sensitiviteit om personen met een aneurysma op te sporen variëren van 80% voor de eerste risicofunctie tot ongeveer 94% voor de andere risicofuncties. Het gedeelte van de studiepopulatie dat een kans had op een abdominaal aneurysma van 1,5% of hoger en dus verwezen zou worden voor echografisch onderzoek, varieerde van 36% in de eerste risicofunctie tot 50% in de andere functies.

Onze resultaten laten zien dat de effectiviteit van een screeningsprogramma voor aneurysma's van de abdominale aorta verbeterd kan worden door individuen met een verhoogd risico te selecteren met behulp van een korte medische vragenlijst.

In hoofdstuk VIII worden verschillende belangrijke aspecten van de klinische epidemiologie van het aneurysma van de abdominale aorta verder besproken. De toegenomen incidentie van abdominale aneurysma's zal van invloed zijn op de werkbelasting van de vaatchirurgische units. Ondanks dat arteriosclerose een belangrijke rol speelt in de etiologie van het aneurysma zal de rol van bindweefselzwakte bij de vorming van abdominale aneurysma's verder onderzocht moeten worden. Met name collageen en elastine afwijkingen zouden een rol kunnen spelen als indicator van een toegenomen risico op ruptuur van aneurysma's. De voor- en nadelen van screening op aneurysma's van de abdominale aorta worden besproken in het licht van huidige wetenschappelijke kennis. Onderwerpen die in dit verband verder worden uitgewerkt zijn het identificeren van individuen met een verhoogd risico, het vaststellen van een grenswaarde van de aorta diameter waarboven sprake is van een aneurysma, de psychologische gevolgen van een screeningsprogramma en de kosten-effectiviteit van screening. Er wordt geconcludeerd dat het momenteel nog te vroeg is om een nationaal screeningsprogramma op aneurysma's van de abdominale aorta te rechtvaardigen.

Dankwoord

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Prof. H van Urk heeft met chirurgische precisie alle manuscripten gelezen en van commentaar voorzien. Hero, met veel plezier denk ik terug aan onze gesprekken en hoop op een produktieve samenwerking in de toekomst.

Prof. A Hofman is één van de grondleggers van het ERGO onderzoek. Bert, ERGO was voor mij, net zoals voor vele andere promovendi, dé kans om wetenschappelijk onderzoek te doen. Bedankt, dat je me die kans hebt gegeven.

Bij prof. JS Laméris heb ik nooit vergeefs aangeklopt. Hij heeft, naast het beoordelen van manuscripten, geholpen bij de training van de echografisten Inge

Haumersen, Sonja Snijders en Ingrid de Boer. Zij hebben de afgelopen jaren ruim 10.000 echo's gemaakt. Door hun nauwkeurige manier van werken hebben ze hiermee de basis gelegd voor dit proefschrift. Bedankt!

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De afdeling huisartsgeneeskunde is nog steeds een gezellige thuisbasis. Daarnaast stelde zij, ook na het formeel verlopen van mijn aanstelling, ruimte en faciliteiten beschikbaar om mijn proefschrift af te maken.

De deelnemers aan ERGO en hun huisartsen in Ommoord wil ik bedanken voor hun medewerking. Zij zijn een goed voorbeeld hoe huisartsgeneeskunde en epidemiologisch onderzoek vruchtbaar samen kunnen gaan.

Dr JF Lange wil ik hier noemen omdat hij mij attendeerde op het belang van onderzoek naar het voorkomen van aneurysma's in de algemene populatie. Johan, ik hoop dat dit produkt van samenwerking tussen chirurg en huisarts naar je zin is.

Tenslotte: mijn paranimfen Rob van Thiel en John van der Werff, hen bedank ik pas als het feest voorbij is.

Curriculum vitae

Bèr Pleumeekers was born on June 6th, 1954 in Gronsveld, the Netherlands. After he graduated from secondary school in 1971 at the St Maartenscollege in Maastricht he attended medical school at the Erasmus University in Rotterdam. He received his medical degree in 1978. After one year of vocational training he was entered in the register of qualified general practitioners of the Royal Dutch Medical Association in 1979. In the same year he started working in a general practice in Rotterdam. Since 1985 he works in collaboration with his wife, Marjan M Lange, who is also a general practitioner. From 1982 to 1984 he studied philosophy at the Erasmus University.

Since 1987 he has been involved in the education of medical students and he developed an educational programme for last-year medical students to facilitate the contact with general practice. Since 1990 he combined his work as general practitioner with scientific work at the Departments of Epidemiology & Biostatistics (head: professor A Hofman) and General Practice (head: professor E van der Does, in 1994 succeeded by professor A Prins) of Erasmus University. In 1990, the studies described in this thesis, were initiated.

From 1989 to 1993 he was a member of the regional board of general practitioners (RHV), during the last year as vice-chairman. The encouragement of the use of electronic medical dossiers in general practice had his special attention. He was one of the initiators of the so called "PIR project": a project to assist general practitioners in implementing computers in daily practice and to stimulate electronic communication by creating a medical computerized network.

Since 1992 he is a member of the management team of ROHAPRO, a computerized network of general practices aimed to study the occurrence and determinants of chronic disease.

He is happily married to Marjan M Lange and they have three lovely daughters: Mieke, Olga and Laura.