

IQWiG Reports – Commission No. S13-04

# **Ultrasound screening for abdominal aortic aneurysms<sup>1</sup>**

**Extract**

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<sup>1</sup> Translation of Chapters 1 to 6 of the final report *Ultraschall-Screening auf Bauchaortenaneurysmen* (Version 1.1; Status: 2 April 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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<sup>2</sup> Due to legal data protection regulations, employees have the right not to be named.

## **Key statement**

### ***Research question***

The goal of this research was

- the benefit assessment of screening for abdominal aortic aneurysms (AAAs) via ultrasound scan in comparison with no screening or another screening strategy regarding patient-relevant outcomes.

### ***Conclusion***

**For men**, this benefit assessment provides proof of a benefit of ultrasound screening for AAA regarding **all-cause mortality, AAA-related mortality, frequency of ruptures** and number of **emergency surgeries**. An indication of harm from ultrasound screening was derived for morbidity associated with **elective surgery** for men.

**For women**, there was no hint of a benefit of ultrasound screening for AAA for **all-cause mortality, frequency of ruptures**, number of **emergency surgeries** and number of **elective surgeries**. There were no data on **AAA-related mortality** for women.

Regarding **health-related quality of life** and **psychosocial aspects**, no conclusion on benefit or harm of ultrasound screening for AAA could be derived for men or for women because the data on health-related quality of life were not evaluable, and there were no data for psychosocial aspects.

# Table of contents

	<b>Page</b>
<b>Key statement</b> .....	<b>iii</b>
<b>List of tables</b> .....	<b>v</b>
<b>List of abbreviations</b> .....	<b>vi</b>
<b>1 Background</b> .....	<b>1</b>
<b>2 Research question</b> .....	<b>3</b>
<b>3 Methods</b> .....	<b>4</b>
<b>4 Results</b> .....	<b>6</b>
<b>4.1 Results of the information retrieval</b> .....	<b>6</b>
<b>4.2 Characteristics of the studies included in the assessment</b> .....	<b>6</b>
<b>4.3 Overview on the extraction of data relevant for the report</b> .....	<b>7</b>
<b>4.4 Assessment of the risk of bias at study level and outcome level</b> .....	<b>8</b>
<b>4.5 Results on patient-relevant outcomes</b> .....	<b>8</b>
4.5.1 Results on all-cause mortality .....	11
4.5.2 Results on AAA-related mortality.....	11
4.5.3 Results on morbidity: frequency of ruptures .....	13
4.5.4 Results on morbidity: emergency surgery .....	13
4.5.5 Results on morbidity: elective surgery .....	14
4.5.6 Harm resulting from screening .....	15
4.5.7 Results on health-related quality of life and on psychosocial aspects.....	15
4.5.8 Recording and presentation of diagnostic accuracy .....	15
4.5.9 Subgroup characteristics and other effect modifiers .....	16
4.5.10 Ongoing studies .....	16
<b>4.6 Conclusions on effect regarding patient-relevant outcomes</b> .....	<b>16</b>
<b>4.7 Evidence map</b> .....	<b>17</b>
<b>5 Classification of the work result</b> .....	<b>18</b>
<b>6 Conclusion</b> .....	<b>21</b>
<b>Appendix</b> .....	<b>22</b>
<b>References for English extract</b> .....	<b>23</b>

**List of tables**

	<b>Page</b>
Table 1: Overview of the results for all patient-relevant outcomes separated by sex for all 3 dates of analysis .....	10
Table 2: Conclusions on effect regarding patient-relevant outcomes .....	17
Table 3: Evidence map regarding patient-relevant outcomes (total period of analysis) .....	17

### List of abbreviations

<b>Abbreviation</b>	<b>Meaning</b>
AAA	abdominal aortic aneurysm
CI	confidence interval
DGG	Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin (German Society of Vascular Surgery and Medicine)
ESVS	European Society for Vascular Surgery
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MASS	Multicentre Aneurysm Screening Study
RCT	randomized controlled trial
SD	standard deviation
SGB	Sozialgesetzbuch (Social Code Book)
USPSTF	U.S. Preventive Service Task Force
VIVA	Viborg vascular screening trial

## 1 Background

On 18 November 2013 the Federal Joint Committee (G-BA) wrote to the Institute for Quality and Efficiency in Health Care (IQWiG) to commission the assessment of ultrasound screening for abdominal aortic aneurysms (AAA).

### Definition of the disease

An AAA is a pathological dilation of the abdominal aorta. About 95% of abdominal aneurysms affect the aorta distal to the origin of the renal arteries (infrarenal aorta); the renal arteries are involved in about 3% [1]. The aortic diameter in healthy people varies, depending on sex and age among other factors. The average infrarenal diameter is about 2 cm [2,3]. An enlargement of the abdominal aortic diameter to  $\geq 3$  cm is usually considered to be an AAA [1,4,5].

### Therapy

In the decision on the treatment of an asymptomatic aneurysm, the risk of rupture is balanced against the patient's life expectancy and the mortality associated with surgery [1]. The risk of rupture depends particularly on the diameter and on the growth rate of an AAA [6]. Aneurysms that do not directly have to be treated surgically because of their small diameter and low growth rate are monitored in the framework of regular assessments (usually via ultrasound) at different intervals depending on the aneurysm diameter [1,4,7]. Aneurysms that require treatment can be repaired by conventional open surgery or by endovascular surgery [1]. In any case, urgent surgery is indicated in symptomatic aneurysms. Ruptured AAA always constitutes an emergency and requires immediate treatment [1].

### Epidemiology and risk factors

Studies on the evaluation of screening programmes have shown a prevalence of AAA (with a diameter of  $\geq 3.0$  cm) of 4 to 8% in over 65-year-old men and of 0.5 to 1.5% in over 65-year-old women [8]. Hypertension, smoking, hypercholesterolaemia [9], advanced age, male sex, Caucasian origin and positive family history [10] are some of the risk factors that have been associated with AAA. More recent studies have indicated a decrease in frequency, both regarding the occurrence of aneurysms themselves [11] and the incidence of ruptured AAA [12]. Screening programmes have reported notably lower prevalences of AAA of 1.5 to 1.9% in England and Sweden in recent years [13].

Various reasons for this trend have been discussed: Smoking is considered to be one of the main risk factors for developing an AAA [14] and is associated with an increased growth rate and an increased risk of rupture [15,16]. The decrease in prevalence has been linked particularly to the decline in smoking rate in the last years [13,17]. Furthermore, particularly a changed management of hypertension and hypercholesterolaemia has also been considered as possible reason for the decrease in prevalence [13,18].

### **Rationale for screening for abdominal aortic aneurysms**

Without treatment, a ruptured AAA leads to rapid death, and mortality is high also with emergency treatment. The number of patients who died pre-hospital from undetected AAA rupture cannot be determined exactly. However, a study has shown that about one third of the patients with ruptured AAA die before reaching the hospital [19]. In patients with ruptured AAA who reach the hospital in time and who can still be operated on, hospital lethality in Germany is about 40% in open surgery, and about 20% in endovascular surgery [20].

In contrast, mortality is lower when aneurysms are treated in elective surgery. According to an international randomized controlled trial (RCT), 30-day mortality in elective surgery is 4.6% in open surgery, and 1.2% in endovascular surgery [21]. Similar numbers based on a registry analysis are observed in Germany (3.6% open surgery; 1.3% endovascular surgery) [20]. Long-term survival after surgery depends on the patient's age, risk factors and initial diagnoses [22]. The aim of AAA screening is therefore to identify, monitor, and treat abdominal aneurysms before rupture occurs. Systematic ultrasound screening for AAA in risk populations is conducted in individual countries such as Sweden, Great Britain and the USA, whereas in other countries this is not the case [23]. These screening programmes differ in their design (e.g. different definitions of a target population).

## **2 Research question**

The goal of this research was

- the benefit assessment of screening for AAAs via ultrasound scan in comparison with no screening or another screening strategy regarding patient-relevant outcomes.

In addition, the diagnostic accuracy of the test procedures is described if this was recorded in the framework of the studies included in this investigation.

### 3 Methods

The target population of the benefit assessment consisted of people who have not yet been diagnosed with AAA. Ultrasound screening for AAA was the experimental intervention. No or a different screening strategy (e.g. different diagnostic techniques) were the comparator intervention.

The following patient-relevant outcomes were considered:

- overall survival
- disease-specific survival
- morbidity
- harm resulting directly and indirectly from screening, including consequences of false screening results and overdiagnoses
- health-related quality of life and psychosocial aspects

Only RCTs were included in the benefit assessment. There was no limitation regarding study duration.

For this purpose, a systematic literature search for primary literature was performed in the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant systematic reviews took place in the databases MEDLINE and Embase in parallel with the search for relevant primary studies. Searches were also conducted in the databases Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The last search was conducted on 1 December 2014.

Systematic reviews and publicly available trial registries were also searched. Furthermore, documents sent by the G-BA and publications that had been provided in the hearing procedure for the preliminary report plan and the preliminary report were also screened. Finally, the authors of relevant study publications were contacted in order to clarify important questions.

The selection of relevant studies was performed by 2 reviewers independently of each other for the result from the bibliographic literature search, from the search in publicly accessible trial registries and from documents sent by the G-BA.

Data extraction was conducted in standardized tables. To evaluate the qualitative certainty of results, the risk of bias at study and outcome level was assessed and rated as low or high respectively. The results of the individual studies were described, organized by outcomes.

If the studies were comparable regarding the research question and relevant characteristics within the group of men or women, the individual results were pooled quantitatively by means of meta-analyses.

Some meta-analyses showed important heterogeneity between the studies and no factor could be identified that explained this heterogeneity. The results of the majority of the individual studies were statistically significant and had the same direction of effect, but were not clearly in the same direction. For better assessment of the borderline cases in these cases, a check of a hypothetical homogeneous situation (“shifted effects”) was conducted as follows: At first it was investigated whether a decrease in value of effect estimates resulted in a homogeneous situation. If the common estimate calculated on this basis was statistically significant, it was used to derive a conclusion on added benefit. Otherwise the results observed were interpreted without shifting of the effect.

In addition, the diagnostic accuracy of diagnostic ultrasound was recorded and descriptively presented if it was described in the framework of the studies included. However, it was specified a priori that no patient-relevant benefit could arise solely on the basis of this supplementary outcome.

## 4 Results

### 4.1 Results of the information retrieval

The systematic literature search in the bibliographical databases resulted in a total number of 766 hits for screening after exclusion of duplicates. In the screening of titles and abstracts, both reviewers agreed on excluding 679 hits as not relevant after consensus on initially discrepant assessments. Hence 88 potentially relevant hits remained from the bibliographical literature search, which were screened in full text. 64 of these hits were excluded due to a lack of relevance. 4 hits were relevant systematic reviews, which were screened for relevant studies. The remaining 20 publications on 4 studies fulfilled the criteria for study inclusion defined for this report according to the agreed assessment of both reviewers.

No additional relevant studies were identified from the search in further search sources (systematic reviews, publicly accessible trial registries, documents sent by the G-BA and information from the hearing on the preliminary report plan and on the preliminary report). Information from enquiries to authors was included in the assessment. Two ongoing studies were identified from the search in trial registries, the relevance of which could not be conclusively determined.

### 4.2 Characteristics of the studies included in the assessment

A total of 4 randomized controlled trials (Chichester [24-30], MASS [31-36], Viborg [37-43] and Western Australia [44-47]) were identified as being relevant for the research question of the present benefit assessment.

The studies conducted on the research question have several factors in common – both regarding the intervention and regarding the methods:

In all studies included, an enlargement of the abdominal aorta diameter of  $\geq 3$  cm was considered as AAA. To identify an AAA, one-off screening via ultrasound scan was conducted in the intervention group in each of the studies, followed by further examinations at intervals of 3 to 12 months when an aneurysm was diagnosed in the screening. The control group had no screening examination.

Full recordings were conducted within the target population of interest. Allocation to the screening or control group was conducted using individual randomization, the study participants were recruited on the basis of personal data available in the respective country: electoral roll in Australia, birth registries in Denmark and health care registry in Great Britain. There was no information about how the participants were notified about the conduct of the study. Data from various sources (particularly national statistics offices, national personal registries, death certificates) were used for analysing the effect of screening on mortality.

Below, the study characteristics are described individually for each study.

15 775 participants aged between 65 and 80 years were included in the **Chichester trial** from Great Britain; 6433 of these participants were men, and 9342 were women. Recruitment started in 1988 and was conducted in 9 general practices in the Chichester region. Repeat ultrasound scans depending on AAA size were comparable to the MASS trial (see next section) – with the difference, that elective surgery was only considered at a diameter of  $\geq 6$  cm.

67 800 men aged between 65 and 74 years were included in the **MASS trial** from Great Britain. Recruitment was conducted in practices in Oxford, Portsmouth, Winchester and Southampton from 1997 to 1999. The men in the screening group received an invitation to participate in screening, which was conducted in general practices. Those men in whom an aneurysm was detected in the ultrasound scan, depending on the size of their aneurysm, were either monitored (yearly for a size between 3.0 and 4.4 cm, or at 3-month intervals for a size of 4.5 to 5.4 cm), or they were recommended surgery (for a size of  $\geq 5.5$  cm or when the AAA had grown for more than 1 cm within one year or when AAA-associated symptoms were present).

From 1994, all men aged 70 to 73 years and men turning 65 years in the following years who were resident in the Viborg County were included in the **Viborg trial** from Denmark. A total of 12 658 men were included in the study until 1998. Men with an aneurysm diameter of  $\geq 5$  cm were referred to a vascular surgeon, the others (diameter of 3 to 4.9 cm) had annual ultrasound scans. Those men who had abdominal aorta dilation between 2.5 and 2.9 cm in the first screening, were offered repeat screening at 5 years.

41 000 men aged 65 to 83 years resident in the metropolitan area of Perth were included in the **Western Australia trial**. The study population was originally defined as men up to the age of 74 years. To achieve the planned statistical power, men up to the age of 79 years were also included. Due to the presentation of age in the electoral roll, on which recruitment was based, eventually men up to the age of 83 years were also included. Randomization was conducted stratified by age (in 5-year groups) and postcode. Recruitment started in 1996. No exact information on the screening strategy was provided in the main publication of the study [46,47]. On the contrary: It was stated that treatment after the ultrasound scan was left to the treating physician. No attempts were made to influence clinical management. However, another publication [44] described that each patient with a suspicious finding was given a letter for his general practitioner containing an exact recommendation for the screening strategy. Men with an aneurysm diameter of 5 cm or larger were recommended to have vascular surgery. All men with an AAA diameter of 3.0 to 4.9 cm received repeat ultrasound scans. Men who had abdominal aorta dilation between 2.0 and 2.9 cm in the first screening, received repeat ultrasound scan at 2 years.

### **4.3 Overview on the extraction of data relevant for the report**

For the present report, data from 4 studies included could be extracted for the outcomes “overall survival”, “disease-specific survival” and “morbidity”. The outcomes extracted from

the studies were operationalized for the present report as follows: overall survival as all-cause mortality, and disease-specific survival as AAA-related mortality. The outcome “morbidity” includes the results on frequency of ruptures, emergency surgery and elective surgery of the abdominal aorta.

Elective surgery was considered a valid surrogate for an increase in morbidity. This was based on the deliberation that such a surgery (open surgery or endovascular surgery) is always associated with hospitalization, which is not regularly the case without surgery.

Results on potential harm resulting from screening were categorized as the corresponding outcomes. There were no data on the consequences of false screening results and overdiagnoses.

The data on health-related quality of life were not evaluable. No data were available on psychosocial aspects.

The diagnostic accuracy of diagnostic ultrasound was described in one study included and descriptively presented in the report.

#### **4.4 Assessment of the risk of bias at study level and outcome level**

The studies Chichester, MASS and Viborg were assessed to have a low risk of bias at study level. The Western Australia trial was assessed to have a high risk of bias because there was an unexplained difference of more than 5% in the number of randomized patients and in the number of patients invited to screening between the full publications of the study. Moreover, quality of life was stated as outcome in the trial registry entry of the study [45], but there were no analyses regarding this outcome. There was explicit information on allocation concealment in the Chichester trial. Allocation concealment remained unclear in all other studies. The lacking information had no influence on the assessment of the risk of bias, however, as it was assumed that allocation concealment was ensured in all studies because randomization was conducted using a registry.

The risk of bias of the results on all-cause mortality, AAA-related mortality, frequency of ruptures and emergency surgery was assessed as low for the studies Chichester, MASS and Viborg. The risk of bias of the results of the Western Australia trial was assessed as high for all 5 outcomes because the high risk of bias at study level directly affected the risk of bias at outcome level. All studies had a high risk of bias in the outcome “elective surgery”. Lack of blinding of the treating physician was the decisive factor for the assessment of the high risk of bias at study level, which directly affected the assessment of the risk of bias at outcome level.

#### **4.5 Results on patient-relevant outcomes**

One of the 4 studies identified included men and women; the other 3 studies explicitly included men only. The proportion of women was 6.8% of the total population. In addition,

the prevalence of the disease is notably higher in men than in women. Men and women are therefore considered separately in this final report.

Data at different dates of analysis were reported in the studies. In the present report, these data were summarized for the meta-analyses at the following dates of analysis: 4 to 5 years, 10 years, and 13 to 15 years. For men, data for all outcomes were available at all dates of analysis. For women, data for the outcomes “all-cause mortality”, “emergency surgery” and “elective surgery” were only available for the date of analysis of 4 to 5 years. For the outcome “frequency of ruptures”, besides the data at the date of analysis of 4 to 5 years, data for the date of analysis of 10 years were also available for women. The pooled results of the 4 included RCTs for the 6 patient-relevant outcomes are presented in Table 1.

Table 1: Overview of the results for all patient-relevant outcomes separated by sex for all 3 dates of analysis

Patient-relevant outcome	Results men (from meta-analyses)	Results women <sup>a</sup>
<b>All-cause mortality</b>		
4–5 years	Heterogeneous data, no calculation of common estimate	OR 1.06; 95% CI [0.93; 1.21]
10 years	OR 0.97; 95% CI [0.94; 1.00] <sup>b</sup>	No data
13-15 years	OR 0.97; 95% CI [0.94; 1.00] <sup>c</sup>	No data
<b>AAA-related mortality</b>		
4–5 years	OR 0.60; 95% CI [0.48; 0.75]	No data
Subgroup < 75 years	OR 0.56; 95% CI [0.44; 0.73]	No data
Subgroup ≥ 75 years	OR 0.88; 95% CI [0.49; 1.59]	No data
10 years	Heterogeneous data (Peto OR 0.54; 95% CI [0.46; 0.63]) <sup>d</sup>	No data
13-15 years	Heterogeneous data (Peto OR 0.63; 95% CI [0.55; 0.73]) <sup>d</sup>	No data
<b>Morbidity: frequency of ruptures</b>		
4–5 years	Peto OR 0.54; 95% CI [0.43; 0.68] <sup>e</sup>	Peto OR 1.32; 95% CI [0.30; 5.83]
10 years	Peto OR 0.54; 95% CI [0.45; 0.63] <sup>a</sup>	Peto OR 1.54; 95% CI [0.68; 3.49]
13-15 years	Heterogeneous data (Peto OR 0.64; 95% CI [0.56; 0.72]) <sup>d</sup>	No data
<b>Morbidity: emergency surgery</b>		
4–5 years	Peto OR 0.42; 95% CI [0.29; 0.62] <sup>e</sup>	Peto OR 1.00; 95% CI [0.06; 15.91]
10 years	OR 0.44; 95% CI [0.35; 0.56]	No data
13-15 years	OR 0.51; 95% CI [0.42; 0.64]	No data
<b>Morbidity: elective surgery</b>		
4–5 years	Heterogeneous data (p < 0.2), no calculation of common estimate	OR 1.99; 95% CI [0.36; 10.88]
10 years	Peto OR 2.33; 95% CI [2.05; 2.65]	No data
13-15 years	Peto OR 2.09; 95% CI [1.86; 2.36]	No data
<b>Health-related quality of life and psychosocial aspects</b>		
	Data on health-related quality of life not evaluable No data on psychosocial aspects reported	
a: Estimates provided are based on one study. b: It is not clear from the CI that the result is statistically significant. The p-value is: p = 0.044. c: It is not clear from the CI that the result is statistically significant. The p-value is: p = 0.028. d: Effect estimate determined with shifted effects. e: Based on studies with high qualitative certainty of results. AAA: abdominal aortic aneurysms; CI: confidence interval; HR: hazard ratio; OR: odds ratio		

#### **4.5.1 Results on all-cause mortality**

For men, the results at the date of analysis of 4 to 5 years were based on data from 4 studies, at the date of analysis of 10 years on 2 studies, and at the date of analysis of 13 to 15 years on 3 studies. For women, data from one study (Chichester) were only available for the date of analysis of 4 to 5 years. The results from 3 studies (Chichester, MASS and Viborg) have a high qualitative certainty of results, the results from one study (Western Australia) have a moderate qualitative certainty of results.

***Date of analysis 4 to 5 years:*** The meta-analysis of all 4 studies for men showed important heterogeneity. This was maintained in the limitation of studies with high qualitative certainty of results so that in both situations calculating a common estimate was not meaningful.

Besides unadjusted rates for all-cause mortality, age-adjusted rates were also reported in the Western Australia trial. Age-standardized rates were therefore considered in a sensitivity analysis. Overall, the sensitivity analysis showed contradictory results depending on the use of adjusted or unadjusted data so that the analysis cannot be used for the assessment.

Due to the statistically heterogeneous data in the unadjusted analysis, no hint of an effect in favour or to the disadvantage of screening was derived for men.

Since for women the results from the Chichester trial were not statistically significant, there was no hint of an effect in favour or to the disadvantage of screening for women.

***Dates of analysis 10 years and 13 to 15 years:*** The results of the meta-analyses for both dates of analysis showed a statistically significant effect for men. Proof of an effect in favour of screening for men was therefore derived for both time points.

***Summary of the overview of the evidence across all dates of analysis:*** The meta-analysis of the studies at the date of analysis of 4 to 5 years showed heterogeneous data for men. The meta-analysis showed a statistically significant effect for men for both later dates of analysis so that proof of an effect in favour of screening can be derived for each of both time points. Overall, proof of a patient-relevant benefit for men was derived across all time points. For women, data were only available for the date of analysis of 4 to 5 years, which showed no statistically significant effect. Hence there was no hint of a patient-relevant benefit of screening for women.

#### **4.5.2 Results on AAA-related mortality**

For men, the results at the date of analysis of 4 to 5 years were based on data from 4 studies, at the date of analysis of 10 years as well as at the date of analysis of 13 to 15 years on 3 studies respectively. No data were available for women. The results from 3 studies (Chichester, MASS and Viborg) have a high qualitative certainty of results, the results from one study (Western Australia) have a moderate qualitative certainty of results.

***Date of analysis 4 to 5 years:*** For men, the meta-analysis of all 4 studies showed a statistically significant effect, which was also confirmed in the exclusive consideration of the results from 3 studies with high qualitative certainty of results. Hence for the date of analysis mentioned, proof of an effect in favour of screening was derived for men.

***Dates of analysis 10 years and 13 to 15 years:*** In the meta-analyses of the 3 studies with high qualitative certainty of results, there was important heterogeneity for both dates of analysis so that calculating a common estimate was not meaningful. No further factors could be identified that could explain the heterogeneity. However, using shifted effects showed a statistically significant effect for both dates of analysis. Proof of an effect in favour of screening for men was derived for both time points.

### **Subgroup analyses – age**

Data from 3 studies were available for a subgroup analysis on age. The data referred exclusively to the outcome “AAA-related mortality” and were only available for the date of analysis of 4 to 5 years: Besides data on men < 75 years, also data on men  $\geq 75$  could also be extracted from the Western Australia trial with moderate qualitative certainty of results. Two studies (MASS, Viborg) only included men < 75 years. In the Chichester trial, the proportion of men  $\geq 75$  years was over 20% so that this study could not be allocated to any of the 2 subgroups.

The interaction test provided an indication of an effect modification by age so that men < 75 years and men  $\geq 75$  years were considered separately. A statistically significant effect was shown for men < 75 years. Hence in analogy to the total group, proof of an effect in favour of screening was derived for the subgroup of men < 75 years. No statistically significant result was shown on the basis of one study for the subgroup of men  $\geq 75$  years. The point estimate of the subgroup of  $\geq 75$ -year-olds was on the same side as the point estimate in the population of men irrespective of age. Due to the indication of an effect modification, the informative value for the subgroup of  $\geq 75$ -year-olds was downgraded and an indication of an effect in favour of screening was derived.

### **Subgroup analyses – further risk factors**

In the Viborg trial, subgroup analyses were conducted at the date of analysis of 5.9 years and at the date of analysis of 13.0 years on the following risk factors: hypertension, myocardial infarction, chronic obstructive pulmonary disease, ischaemic heart disease (excluding myocardial infarction), peripheral arterial occlusive disease, and stroke or transient ischaemic attack. There was no indication of an effect modification for any of these risk factors.

***Summary of the overview of the evidence across all dates of analysis:*** For men, the meta-analyses at the date of analysis 4 to 5 showed proof of an effect in favour of screening. Proof of an effect in favour of screening was also derived for the dates of analysis of 10 years and 13 to 15 years. Overall, there was proof of a patient-relevant benefit in favour of screening for

men across all time points. No data on this outcome were available for women so that no conclusion can be drawn.

### **4.5.3 Results on morbidity: frequency of ruptures**

For men, the results at the date of analysis of 4 to 5 years were based on data from 4 studies, at the date of analysis of 10 years on 1 study, and at the date of analysis of 13 to 15 years on 3 studies. For women, data from one included study (Chichester) were available for the dates of analysis of 4 to 5 and 10 years. The results from 3 studies (Chichester, MASS and Viborg) have a high qualitative certainty of results, the results from one study (Western Australia) have a moderate qualitative certainty of results.

***Date of analysis 4 to 5 years:*** For men, the meta-analysis of all 4 studies showed important heterogeneity so that the calculation of a common estimate was not meaningful. The exclusive consideration of the 3 studies with high qualitative certainty of results showed a statistically significant effect. Hence proof of an effect in favour of screening was derived for men. Since for women the results from the Chichester trial were not statistically significant, there was no hint of an effect in favour or to the disadvantage of screening for women.

***Date of analysis 10 years:*** Based on the data of one study (MASS) with high qualitative certainty of results and a statistically significant result, an indication of an effect in favour of screening for men was derived. Since for women the results from the Chichester trial were not statistically significant, there was no hint of an effect in favour or to the disadvantage of screening for women.

***Dates of analysis 13 to 15 years:*** The meta-analysis of the studies, which all had high qualitative certainty of results, showed important heterogeneity so that calculating a common estimate was not meaningful. No further factors could be identified that could explain the heterogeneity. Using shifted effects resulted in a statistically significant effect. Proof of an effect in favour of screening was derived for men.

***Summary of the overview of the evidence across all dates of analysis:*** For men, the meta-analyses at the date of analysis 4 to 5 years showed proof of an effect in favour of screening. Based on one study with high qualitative certainty of results and a statistically significant result, an indication of an effect in favour of screening at the date of analysis of 10 years for men was derived. Proof of an effect was also derived for the date of analysis of 13 to 15 years. Overall, proof of a patient-relevant benefit of screening for men was derived across all time points. For women, data were available for the dates of analysis of 4 to 5 years and of 10 years, which showed no statistically significant effect. Hence there was no hint of a patient-relevant benefit of screening for women.

### **4.5.4 Results on morbidity: emergency surgery**

For men, the results at the date of analysis of 4 to 5 years were based on data from 4 studies, at the date of analysis of 10 years as well as at the date of analysis of 13 to 15 years on

3 studies respectively. For women, data from one study (Chichester) were available for the date of analysis of 4 to 5 years. The results from 3 studies (Chichester, MASS and Viborg) have a high qualitative certainty of results, the results from one study (Western Australia) have a moderate qualitative certainty of results.

***Date of analysis 4 to 5 years:*** For men, the meta-analysis of the 4 studies with high and moderate qualitative certainty of results showed important heterogeneity so that the calculation of a common estimate was not meaningful. The meta-analysis in exclusive consideration of the results from 3 studies with high qualitative certainty of results showed a statistically significant effect for men. Hence proof of an effect in favour of screening was derived for men. Since for women the results from the Chichester trial were not statistically significant, there was no hint of an effect in favour or to the disadvantage of screening for women.

***Dates of analysis 10 years and 13 to 15 years:*** For both dates of analysis, the meta-analyses of the studies, which all had a high qualitative certainty of results, showed a statistically significant effect for men. Hence for both dates of analysis, proof of an effect in favour of screening was derived for men.

***Summary of the overview of the evidence across all dates of analysis:*** For men, the meta-analyses at all dates of analysis showed proof of an effect in favour of screening. Overall, proof of a patient-relevant benefit for men was therefore derived across all time points. For women, data were only available for the date of analysis of 4 to 5 years, which showed no statistically significant effect. Hence there was no hint of a patient-relevant benefit of screening for women.

#### **4.5.5 Results on morbidity: elective surgery**

For men, the results at the date of analysis of 4 to 5 years were based on data from 4 studies, at the date of analysis of 10 years as well as at the date of analysis of 13 to 15 years on 3 studies respectively. For women, data from one study (Chichester) were available for the date of analysis of 4 to 5 years. The results from all 4 studies had moderate qualitative certainty of results.

***Date of analysis 4 to 5 years:*** For men, the meta-analysis of the studies, which all had moderate qualitative certainty of results, showed important heterogeneity so that calculating a common estimate was not meaningful. The effects of the 4 studies were clearly in the same direction, however, in direction of an increased number of elective surgeries in the screening group. The prediction interval covers the zero effect so that it cannot be excluded that individual studies may have no effect or an effect. For morbidity associated with elective surgery, an indication of an effect to the disadvantage of screening was derived for men. Since for women the results from the Chichester trial were not statistically significant, there was no hint of an effect in favour or to the disadvantage of screening for women for morbidity associated with elective surgery.

***Dates of analysis 10 years and 13 to 15 years:*** The meta-analysis of 3 studies, which have a moderate qualitative certainty of results, showed a statistically significant effect to the disadvantage of screening for men for both dates of analysis. For both dates of analysis, an indication of an effect to the disadvantage of screening for men was derived for morbidity associated with elective surgery.

***Summary of the overview of the evidence across all dates of analysis:*** For morbidity associated with elective surgery, the meta-analyses showed an indication of an effect to the disadvantage of screening for men for each of the 3 dates of analysis. In the overall consideration across all time points, an indication of harm to the disadvantage of screening for men was derived for morbidity associated with elective surgery. For women, data were only available for the date of analysis of 4 to 5 years, which showed no statistically significant effect. Hence there was no hint of a patient-relevant benefit or harm of screening for women.

#### **4.5.6 Harm resulting from screening**

Results on potential harm resulting from screening were categorized as the corresponding outcomes. No data on consequences of false screening results and overdiagnoses were available.

#### **4.5.7 Results on health-related quality of life and on psychosocial aspects**

Data on the outcome “health-related quality of life” were reported in the Viborg trial and in the MASS trial. In the MASS trial, quality of life was investigated in a sample of the intervention group, which was representative according to the authors, and in a sample of the control group, which was representative according to the authors, 6 weeks after the ultrasound scan. Based on the information in the study, it cannot be checked whether people in the sample had the same demographic characteristics as the total population. Upon enquiry, the authors of the study confirmed that it was a representative sample, but they did not send any data or explanations for the statement to be checked. Data on quality of life were also recorded in the Viborg trial, but only in the intervention group. Subjects who participated in the screening were compared with subjects who were invited and refused screening. The data therefore constituted no comparison of the intervention and the control group and were not evaluable.

No data on psychosocial aspects were reported in the studies included.

#### **4.5.8 Recording and presentation of diagnostic accuracy**

Diagnostic accuracy of ultrasound was reported in the Viborg trial [48]. Diagnostic ultrasound had a sensitivity of 98.9%; 95% confidence interval (CI) [96.2; 99.9] and specificity of 99.8%; 95% CI [98.5; 99.2] in the distal infrarenal aorta and a sensitivity of 87.4%; 95% CI [75.2; 95.9] and a specificity of 99.9%; 95% CI [99.8; 99.9] in the proximal infrarenal aorta.

#### **4.5.9 Subgroup characteristics and other effect modifiers**

The subgroup analyses by age, sex and risk factors were already addressed under the respective outcomes if corresponding data were available. Due to a lack of sufficient data, no analyses were possible on further subgroup characteristics or effect modifiers, particularly on the design of screening and treatment strategy.

#### **4.5.10 Ongoing studies**

The search in trial registries identified one ongoing study in Korea [49] („The Effect of Abdominal Aortic Aneurysm Screening on Mortality in Asian Population“), the relevance of which for the present report could not be clarified because no full publication is available yet. It cannot be assessed whether the study has a randomized design because there are contradictory data in the trial registry.

The bibliographic literature search and the search in trial registries (NCT00662480) additionally identified the ongoing study „The Viborg vascular screening trial“ (VIVA), which generally might be relevant for the research question investigated in the present report, but for which to date no results on patient-relevant outcomes are available yet. The aim of the study is to assess the efficacy and efficiency of a combined screening programme for AAA, peripheral arterial occlusive disease and arterial hypertension.

#### **4.6 Conclusions on effect regarding patient-relevant outcomes**

The following Table 2 summarizes the aforementioned conclusions on effect at the 3 dates of analysis on all outcomes.

Table 2: Conclusions on effect regarding patient-relevant outcomes

	All-cause mortality	AAA-related mortality	Morbidity			Health-related quality of life and psychosocial aspects
			Frequency of ruptures	Emergency surgery	Elective surgery	
<b>Date of analysis 4 to 5 years</b>						
Men	↑↓	↑↑	↑↑	↑↑	↓	-
Women	↔	-	↔	↔	↔	-
<b>Date of analysis 10 years</b>						
Men	↑↑	↑↑	↑	↑↑	↓	-
Women	-	-	↔	-	-	-
<b>Date of analysis 13 to 15 years</b>						
Men	↑↑	↑↑	↑↑	↑↑	↓	-
Women	-	-	-	-	-	-
-: no data available (AAA-related mortality and psychosocial aspects) or: data not applicable (health-related quality of life) ↑↑: proof of effect in favour of screening ↑: indication of effect in favour of screening ↓: indication of effect to the disadvantage of screening ↑↓: heterogeneous data, therefore no hint in favour or to the disadvantage of screening ↔: no hint in favour or to the disadvantage of screening						

#### 4.7 Evidence map

The following Table 3 presents the evidence map regarding patient-relevant outcomes. It contains the overall conclusion on patient-relevant benefit and harm across all analysis dates.

Table 3: Evidence map regarding patient-relevant outcomes (total period of analysis)

	All-cause mortality	AAA-related mortality	Morbidity			Health-related quality of life and psychosocial aspects
			Frequency of ruptures	Emergency surgery	Elective surgery	
<b>Men</b>	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↓	-
<b>Women</b>	↔	-	↔	↔	↔	-
-: no data available (AAA-related mortality and psychosocial aspects) or: data not applicable (health-related quality of life) ↑↑↑: proof of benefit of screening ↓: indication of harm resulting from morbidity associated with elective surgery ↔: no hint of benefit or harm of screening						

## 5 Classification of the work result

The present benefit assessment concludes that AAA screening in men aged 65 years and older reduces all-cause mortality and AAA-related mortality as well as frequency of ruptures and number of emergency surgeries. At the same time, the results showed that the number of elective surgeries in men is increased by the introduction of screening. For women, the overall data availability is poor. Regarding all-cause mortality, frequency of ruptures, emergency surgery and elective surgery, there was no hint of benefit or harm of screening; there were no results for the outcome “AAA-related mortality”.

The present report was based on 4 randomized trials, which had been initiated in the 1990s.

### Decreasing prevalence

As described in Chapter 1, data are available for several Western European countries that show that incidence and prevalence of AAA have decreased in these countries in the last 15 to 20 years and are now notably lower than the ones observed in the studies included. Even though no such data are available for Germany, it can be assumed that a similar development has also occurred here, particularly as decreasing cigarette consumption has been held responsible for the decreasing prevalence [13,17], and as the number of heavy smokers decreased notably also in Germany in the period between 1998 and 2009, particularly in men [50]. Hence the absolute effect of screening may be smaller under today’s conditions than the one observed in the studies included – i.e., more men may have to be screened today to avoid one death than was the case in the studies.

The number of people to be screened was calculated on the basis of the results from 3 studies (Chichester, MASS, Viborg) at the date of analysis of 13 to 15 years. The number of people to be screened to avoid one AAA-related death is 210; 95% CI [167; 283]. The corresponding number related to all-cause mortality for the same date of analysis is 138; 95% CI [73; 1393].

In comparison, Svensjö et al. 2013 [51] argued on the basis of registry data from Sweden that today the number of people to be screened in order to avoid one AAA-related death, is 530 at the date of analysis of 13 years. This means that 3 times as many patients would have to be screened today than about 10 years ago in order to achieve the same (absolute) effectiveness of a screening programme.

### Age shift

There are also indications that the patients’ age at which a clinically relevant AAA occurs has markedly shifted upwards. In an English investigation, the age of patients with AAA at risk of rupture increased by 5 to 10 years in the period of 1997 to 2009 [13]. An analysis of data on ruptured AAA for the years 2005 to 2010 has resulted in a mean age of 78.2 (standard deviation [SD] 8.0) years in England, and in a mean age of 76.6 (SD 9.6) years in the USA [52]. According to Anjun and Powell 2012, the age of patients with AAA at risk of rupture, increased by 5 to 10 years since 1997 [13]. In Germany, the proportion of patients over

80 years of age of the total population of patients who had surgery for intact AAA increased from 8.2% to 19.1% between 1999 and 2010 [20]. Against this background, the question arises whether today greater effects would be achieved in older men, and whether the lower age limit of 65 years is still the best age for population screening.

### **Risks of AAA screening**

Besides having a possible benefit, screening programmes are always also associated with harm [53]. The aim of AAA screening is to avoid ruptures and associated deaths by early detection and treatment of the AAAs found, particularly via endovascular intervention, but also via elective open surgery. Even though elective surgery can prevent ruptures, they are also associated with a marked risk of postoperative complications such as bleeding, pneumonia, peripheral ischaemia, myocardial infarction, stroke, etc. [54]. Endovascular techniques, which today are the preferred methods, are associated with lower perioperative mortality than open surgery [21], but require continuous postoperative monitoring and possibly follow-up interventions [55].

The complications associated with elective surgery could not be assessed in the present report because no separate data were reported in the 4 RCTs included.

It is conceivable that the increased number of elective surgeries found in the studies and the associated complications result in perioperative deaths in the screening group. Such an acute increase in mortality in the screening group might lead to a contradiction to the long-term reduction in mortality. On the one hand, relevant crossing of the survival curves would result in problems of statistical analysis (violation of the proportional hazards assumption). On the other hand, the interpretation of the result would be made more difficult because, in an extreme scenario, the mean survival time in the screening group would decrease despite the long-term survival advantage. However, crossing survival curves were not observed in the studies that reported such curves. At the same time, the hazard ratio and Peto odds ratio effect estimates for the outcome “AAA-specific mortality” and at the date of analysis of 4 to 5 years (if reported) were close, which in the observed low prevalence indicates similar observation periods in both groups. Furthermore it should be considered that perioperative deaths in the screening group do not occur directly as a result of screening, but that both the preparation of the operation and the occurrence of deaths after an operation lead to a delay. Hence overall it can be assumed that the possible increase in early mortality due to elective surgery does not raise doubts about the conclusion regarding all-cause mortality.

Moreover it can be assumed that overdiagnosis and overtreatment also occur in the framework of AAA screening. According to the definition of the present report, overdiagnosis occurs when a patient is diagnosed with an AAA that would not become clinically apparent in the patient’s lifetime. Overtreatment means that a patient diagnosed with AAA has elective surgery and is therefore subject to the described risks of elective surgery, although their AAA would not have caused any symptoms during the course of the patient’s remaining lifetime. Overdiagnosis and overtreatment can neither be avoided nor directly determined. It would be

possible, however, to estimate the frequency of overdiagnosis [56], which is associated with methodological difficulties, however. There is currently no consensus on how to best estimate overdiagnosis rates [56,57]. A current work of Johansson et al. 2015 [58] also pointed out that no exact data for overdiagnosis could be calculated for AAA screening.

In the framework of the present benefit assessment, there were also no evaluable data on the question in how far the knowledge of a finding classified as suspicious, but not requiring surgery, affects the quality of life of the screening participants. The group of these people, whose aneurysm size is not yet an indication for surgery, is far larger than the group of screening participants with immediate indication for surgery. It can be plausibly assumed, however, that the diagnosis of AAA and the subsequent check-up examinations constitute a burden for these people – even though their AAA might require surgery.

### **Considerations on the design of screening programmes based on guidelines**

In a systematic review, Ferket et al. 2012 [59] searched for guidelines up to 2010. 7 guidelines could be included on the topic. All guidelines analysed by Ferket et al. 2012, as well as the current recommendation of the U.S. Preventive Service Task Force (USPSTF) and of the European Society for Vascular Surgery (ESVS), recommend elective surgery or referral to a vascular surgeon for men with an AAA diameter of  $\geq 5.5$  cm. The German Society of Vascular Surgery and Medicine (DGG) recommends considering elective surgery in men with an AAA diameter of 5 to 5.5 cm [8]. This threshold value was confirmed in 2 randomized studies [60,61], both of which found no advantage of a surgical approach in comparison with a conservative approach in aneurysms  $< 5.5$  cm.

The recommendations of the guideline differ regarding intervals and threshold values in the management of smaller AAAs. There were also differences in the RCTs regarding recommended intervals and threshold values in the monitoring of smaller AAAs. The corresponding heterogeneity of the guidelines therefore also reflects the fact that no optimum strategy can be derived directly from the RCTs.

In the case that population-based AAA screening is introduced in Germany, suitable accompanying quality assurance measures (e.g. recording of the AAA diameter at the time point of the operation and recording of perioperative morbidity and lethality) should be implemented at the same time to ensure clear case definitions, the specification of clear quality standards and consistent follow-up, if possible, of people with a suspicious finding or with diagnosis of AAA in the screening. In addition, it would be desirable to have information material for the target screening group, which addresses the advantages and disadvantages of AAA screening in a balanced way, to enable informed decision making.

## 6 Conclusion

**For men**, this benefit assessment provides proof of a benefit of ultrasound screening for AAA regarding **all-cause mortality, AAA-related mortality, frequency of ruptures** and number of **emergency surgeries**. An indication of harm from ultrasound screening was derived for morbidity associated with **elective surgery** for men.

**For women**, there was no hint of a benefit of ultrasound screening for AAA for **all-cause mortality, frequency of ruptures**, number of **emergency surgeries** and number of **elective surgeries**. There were no data on **AAA-related mortality** for women.

Regarding **health-related quality of life** and **psychosocial aspects**, no conclusion on benefit or harm of ultrasound screening for AAA could be derived for men or for women because the data on health-related quality of life were not evaluable, and there were no data for psychosocial aspects.

## **Appendix**

*The appendix is included in the full German report (see <https://www.iqwig.de/de/projekte-ergebnisse/projekte/nichtmedikamentose-verfahren/s13-04-ultraschall-screening-auf-bauchaortenaneurysmen.3767.html>)*

## References for English extract

Please see full final report for full reference list.

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