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Relatively High Pulmonary and Cardiovascular Mortality Rates in Screening-detected Aneurysmal Patients Without Previous Hospital Admissions

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Background. *Men with abdominal aortic aneurysm (AAA) who are not hospitalised for pulmonary and cardiovascular diseases may have higher mortality due to such disorders.*
Material and methods. *Previous discharge diagnoses and causes of death were collected for 4,816 men aged 64–73 years attending mass screening for AAA. Of these, 191 (4%) had an AAA. Overall, cardiovascular- and pulmonary-disease-specific mortality was compared for men with and without AAA stratified for earlier pulmonary or cardiovascular hospitalisations by Cox's proportional hazards regression while adjusting for age. Absolute risk differences after five years were calculated by life table analysis.*
Results. *The median observation time was 63 months. 362 men died from cardiovascular causes other than AAA, and 144 died from pulmonary causes. The cardiovascular mortality was significantly higher in aneurysm patients without previous related hospitalisation (HR = 4.35, 95% CI: 2.73–6.94, P < 0.001) with an absolute mortality difference after 5 years of 16.3% (95% CI: 10.2–22.5%). Pulmonary-cause mortality was higher among men with AAA both with and without previous hospitalisation for pulmonary causes (HR = 3.05; 95% CI: 1.19–7.83, P = 0.020, and HR = 3.29; 95% CI: 1.78–6.08, P < 0.001, respectively).*
Conclusions. *Men with AAA who had not been hospitalised for cardiovascular diseases have more than four times higher cardiovascular mortality. Studies of cohorts being offered relevant prophylaxis may clarify the potential benefits of general preventive actions.*

Keywords: Mass screening; Abdominal aortic aneurysm; Prevention; Atherosclerosis; Statins; Aspirin.

Introduction

About 1%–3% of men aged 65 or more experience rupture of an abdominal aortic aneurysm (AAA), an event with a mortality of 85–90%. By contrast, only 5%–7% die from AAA after an elective repair. However, AAA seldom causes symptoms before rupture. The mortality differential coupled with the asymptomatic phase before rupture is a good argument for considering screening for AAA.[1–5]

Since AAA is associated with chronic obstructive pulmonary disease (COPD) and cardiovascular disease,[1] ongoing screening could provide an opportunity to prevent morbidity and mortality from other causes through appropriately targeted interventions. Such interventions ought to be started during and after hospital admissions for cardiovascular disease or COPD. An important remaining question is whether men with AAA not previously hospitalised with cardiovascular disease or COPD have higher mortality due to these disorders and may therefore benefit from preventive actions.

To explore these issues, we investigated the association between a history of cardiovascular or pulmonary hospitalisation and pulmonary and cardiovascular mortality in men with AAA.

Material and Method

Study subjects were participants in a randomised study of AAA screening conducted in Viborg County, Denmark. From 1994 to 1998, all male county residents aged 64–73 years had been randomised to AAA screening ($N = 6{,}333$) or to control group ($N = 6{,}306$).

The details of the trial have been described elsewhere.[4] Briefly, men randomised to screening were

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invited for an abdominal aortic ultrasonographic scan at their local hospital[4] The B-mode scans were carried out with a small portable Phillips SDR 1550 with linear 4 mHz transducer and calliper light pen. The maximal infrarenal aortic diameter was measured in all attenders in which the aorta could be visualised. An AAA was defined as a maximal diameter of 30 mm or more. Patients with an AAA were offered annual follow-up examinations for further expansion. Patients with AAA sized 5.0 cm or more were referred to be evaluated for vascular surgery. No general pulmonary and cardiovascular preventive actions were taken. Of the 6,333 men randomised to screening, 4,852 (77%) were screened for AAA, 4816 (99%) had visible aortas and were eligible for the present study.

For all participants, we ascertained all discharge diagnoses of COPD and cardiovascular diseases, including hypertension, recorded before the date of enrolment in the National Patient Registry. This registry, established in 1977, records civil registration number, dates of hospitalisation and up to 20 discharge diagnoses. Diagnoses were coded using the Danish version of the International Classification of Diseases (ICD), 8th revision until the end of 1993, and 10th revision thereafter.[6] The codes were used to classify the participants according to previous cardiovascular manifestations and COPD (Table 1).

Leading and participating causes of death occurring between the enrolment date and 31.12.1999 were obtained from the national Registry of Causes of Death. Using the ICD-10, we classified causes of death as cardiovascular (ICD-10 codes starting with I) or pulmonary (ICD-10 codes starting with J).

AAA-related deaths − i.e., deaths caused by ruptured AAA or AAA-related surgery − were censored from the analyses. The hospital and autopsy records of the AAA-related deaths were reviewed by two vascular surgeons, who classified the certainty with which death was caused by AAA as ''certain'', ''probable'', or ''unlikely''. The surgeons were unaware of each other's judgements or of the subjects' randomisation status in the original trial. Criteria were not formulated in advance. Deaths classified by both surgeons as ''certain'' or ''probable'' were considered to be caused by AAA. Other combinations of the two judgements (''probably'' and ''unlikely'', both ''unlikely) were classified as deaths due to other causes. No efforts were made to obtain agreement.[4,5]

Among the men screened for AAA, we compared overall mortality for those with and without AAA detected. We used Cox's proportional hazards regression without and with adjustment for age and previous hospitalisation for pulmonary or cardiovascular diseases. We then examined pulmonary and cardiovascular mortality separately for men with and without previous hospitalisation for those diseases. Kaplan Meier plots were produced for graphical illustration and used to judge whether the assumption of proportional hazards were present.

Finally, we calculated absolute risk and absolute risk difference for death by these causes.

SPSS 10.0 and PEPI were used as statistical software.

The trial was approved by the local ethics committee and reported to the Danish Registry Board.

The author has no potential conflicts of interests.

In accordance with the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors, the trial is registered at clinical trials with the registration number: ISRCTN65822028.

Table 1. Classification of previous hospital admissions for AAA-related diseases according to the 8th and 10th WHO classification of diseases (ICD)

Included cardiovascular and pulmonary diseases	Included ICD classification codes
Arterial Hypertension	40000-40499,41009,41109,41209, 41309, 41409, 43000 + 09,43100 + 09, 43200 + 09, 43309, 43409, 43509, 43600-09, 43700-09, 438.00-99, I10-I15
AMI[a]	41009 + 41099, I21-I23
COPD[b]	49100-493.99, 517.00-518.99, J40-J47
Ischemic heart disease excl. AMI	412.00-414.99, I20-I25 (excl. AMI)
PAD[c]	440.09, 440.20,440.28-440.99, 444.00-444.19, 444.41-445.99, I70 (excl. I70.1), I73-I74 (excl.I74.2),
Stroke el. TCI[d]	431.00-435.99, 436.01-436.99, I61-I65

[a] Acute myocardial infarction.
[b] Chronic obstructive pulmonary disease.
[c] Distal peripheral occlusive vascular disease.
[d] Transient cerebral ischaemia.

Results

Of the 4,852 men screened for AAA, 4,816 (99%) had the aorta successfully imaged, and 191 (4%) had an AAA. The median follow-up time was 62 months (25 and 75 percentiles: 40 and 67 months). Seven men died of AAA-related causes. During the observation period, 593 men died of non-AAA related causes; 325 (54%) of them died at a hospital. The primary or participating cause of death was a cardiovascular disease among 362 (61%) men, and pulmonary disease among 144 (24%) men.

Table 2 shows mean age at enrolment, number of deaths and prevalence of hospitalisation for cardiovascular disorders and COPD. Compared with men without AAA, nearly twice as many men with AAA

Table 2. Age and previous hospitalisations due to cardiovascular disease or pulmonary disease among men with and without AAA detected by screening

		Without AAA		With AAA	
		N	(25)-50-(75) percentiles	*N*	(25)-50-(75) percentiles
Age (years)		4625	(65.2) 66.5 (69.7)	191	(65.3) 67.5 (70.7)
Aortic diameter (mm)		4625	(16) 18 (19)	191	(31) 34 (41)
Previous CV	No	3603	77.9%	109	68.1%
	Yes	1022	22.1%	82	31.9%
Previous COPD	No	4316	93.3%	175	91.6%
	Yes	309	6.7%	16	8.4%

CV: cardiovascular disease.
COPD: chronic obstructive pulmonary disease.

had a history of hospital admission for cardiovascular disease (32% vs. 22%, Chi Square test: $P < 0.001$).

Table 3 describes overall, cardiovascular and pulmonary-related mortality among men with and without AAA.

It is striking that two thirds of men with AAA who died of pulmonary related causes had no history of hospital-recorded COPD diagnosis, and about half of the cardiovascular deaths in this group occurred in men without a previous hospital record of cardiovascular manifestations.

Men with AAA had significantly higher overall mortality than men without AAA (Crude hazard ratio: 2.11; 95% CI: 1.73−2.59) − even after adjustment for age and a history of cardiovascular or COPD hospital admission (hazard ratio = 1.92; 95% CI: 1.43−2.58, $P < 0.001$, Table 3, Fig. 1). The absolute risk difference was 14% (Table 4). Stratified analysis revealed that cardiovascular mortality was significantly higher in men with AAA who had not been previously hospitalised for a cardiovascular cause (hazard ratio = 4.35, 95% CI: 2.73−6.94, $P < 0.001$, Table 2, Fig. 2) with an absolute risk difference after 5 years of 16.3% (95% CI: 10.2−22.5%) (Table 4, Fig. 2). Pulmonary related mortality was higher in men with AAA with and without COPD admissions for pulmonary causes (hazard ratio = 3.05; 1.19−7.83, $P = 0.020$, and hazard ratio = 3.29; 1.78−6.08, $P < 0.001$, respectively) (Table 3, Fig. 3). The absolute risk difference was 20% among those previously submitted to hospital due to pulmonary problems, and 6% among those never admitted to hospital due to pulmonary problems (Table 4).

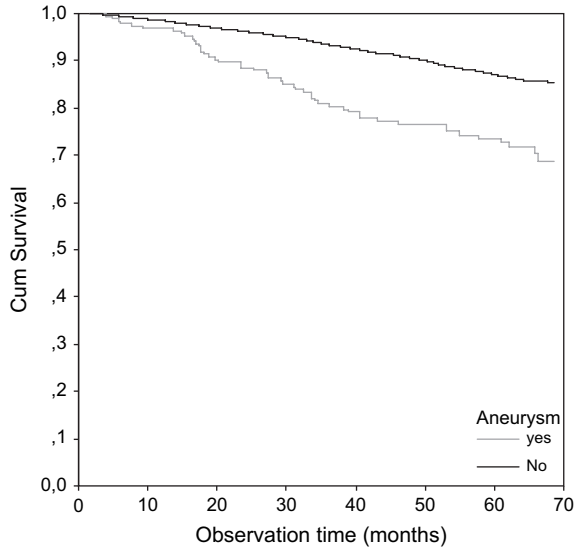
Discussion

This study demonstrated that cardiovascular and pulmonary caused mortality were higher in men with AAA never admitted to hospital due to cardiovascular diseases and COPD. These findings suggest that patients with AAA may benefit from screening for cardiovascular and pulmonary disease and appropriate treatment. The absolute risk difference in cardiovascular related mortality was as high as 16%, so a substantial benefit of preventive actions could be

Table 3. Mortality of men with and without AAA

		Non-AAA $N = 4625$	AAA $N = 191$	Hazard ratio[a]	95% C.I.	*P*-value
Pulmonary deaths	All pulmonary deaths	127	17	3.00[c]	1.80−5.02	<0.001
	Without previous COPD admission	81	12	3.29[c]	1.78−6.08	<0.001
	With previous COPD admission	46	5	3.05[c]	1.19−7.83	0.020
Cardiovascular deaths	All cardiovascular deaths	323	39[b]	3.00[c]	2.15−4.19	<0.001
	Without previous CV admission	158	20[b]	4.35[c]	2.73−6.94	<0.001
	With previous CV admission	165	19[b]	1.50[c]	0.93−2.41	0.097
Deaths of any cause	All deaths	544	49[b]	1.92[c]	1.43−2.58	<0.001

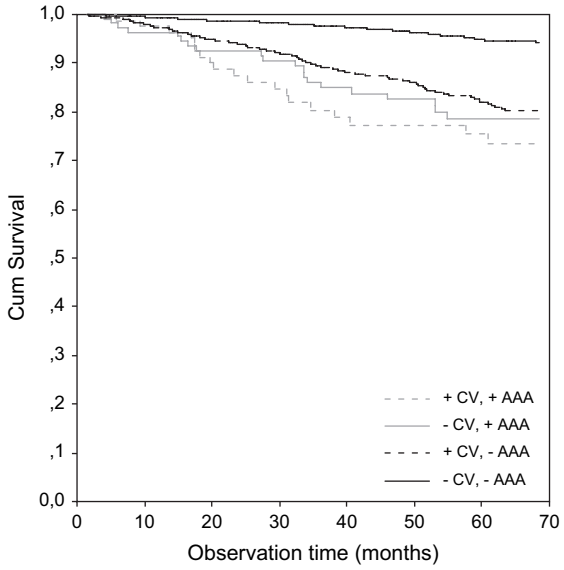
CV: cardiovascular disease.
COPD: chronic obstructive pulmonary disease.
All deaths are adjusted for age, previous cardiovascular disease and COPD caused hospital admissions.
Total, cardiovascular and pulmonary mortality with and without stratification for history of relevant hospitalisations based on participating causes of death. Hazards ratios from the Cox's regression compare men with and without AAA.
[a] Hazard ratios comparing men with and without AAA.
[b] Excluding AAA-related deaths.
[c] Adjusting for age and concerning pulmonary deaths adjusted for previous cardiovascular caused admissions, and concerning cardiovascular related deaths adjusted for previous COPD admissions.



	0	10	20	30	40	50	60
+ AAA	191	185	161	142	132	116	99
- AAA	4625	4569	4112	3770	3668	3204	2737

(Crude hazard ratio: 2.11; 95% CI: 1.73-2.59, P < 0.001) – after adjustment for age and a history of cardiovascular or COPD hospital admission (hazard ratio = 1.92; 95% CI: 1.43-2.58, P < 0.001)

Fig. 1. Survival curves for men with and without AAA detected by screening.



	0	10	20	30	40	50	60
+CV, + AAA	82	80	70	59	54	47	41
- CV, + AAA	109	105	91	83	78	69	58
+CV, - AAA	1022	988	879	791	752	655	553
- CV, - AAA	3603	3571	3233	2979	2916	2549	2184

Cox´s regression analysis adjusting for age and previous admissions for pulmonary disease for men without a history of CV, comparing men with and without AAA: hazard ratio: 4.35 (95 % CI: 2.73-6.94), P < 0.001.

Fig. 2. Survival until cardiovascular death in groups classified according to presence of AAA and a history of cardiovascular atherosclerotic disease (CV).

achieved. The ultimate scientific proof of this would, of course, require a randomised trial.

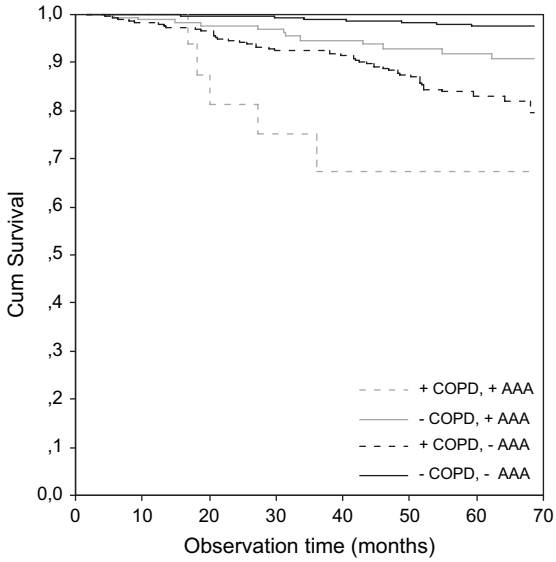
We have earlier reported that almost all the men with an AAA diagnosed by screening in this trial had signs of impaired pulmonary function,[7] but we do not have data concerning cardiovascular disease, except that approximately 50% of them had a systolic ankle-brachial blood pressure index below 95%.[8] So it would probably be possible to define a high-risk group for cardiovascular or pulmonary death by a careful clinical examination, but frequently present latent coronary and cerebral atherosclerotic lesions would not be discovered.[9] So it may be reasonable to consider all men with an AAA to have a higher risk of cardiovascular mortality, especially in the light of the finding that cardiovascular survival of men with an AAA and no history of cardiovascular hospitalisation is similar to that of men with previous cardiovascular disease and no AAA.

There are several limitations of our study: selection bias may have happened due to non-attenders of screening but the attendance rate of 77% was relatively high. Selection bias may also have occurred by those

Table 4. Absolute risk and absolute risk difference after five years of deaths of any cause, pulmonary and cardiovascular caused deaths according to previous hospital admissions due to cardiovascular manifestations or pulmonary disease

Cumulative proportion of deaths after 5 years		Absolute risk		Absolute risk difference (95% CI)
		Non-AAA $N = 4625$	AAA $N = 191$	
Deaths of any cause	All deaths	12.81%	26.87%	14.06% (7.43−20.69%)
Pulmonary deaths	All pulmonary deaths	3.21%	10.46%	7.25% (2.61−11.89%)
	Without previous COPD admission	2.18%	7.89%	5.71% (1.59−9.83%)
	With previous COPD admission	16.99%	37.04%	20.01% (12.84−27.26%)
Cardiovascular deaths	All cardiovascular deaths	7.96%	23.17%	15.21% (8.90−21.51%)
	Without previous CV admission	5.05%	21.39%	16.34% (10.22−22.46%)
	With previous CV admission	16.99%	25.53%	8.54% (1.99−15.09%)

CV: cardiovascular disease.
COPD: chronic obstructive pulmonary disease.



	0	10	20	30	40	50	60
+COPD,+ AAA	16	16	14	10	9	8	6
- COPD,+ AAA	175	169	147	132	123	108	93
+COPD,- AAA	309	303	279	250	240	202	165
- COPD,- AAA	4316	4266	3833	3520	3428	3002	2572

Cox´s regression analysis adjusting for age for men without a history of COPD, comparing men with and without AAA: hazard ratio: 3.29 (95 CI: 1.78-6.08), P < 0.001.

Cox´s regression analysis adjusting for age for men with a history of COPD comparing men with and without AAA: hazard ratio: 3.05 (95 CI: 1.19-7.83), P < 0.001.

Fig. 3. Survival with pulmonary disease stratified by presence of an AAA and a pre-exisisting chronic obstructive pulmonary disease (COPD).

dying of other reasons. However, the proportion of previous cardiovascular hospital admissions in men with AAA was similar to the others (40% vs. 32%, $P = 0.761$).

Secondly, misclassification of causes of death and causes of hospital admissions is probably likely. The autopsy rate in Denmark is very low, which may affect the validity of the cause of death assignment. While some cardiovascular diagnoses in the National Patient Registry (such as hypertension) are considerably misclassified,[10] other cardiovascular diagnoses (such as acute myocardial infarction) were shown to be highly valid.[11] The positive predictive value of registered COPD diagnosis is as high as 90%.[12] The magnitude of any errors is unknown in our study population. However, misclassification rates are likely to be similar in the two groups, and if not, it could be expected that men with a known AAA are more likely to have additional cardiovascular diagnoses.[1]

There are several general cardiovascular and pulmonary preventive actions which could be appropriate for men with an AAA, especially smoking cessation,[13] since the proportion of current smokers is high in AAA patients. Vaccinations against pneumococcus, haemophilus influenzae, and influenza[14] for pulmonary prophylaxis could be considered, and low dose aspirin,[15] cholesterol lowering treatment,[16] and proper antihypertensive treatment[17] for cardiovascular prevention.

The role of statins in conservatively treated cases of AAA is unresolved; statins have anti-inflammatory effects that could decrease the expansion rate of the aneurysms, while wall concentrations of MMP9 – known to be associated with aneurysmal progression – are reported to be lower in statin-treated cases.[18] On the other hand, lipoprotein (a) inhibits the activation of plasminogen, and plasminogen seems to play a central role in the activation of the proteases involved in the aortic matrix degradation. Thus, lowering lipoprotein (a) could increase the aneurysm expansion rate.[19]

An additional question would be whether such actions are cost effective. The absolute cardiovascular mortality risk difference was 16%. If the benefit of diet instruction and 40 mg of Simvastatin is as efficient as in the British Heart Protection Study,[20] such simple action would save approximately 3.2% of all aneurysmal patients from dying prematurely within five years. The Danish five year costs for such a drug dose is 1919 DKr (Zocolip, 98 pieces = 103 DKr), corresponding to 59,968 Dkr per saved life (Euro 8,049 or £ 5,636). However, this will not be the net costs because the risk of suffering a major cardiovascular event is lowered, so that hospital expenses are prevented in addition.

Our results suggest that all patients with an AAA may benefit from general preventive pulmonary and cardiovascular interventions. The ultimate evidence would be a randomised trial but whether this is ethically acceptable can be questioned due to the relatively high mortality and the relatively safe preventive actions. Consequently, additional cohort studies of patients being offered relevant prophylaxis including costs would be very relevant.

Conclusion

Men with AAA detected by screening who have not been hospitalised due to a cardiovascular disease have higher cardiovascular mortality. Consequently, they may benefit from general preventive actions. Studies of cohorts being offered relevant prophylaxis may help to clarify the potential benefits of such prevention.

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