Treatment of ruptured abdominal aortic aneurysms in the Amsterdam area

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CHAPTER 2

SYSTEMATIC REVIEW AND META-ANALYSIS OF POPULATION-BASED MORTALITY FROM RUPTURED ABDOMINAL AORTIC ANEURYSM

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ABSTRACT

Background - A substantial proportion of patients with a ruptured abdominal aortic aneurysm (rAAA) die outside hospital. The objective of this study was to estimate the total mortality, including prehospital deaths, of patients with rAAA.

Methods – This was a systematic review and meta-analysis following the MOOSE guidelines. The Embase, Medline and Cochrane library databases were searched. All population-based studies reporting both prehospital and in-hospital mortality in patients with rAAA were included. Studies were assessed for methodological quality and heterogeneity, and pooled estimates of mortality from rAAA were calculated with a random-effects model.

Results - From a total of 3667 studies, 24 retrospective cohort studies, published between 1977 and 2012, met the inclusion criteria. The quality of included studies varied, in particular the methodology of determining the prehospital deaths from rAAA. The estimated pooled total mortality rate was 81% (95% CI, 78-83%). A decline in mortality was observed (p=0.002) over time: the pooled estimate of total mortality in high-quality studies before 1990 of 86% (95% CI, 83 -89%), compared to 74% (95% CI, 72 to 77%) since 1990. Some 32% (95%CI, 27-37) of patients with rAAA died before reaching hospital. The in-hospital non-intervention rate was 40% (95% CI, 33 to 47%), which also declined over the years.

Conclusions - The pooled estimate of total mortality from rAAA is very high, although it has declined over the years. Most patients die outside hospital, and there is no surgical intervention performed in a considerable number of those who survive to reach hospital.

INTRODUCTION

A ruptured aneurysm abdominal aortic aneurysm (rAAA) is a condition in which acute surgical intervention is required to prevent death. Most relevant literature is limited to reports of survival of patients presenting to hospital. It is assumed that a substantial proportion of patients with an rAAA die outside hospital.
To determine the total mortality of patients with rAAA, the incidence of patients dying from rAAA without attending a hospital has to be determined, as do the death and survival rates of patients who reach hospital in the same interval from the same population. Although population-based studies have been published, it is unclear whether there have been improvements in overall mortality over time. Accurate information on prehospital mortality, the non-intervention rate (patient who die in the hospital without undergoing surgery) and perioperative mortality is important in order to determine potential areas to improve survival following rAAA.
This systematic review assessed the available evidence from population-based studies; a meta-analysis was done with the aim of estimating the prehospital mortality rate, the non-intervention rate and the perioperative mortality from rAAA.

METHODS

This systematic review was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[1]

Search strategy
The MEDLINE, Embase and Cochrane databases were searched for relevant articles. A search strategy was constructed and executed by one investigator aided by a clinical librarian, who specifically searched for studies reporting on the overall, total, case, population and community mortality of patients with rAAA. The initial search was broad and was not restricted to year of publication, language, design or any other characteristics. The last search was performed in January 2013. The search-terms are listed in full in Appendix 1. References from relevant articles were searched manually to identify possible missing articles.

Study Selection
Two independent reviewers (JJR, MJL) screened all titles and retrieved abstracts for relevant studies. Full text of articles were retrieved if the abstract or title suggested a description of total mortality of patients with rAAA or total mortality of patients with acute aortic aneurysms.
Studies reporting both mortality of patients admitted to hospital with rAAA, and community or prehospital deaths from rAAA, in the same interval and population, were eligible for inclusion. Only studies describing an unselected, general population were included. Studies clearly reporting results of elective aneurysm surgery or outcomes of hospitalised patients only were excluded. Studies reporting on a pre-selected patient cohort and those following patients rejected for elective surgery were excluded.
Multiple articles describing the same population and interval were compared for completeness. The most informative study was included and data were combined from other articles. Studies in a language other than English, French, German or Dutch combined with an unpromising title, were excluded at this point. Commentaries lacking original new data and reviews combining previously published data were excluded.

Studies reporting mixed-case series (such as thoracic, symptomatic and inflammatory aneurysms) were included only if a clear distinction between the different diagnoses could be made in the results section. Inclusion was not limited by a minimum number of patients, or year of publication. In the event of doubt or disagreement between the reviewers, the full text was retrieved and a third observer was consulted if disagreement persisted.

Data collection and quality assessment

The same independent investigators acquired data and assessed the quality of all articles included using a checklist based on the MOOSE guidelines[1], Newcastle-Ottowa guidelines[2] and Dutch Cochrane Centre checklist for observational research. These guidelines are primarily designed for observational research of interventions and are not designed for population studies. The guidelines were modified to assess studies for confounding factors and study quality; higher-quality studies were used in a sensitivity analysis. The degree of selection bias was assessed by the completeness of the description of the population included. Information bias was assessed by grading the method of identifying prehospital deaths from rAAA as well as the method of identifying hospitalised patients with rAAA. A full description of the criteria used is shown in *Table 1*. A total quality score was used to identify high-quality studies; defined as those with a score equal to or greater than the median score of all studies.

Table 1 *Overview of point system used to grade included article for quality of methodology*

(A) Quality of description of included population and area

2 points	clear description of size and region in combination with description of participating centres in region. All patients in a well-defined area included
1 point	unclear or incomplete description of geographical area and its residents and hospitals
0 points	description of either population or investigated area

(B) Quality of methodology for identifying rAAA community deaths from rAAA

2 points	cause of death in the community determined mainly with autopsy (high autopsy-rate over 30%)
1 point	cause of death in the community was determined using a combination of a low autopsy-rate with some form of cause of death (ICD) register.
0 points	only a cause of death register/national health statistics (ICD registrar) used or no description given

(C) Quality of methodology for identifying patients with rAAA admitted to hospital

2 points	combination of postmortem register, operation and hospital records. accurate description of patients treated surgically.
1 point	only hospital records or operation records used in combination with a register/national health statistics (ICD register)
0 points	only a register/national health statistics (ICD register) used or no description given

All articles were assessed by two observers.

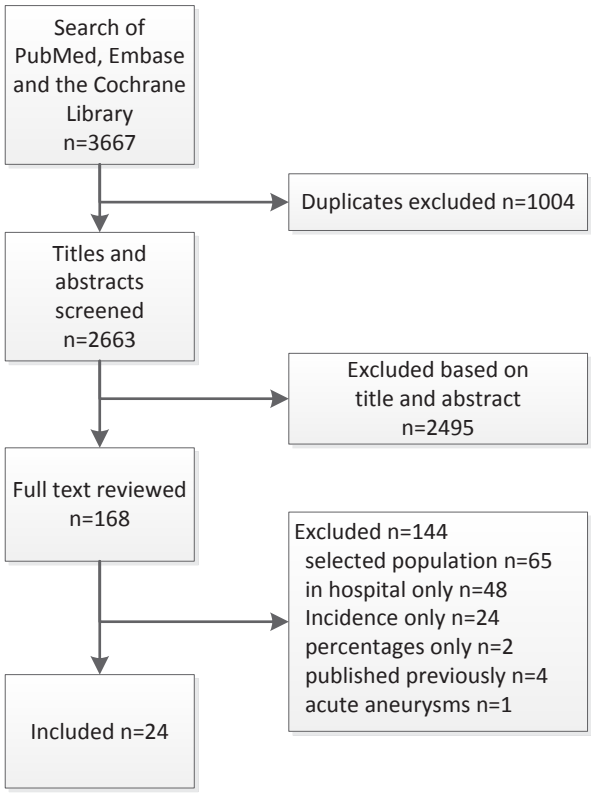
Study characteristics

If available, the total number of patients in the studied population was reported, as well as the year of start and duration of the study. The midpoint of the study period was calculated from this data. The incidence of rAAA in the region was calculated from the data and reported as rAAA per 100 000 inhabitants per year. Data on the number of patients diagnosed with rAAA, and their sex distribution and mean age were also collected if available. To indicate a source of bias in identifying prehospital deaths, the autopsy rate of the general population was also collected.

Outcome

The total mortality of rAAA was reported as the combined percentage of both prehospital deaths and in-hospital deaths of all rAAA diagnosed in the population. The mortality of rAAA was further specified by reporting the locations of deaths from rAAA. The number of patients with rAAA who died in the community before reaching hospital was specified, as well as the number of patients with rAAA who presented to hospital but died before undergoing surgical treatment. Finally, patients who underwent surgery but subsequently died were identified. Absolute numbers of patients from the original articles were used where possible. If the original article reported only percentages, the absolute number of patients was calculated based on the available data. The distribution of death according to location (prehospital, in-hospital without surgery, in-hospital with surgery) was reported as a percentage of all rAAA. The perioperative mortality was defined as the number of patients who died of all patients treated surgically. The non-intervention rate for surgery was defined as the number of patients who presented to hospital but died without undergoing surgery as a percentage of all those who reached hospital.

Figure 1 *Flow chart showing selection of articles for review*



Analysis

Heterogeneity of the total mortality rate was expressed with the I^2-statistic. If I^2 exceeded 50%, moderate (>50%) to high (>75%) heterogeneity was assumed.[3] The pooled estimated mortality rate was calculated using a DerSimonian-Laird random-effects model. Individual and pooled mortality rates were expressed as a percentage with the corresponding 95% confidence interval (CI). A prespecified sensitivity analysis was performed by pooling the total mortality rates of the high-quality studies. A metaregression analysis was carried out to analyse the influence of study midpoint on total mortality. This analysis was done for all studies and for high-quality studies only. Eggers test was used to assess possible publication bias among all studies and for high-quality studies only. P<0.05 was considered statistically significant. All data were analysed by two independent researchers with SPSS statistical software (IBM PSAW SPSS release 18.0.2), STATA (Stata Corp LP, College station, Texas, USA) and Statsdirect (Statsdirect, Altrincham, UK, version 2.7.8).

RESULTS

The search identified 3667 studies of which 1004 were marked as duplicates, resulting in 2663 individual titles and abstracts that were screened for eligibility. A total of 2495 papers were excluded directly based on title and abstract alone. (*Figure 1*). Some 168 papers were reviewed in more depth. The majority were excluded as they reported only an in-hospital population (n=48) or a selected population (n=65). Of the remaining articles, an additional 31 were excluded for reasons shown in *Figure 1*. Two studies[4;5] were excluded as they were duplicate publication on the same cohort from a different study[6], but they were searched for additional methodological information and data on the study cohort. Twenty-four articles[6-29] describing population and in-hospital mortality and survival of a unique cohort of patients met our inclusion criteria and remained for data extraction.

Quality assessment

The studies were highly heterogeneous in their design and the extent of reporting on methodology. The population and geographical regions were well described and well defined in 16 of 24 articles. The methods of identifying prehospital deaths from rAAA differed widely and were frequently not described extensively. Some studies reviewed only prehospital deaths where diagnosis was confirmed at autopsy[7;14;19;23;25], whereas others determined the number of prehospital deaths as reported by the register of International Classification of Disease (ICD). Overall, the autopsy rate of the population was poorly and inconsistently described. Methods of identifying hospitalized patients with rAAA were well described. In most studies, operation registers as well as diagnosis registers and hospital records were analysed. The total quality score of the articles ranged from 0 to 6 (median 4) points. Thirteen (13) studies scored 4 points or higher and were considered high-quality studies. *(Table 2)* Analysis of possible publication bias showed a significant bias when all studies were pooled (p<0.001). No statistical publication bias was found among the high-quality studies (p=0.057).

Table 2. *Overview of articles reporting on total mortality of ruptured abdominal aortic aneurysm*

Reference	year	duration (yrs)	midpoint of study	size of population	sex-ratio m:f	mean / median age	no. of rAAA	incidence of rAAA (per 100.000)	quality score *	autopsy rate %
Rantakokko V[7]	1983	20	1969	140 000	na	na	135	4.82	0/1/1 (2)	na
Drott C[8]	1992	37	1971	397 000	2.89/1	74	611	4.16	2/1/2 (5)	na
Armour RH[9]	1977	5	1975	175 000	11.5/1	na	25	2.86	2/0/2 (4)	na
Bengtsson H[10]	1993	16	1979	237 000	2.58/1	77	215	5.67	2/2/2 (6)	85
Ingoldby CJ[11]	1986	10	1979	248 000	na	72	260	10.48	2/1/1 (4)	na
Johansson G[12]	1986	1	1981	1 500 000	2.26/1	na	88	5.87	2/2/2 (6)	61
Meddings RN[13]	1991	12	1983	150 000	3.3/1	na	86	4.78	2/0/1 (3)	na
Mealy K[14]	1988	8	1983	240 100	3.1/1	76.7	266	13.85	2/1/2 (5)	na
Thomas PRS[15]	1988	6	1984	215 800	2.89/1	na	183	14.13	2/1/1 (4)	na
Budd JS[16]	1989	6	1985	240 000	4.97/1	73.9	197	13.68	1/1/2 (4)	na
Lindholt JS[17]	1995	6	1989	230 000	2.33/1	75	81	5.87	2/0/0 (2)	na
Johansson G[18]	1994	1	1990	1 600 000	0.93/1	75	125	7.81	2/2/1 (5)	45
Semmens JB[6]	2000	10	1990	1 550 000	2.88/1	75.7	873	5.63	0/0/0 (0)	na
Choksy SA[19]	1999	10	1991	370 000	5.95/1	76	139	3.76	2/1/2 (5)	na
Adam DJ[20]	1999	7	1993	1 200 000	na	73	972	11.57	2/0/0 (2)	na
Kantonen I[21]	1999	5	1994	5 100 000	na	na	1247	4.89	1/1/1 (3)	na
Heikkinen M[22]	2002	8	1994	430 000	5/1	73.9	221	6.42	2/0/1 (3)	na
Rose J[23]	2001	5	1996	1 080 000	2.70/1	75	329	6.09	1/1/2 (4)	na
Cassar K[24]	2001	8	1996	204 004	4/1	75	198	12.13	2/0/1 (3)	na
Qureshi NA[25]	2007	15	1997	350 000	2.4/1	75	468	8.91	1/1/2 (4)	na
Souza VC[26]	2005	4	1998	na	2.84/1	78.4	515	na	0/0/0 (0)	na
Lindholt JS[29]	2012	14	2001	na	na	na	6954	na	1/0/0 (1)	15
Acosta S#[27]	2006	5	2003	264 000	4.64/1	77	141	10.68	2/1/2 (5)	25
Hafez H[28]	2009	3	2007	811 000	na	na	341	14.02	2/0/1 (3)	na
Overall		9	1990	307 000			14670^		4	

*Values are median except ^total. If more than one population size, incidence rate, mean age or sex ratio was reported, an average was calculated. If not reported, the incidence was calculated from population size, total number of rAAA and duration of study. * Methodological score as described in table 1.; values are shown for each aspect (A/B/C), along with total score in parenthesis. The score per assessed part of methodology is reported as well as the added total. (s) denotes an area in which a screening programme was in effect during the investigated period. n.a. Data not available.*

Study characteristics

Studies reported patient data from as early as 1952 with a median duration of inclusion of 7 years (range 1-37 years), and were published from 1977 to 2012. A total of 14 670 patients with rAAA were described with a median of 218 (range 25 to 6954) per study. The median sample population was 307 000 inhabitants (range 140 000 - 5 100 000), residing in Finland, Sweden, Denmark, the United Kingdom, Australia and New Zealand. The incidence of rAAA as calculated ranged from 2.81 to 14.13 per year per 100 000 inhabitants per year. A screening programme was in effect in some of the regions studied during the study interval *(table 2)*.

Mortality

The total mortality of patients with rAAA ranged from 67 to 94%. As heterogeneity among studies was very high (I^2=89% (95% CI, 87 to92%)), a random effects model was used to estimate the total mortality, which was 81% (95% CI, 78 to 83%). *(Table 2, Figure 2)*. When chronologically arranged according to midpoint of study, a decline of mortality over time was observed. The pooled estimated mortality of studies up to 1990 was 84% (95%CI, 81 to 87%), compared with a pooled estimated mortality of 78% (95% CI, 75 to 81%) in studies since 1990. Based on the metaregression analysis, the midpoint of study was of significant influence on total mortality (p=0.014) *(fig 3)*.

Three studies did not sufficiently describe the locations where patients with an rAAA died[21;23;29]. The distribution according to location was therefore determined from the remaining 21 studies. The distribution of patients dying at home or in hospital, both before surgery and after surgery, differed vastly and was significantly heterogeneous *(Table 2)*. Of all patients with rAAA, 32% (95% CI, 27 to 37%) died in the community, without being presented at hospital. Of all patients presented at hospital, the pooled estimated non-intervention rate for surgery was 40% (95% CI 33 – 47%). This corresponded with 27% (95% CI, 21 to 33%) of all rAAA patients. Of all surgically treated patients the pooled estimate of perioperative mortality was 53% (95% CI 48 – 59). This corresponded with 21% (95% CI, 17 to 24%) of all rAAA patients. The pooled estimate total mortality of the 21 studies was 82% (95% CI, 79 to 84%).

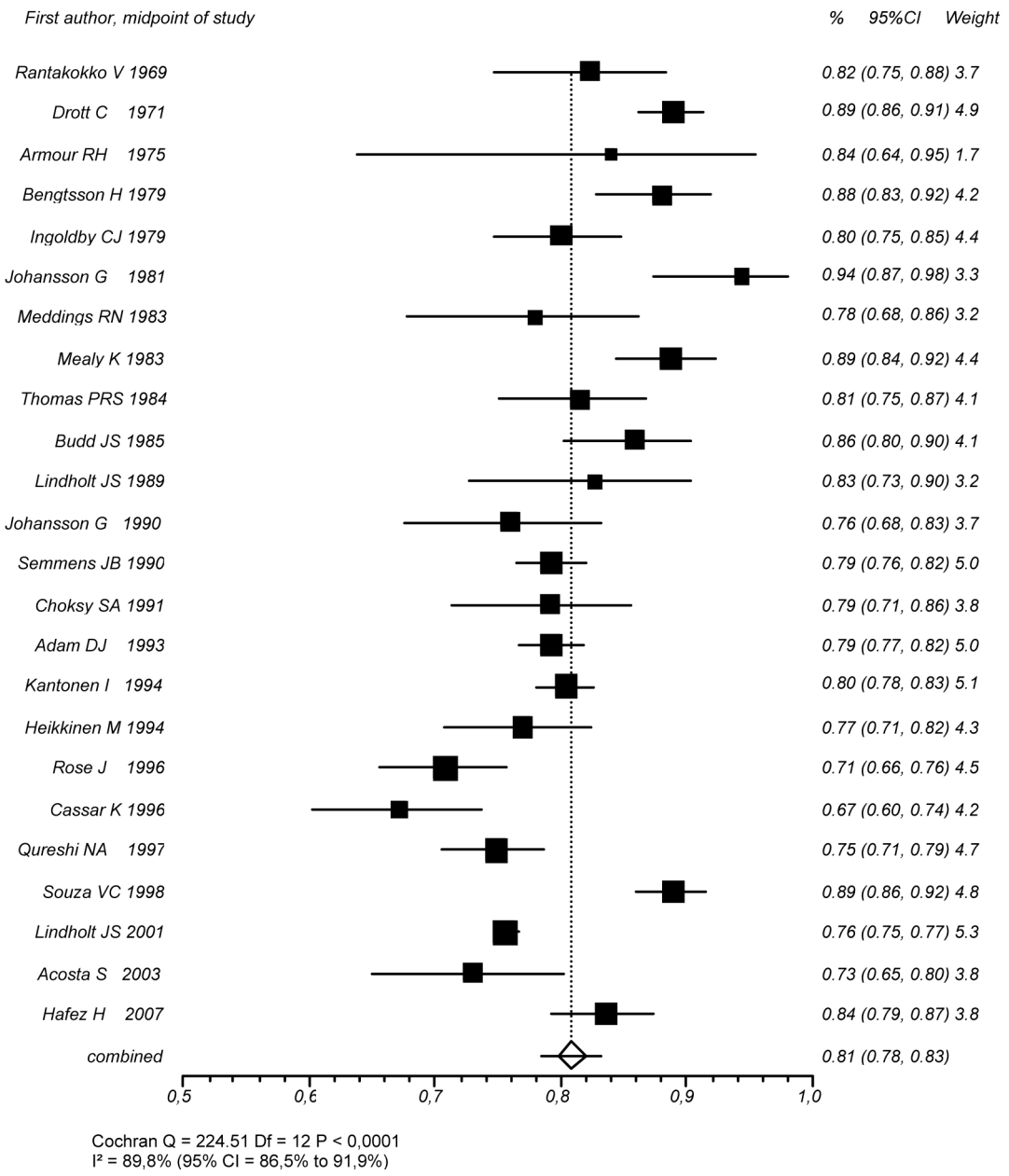
Thirteen studies were identified from the sensitivity analysis as high-quality studies. The pooled total mortality estimate of high-quality studies was 82% (95% CI, 78 to 86%)(*Figure S1, appendix*). The mortality rates of these studies varied from 73% to 94% and the study results were also very heterogeneous (I^2=86% (95% CI, 79 to 91%). When chronologically arranged according to midpoint of study, a significant decline of mortality over time was observed (*Table 2, Figure 3, Figure S1)*. The pooled estimated mortality of all high-quality studies up to 1990 was 86% (95%CI, 83 to 89%), compared with a pooled estimated mortality of 74% (95% CI, 72 to 77%) in high-quality studies since 1990. Metaregression analysis showed a significant influence of midpoint of study on mortality (p=0.002), *Figure 3*. The prehospital mortality of high-quality studies up to 1990 was 37% (95% CI, 28 to 47%) compared with 32% (95% CI, 17 to 49%) of studies since 1990. The non-intervention rate for surgery up to 1990 was 46% (95% CI, 34 to 57%) compared with 26% (95% CI, 7 to 51%) since 1990. The pooled estimate of perioperative mortality was 57% (95% CI, 52 to 63%) up to 1990 and 49% (95% CI, 45 to 55%) since 1990.

Table 3 *Total Mortality and total number of deaths in different circumstances*

			Deaths^						
Reference	Midpoint of study	Total number rAAA	Prehospital deaths	In-hospital no surgery	In-hospital perioperative	Total deaths	Non-intervention rate	Perioperative mortality	Total mortality % (95%CI)
Rantakokko V[7]	1969	135	24 (18)	46 (35)	41 (30)	111	41	63	82 (75 to 88)
Drott C[8]	1971	611	145 (24)	282 (46)	116 (19)	543	61	63	89 (86 to 91)
Armour RH[9]	1975	25	11 (44)	9 (36)	1 (04)	21	64	20	84 (64 to 95)
Bengtsson H[10]	1979	215	91 (42)	63 (29)	35 (16)	189	51	57	88 (83 to 92)
Ingoldby CJ[11]	1979	260	92 (35)*	65 (25)*	49 (19)*	208	39	49	80 (75 to 85)
Johansson G[12]	1981	88	24 (27)	51 (58)	8 (09)	83	80	62	94 (87 to 98)
Meddings RN[13]	1983	86	11 (13)*	25 (29)*	30 (35)*	67	34	61	78 (68 to 86)
Mealy K[14]	1983	266	169 (64)*	18 (07)*	48 (18)*	236	19	62	89 (84 to 92)
Thomas PRS[15]	1984	183	64 (35)	44 (24)	41 (22)	149	37	55	81 (75 to 87)
Budd JS[16]	1985	197	62 (31)	47 (24)	60 (30)	169	35	68	86 (80 to 90)
Lindholt JS[17]	1989	81	37 (46)	22 (27)	8 (10)	67	50	36	83 (73 to 90)
Johansson G[18]	1990	125	46 (37)	28 (22)	21 (17)	95	35	41	76 (68 to 83)
Semmens JB[6]	1990	873	379 (43)	211 (24)	102 (12)	692	43	36	79 (76 to 82)
Choksy SA[19]	1991	139	54 (39)	24 (17)	32 (23)	110	29	51	79 (71 to 86)
Adam DJ[20]	1993	972	219 (23)	413 (42)	138 (14)	770	55	41	79 (77 to 82)
Kantonen I[21]	1994	1247#	237 (19)	na	na	1002	na	na	80 (78 to 83)
Heikkinen M[22]	1994	221	50 (23)	60 (27)	60 (27)	170	31	54	77 (71 to 82)
Rose J[23]	1996	329#	na	na	na	233	na	na	71 (66 to 76)
Cassar K[24]	1996	198	32 (16)	57 (29)	44 (22)	133	34	40	67 (60 to 74)
Qureshi NA[25]	1997	468	201 (43)	24 (05)	125 (27)	350	9	51	75 (71 to 79)
Souza VC[26]	1998	515	163 (32)	100 (19)	*195 (38)*	458	28	77	89 (86 to 92)
Lindholt JS[29]	2001	6954#	na	na	1454 (20)	5260	na	47	76 (75 to 77)
Acosta S#[27]	2003	141	23 (16)	51 (36)	29 (21)	103	43	43	73 (65 to 80)
Hafez H[28]	2007	341	113 (33)	95 (28)	77 (23)	285	42	58	84 (79 to 87)
Pooled point estimate			32% (27,37)	27% (21, 33)	21% (17 ,24)		40% (33,47)	53% (48,59)	81% (78 ,83)
Heterogeneity (I^2)			95%	96%	91%		95%	95%	89%

*Values in parenthesis are ^percentage of all ruptured abdominal aortic aneurysms (rAAA) and 95% confidence intervals. Studies are sorted according to midpoint year of study. * Summed total number of patients does not equal reported number of patients in study. #Study did not adequately report location of death of patients with rAAA, and was not used to calculate the point estimate for mortality according to location. na denotes not available.*

Figure 2. Total mortality of included studies

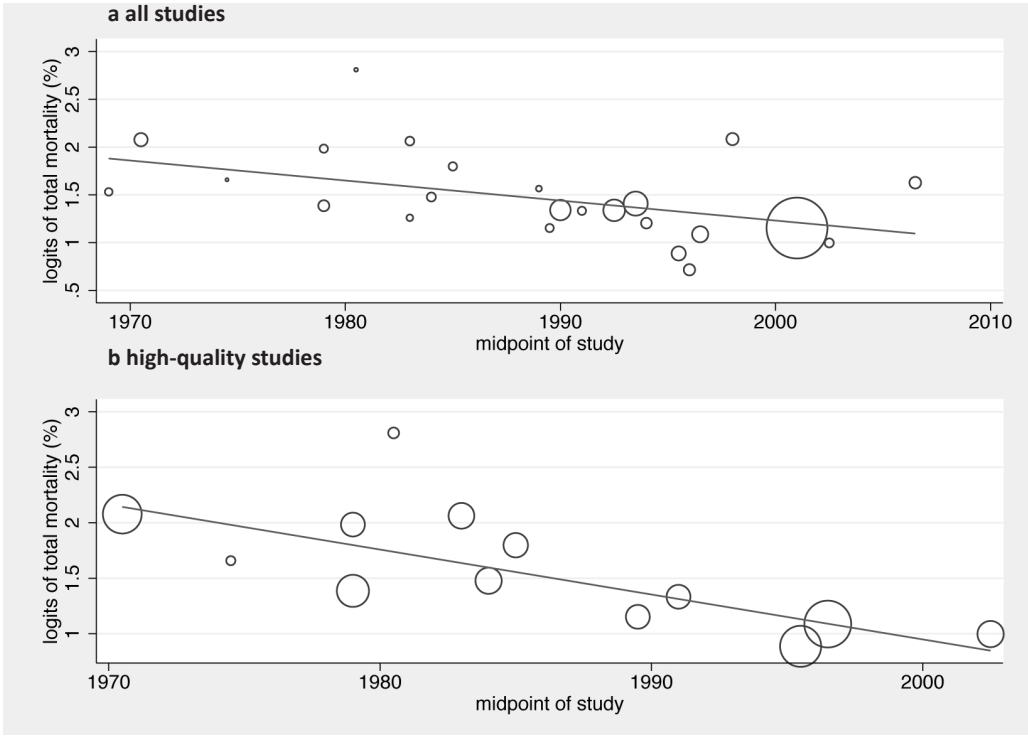


Total mortality in all included studies of ruptured abdominal aortic aneurysm. Studies are listed according to the midpoint of the study interval. The point estimate of total mortality for eacht study and the pooled estimate are shown with 95 per cent confidence intervals. (CI). A random-effects model was used.

DISCUSSION

This meta-analysis showed a pooled point estimate for total mortality for all rAAAs of 81 (78 to 83) per cent. Overall mortality has declined significantly over the years; this is especially clear in the high-quality studies *(Fig. 3)*. An important finding of the systematic review is that approximately 32 per cent of all people with an rAAA die before reaching hospital. Pooling of the studies shows that 40 per cent of patients who reach hospital die without undergoing surgery. Although it is obvious that much effort should be put into improving perioperative mortality to improve the prognosis of patients with rAAA, there are also other significant opportunities for improvement in the prehospital phase and in the intervention rate. It is difficult to reduce the proportion of patients who die in the prehospital phase without any medical intervention.

Figure 3 Metaregression analysis



*Metaregression analysis of total mortality in **a** all studies and **b** high-quality studies. Each study is represented by a circle, with size according to number of included patients. The regression line is plotted. The regression analysis studied the influence of midpoint of the study interval on total mortality. **a** p=0.014, **b** p=0.002*

A screening programme was in effect in certain studies in this meta-analysis. Screening programmes could result in a lower rate of rAAA and therefore subsequent mortality[30]. A screening programme can result in increased awareness of rAAA and might lead to better outcome.

A screening programme alone, however, will not improve the chances of survival of a patient once rupture has occurred, and changes in the structure of care, both before and in hospital, are required to reduce mortality further.
Ways to improve care include a policy of permissive hypotension, or controlled hypotension until bleeding can be controlled surgically.[31,32] Results could also be improved by centralizing hospital care for patients with a suspected ruptured aneurysm. Centralization means that patients are transported immediately to a high-volume, dedicated expert centre. The longer transport time to a vascular centre does not seem to have a negative influence on survival for reasons such as lower turn-down rates, availability of special skills and infrastructure[28].

A total of 40 per cent of patients who reached hospital were not treated surgically. Although some patients with rAAA decline surgical treatment because of advanced age or co-morbidity, this proportion remains significant. The fall in non-intervention rate from 46 per cent up to 1990 to 26 per cent since then goes some way towards explaining the improved survival from rAAA. As the included studies did not specifically evaluate non-intervention rates, most did not report the reasons for withholding treatment. Without details of haemodynamic stability, resuscitation rates, co-morbidity and age, considerations regarding patient selection for surgery or change thereof remain speculative. A few studies reported that patients presented to hospitals without a vascular unit and were therefore not operated on. Round-the-clock availability of vascular surgeons and interventional radiologists is likely to improve outcomes from rAAA. Direct availability of computed tomography angiography for preoperative assessment could also contribute to improved results.
This meta-analysis showed a pooled perioperative mortality rate of approximately 53 per cent, which is high compared with contemporary results[33-35]. Although the analysis showed that perioperative mortality is of limited influence, a reduction in perioperative mortality will lower total mortality. New surgical techniques such as endovascular aneurysm repair are devoted to reducing perioperative mortality. The results of the recently published Amsterdam Aneurysm Trial show that an overall regional 30-day perioperative mortality rate of 30 per cent for rAAA can be achieved with a centralized approach[36].

The present study has some inherent limitations, mostly as a result of information bias. There was significant heterogeneity in the methodology used to determine the number of prehospital deaths from rAAA. Registration of patients dying from rAAA outside hospital is inaccurate[37,38]. Not every death from rAAA in the community is identified as such[38]. Fewer post-mortem examinations are conducted for community deaths[39,40]. Without a complete autopsy rate for all sudden deaths in the community, identifying prehospital deaths from rAAA is inaccurate[41-43]. High-quality studies combining results of high autopsy rates (over 30 per cent) and national statistics registries were uncommon.
The observed lower total mortality rate in recent decades could represent shifting methodology in identifying and registering patients with rAAA. This could be a result of several different parameters such as: increased awareness of the disease, changes in infrastructure and diagnosis, or even decreased smoking habit[44]. Based on the present data it is difficult to determine the exact cause of decreased mortality over time, which is likely to be due to a combination of different preoperative and perioperative factors.
Most studies dated from before the endovascular era, which may limit their applicability to contemporary practice. Finally, approximately half of the studies were carried out in the UK, and the rest in Australia, Denmark, Sweden and Finland with different infrastructure, population density and rAAA protocol, which may limit the generalizability of these results to other regions.

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