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Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm

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Abstract

Objective To assess whether screening for abdominal aortic aneurysms in men reduces mortality.

Design Population based randomised controlled trial of ultrasound screening, with intention to treat analysis of age standardised mortality.

Setting Community based screening programme in Western Australia.

Participants 41 000 men aged 65-83 years randomised to intervention and control groups.

Intervention Invitation to ultrasound screening.

Main outcome measure Deaths from abdominal aortic aneurysm in the five years after the start of screening.

Results The corrected response to invitation to screening was 70%. The crude prevalence was 7.2% for aortic diameter ≥ 30 mm and 0.5% for diameter ≥ 55 mm. Twice as many men in the intervention group than in the control group underwent elective surgery for abdominal aortic aneurysm (107 v 54, P $= 0.002$, χ^2 test). Between scheduled screening and the end of follow up 18 men in the intervention group and 25 in the control group died from abdominal aortic aneurysm, yielding a mortality ratio of 0.61 (95% confidence interval 0.33 to 1.11). Any benefit was almost entirely in men aged between 65 and 75 years, where the ratio was reduced to 0.19 (0.04 to 0.89).

Conclusions At a whole population level screening for abdominal aortic aneurysms was not effective in men aged 65-83 years and did not reduce overall death rates. The success of screening depends on choice of target age group and the exclusion of ineligible men. It is also important to assess the current rate of elective surgery for abdominal aortic aneurysm as in some communities this may already approach a level that reduces the potential benefit of population based screening.

Introduction

Despite advances in vascular surgery and intensive care, the overall case fatality of rupture of an abdominal aortic aneurysm is still around 80%.[1] In addition, the incidence of such events seems to have risen over the past two decades.[2–4] This contrasts with trends seen in coronary heart disease and stroke, suggesting that measures introduced to reduce the impact of occlusive arterial disease have not been effective.

The feasibility of population based screening for such aneurysms by using ultrasound has been established over the past 15 years.[5–7] These early studies generated considerable debate about the merits of population screening, resulting in calls for randomised controlled trials.[8–10] In the first such trial, Scott et al

reported a large (50%) but non-significant reduction in mortality with screening.[11] Since then two randomised trials and several non-randomised studies have all indicated that screening in men saves lives cost effectively.[12–16] We designed a trial to complement these, focusing on men aged 65 to 74 years but also including an older group.

The Western Australia trial of screening for abdominal aortic aneurysms is a population based randomised controlled trial to determine whether a single ultrasound screen for abdominal aortic aneurysms[17] reduces deaths among those to whom it is offered. The trial was designed to cover an entire metropolitan community and assess the effectiveness of introducing population screening into an existing healthcare system. Western Australia is an ideal location for such a trial: the population is geographically isolated and stable, all deaths and hospital admissions are linked within a unified database system, and much is already known about local trends and outcomes for abdominal aortic aneurysm.[1 3 18 19] Here we report on the early effect of screening on mortality in the trial.

Methods

Study population

To provide the most rigorous possible test of the utility of screening, we designed the trial as a population based study with the primary end point, mortality from abdominal aortic aneurysm, to be analysed on an intention to treat basis. We planned to have 90% power to detect and declare significant (two sided $\alpha = 0.05$) a relative reduction of 50% in mortality among men invited for screening over five years from the start of screening. Using available pilot data, we estimated that the control group would need to contain about 20 000 men to experience 55 deaths from abdominal aortic aneurysm.[3]

Men were identified from an electronic copy of the electoral roll, enrolment to vote being compulsory for all Australian adults. The ideal target age range for screening is 65-74 years, but the electoral roll listed fewer than 40 000 men in this age group in the main metropolitan area of Perth (the capital city of Western Australia) and satellite towns. The addition of men aged 75-79 years increased the potentially available number to about 50 000. We excluded 8801 because they lived in the furthest satellite town (about 35 km away from Perth), and we did not have the resources to set up a screening clinic in this location. We achieved our required sample size without including them.

At the beginning of the trial we selected all 41 000 men on the electoral roll who were resident in Perth and were expected to be 65-79 years old at the projected mid-point of screening.
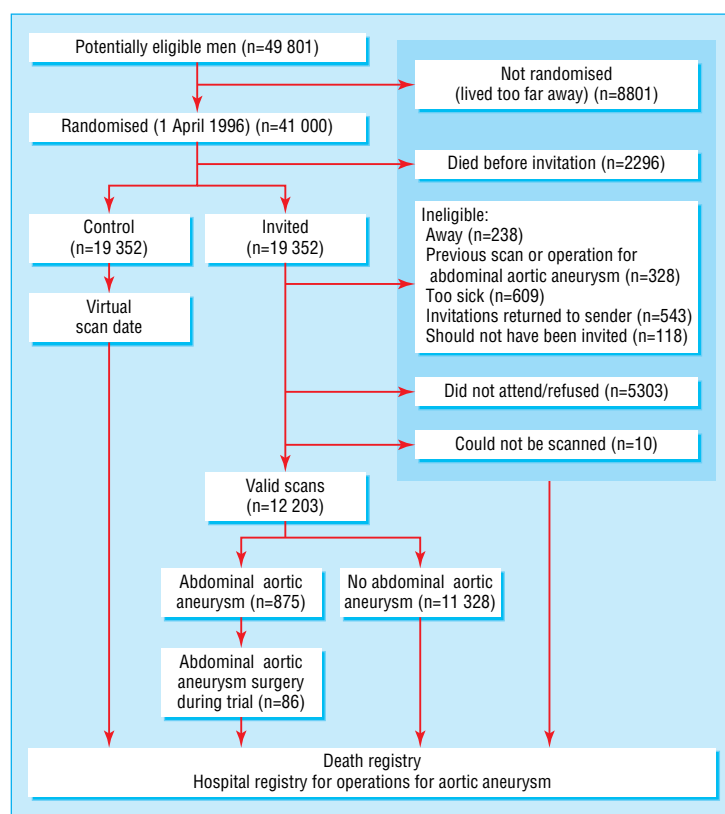
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Fig 1 Summary of trial of screening for abdominal aortic aneurysm

Men were randomised into intervention and control groups of equal size defined by five year age group and postcode. Men in the control group were allocated a "virtual" date of screening, which was the median scheduled date of examination for men from the same postcode area randomised to the intervention group. Men in the intervention group were sent a letter explaining the study and an appointment for a scan. Men who did not take up the initial invitation to screening were sent a second letter.

At the five screening clinics the greatest transverse and anteroposterior diameter was measured with a Toshiba Capasee ultrasound machine with a 3.75 MHz probe (Toshiba Australia, North Ryde, NSW). On leaving the clinic, each man was given a letter containing the results of his scan, with a copy for his general practitioner. The general practitioner arranged any follow up investigations or referral to a surgeon. We made no attempt to influence any aspects of clinical management, in particular with regards to threshold for intervention or method of repair.

Procedures for follow up

We used electronic record linkage to population based named identified records for deaths and admissions to hospital in Western Australia to identify end points in the target population. When linkage to a death registration was confirmed, a researcher who was unaware of group allocation coded up to four causes of death from the text of the original death certificate. Deaths with mention of abdominal aortic aneurysm were identified for further blinded independent confirmation of the contribution to death of the aneurysm or surgery for the aneurysm. We also used electronic record linkage to identify all men undergoing surgery for abdominal aortic aneurysm, either before or after scheduled screening. For admission dates before 1988 we used a combination of international classification of disease, ninth revision,

(ICD-9) diagnosis codes (441.30 or 441.40) and International Classification for Procedures in Medicine (ICPM) code (58.53). Patients admitted from 1988 to 31 June 1999 were identified with the combined ICD-9 clinical modification (ICD-9-CM) diagnosis codes (441.30 or 441.40) and ICD-9-CM procedure code (38.44). Patients admitted after 1 July 1999 were identified with ICD-10 codes (I71.3 or I71.4).

Statistical methods

We initially compared crude and age standardised mortality from definite abdominal aortic aneurysm in the two groups between each man's actual or virtual date of screening and the end of follow up on 31 March 2001, which was five years after the trial began. Principal results are presented as ratios and corresponding 95% confidence intervals for mortality for abdominal aortic aneurysm adjusted in single year strata to the age structure of the male population of Western Australia. To facilitate comparison with studies such as the multicentre aneurysm screening study (MASS),[15] our secondary analyses included the mortality rate ratio for deaths from abdominal aortic aneurysm in men aged 64-75 years. Finally, we examined mortality from all causes over the five years of the programme.

Results

Figure 1 shows the flow of participants through the study. The 41 000 men randomised to the two groups were balanced for age (mean (SD) 72.6 (4.7) v 72.6 (4.7) years). Screening was completed over a period of 32 months, and the median follow up was 43 (range 27-61) months. Because of the method of recording age in the electoral roll, some men were older than the target age range by the time they were invited for screening and, as a result, 725 (5.9%) of those who attended were aged 80-83 years.[17]

Table 1 Elective and emergency procedures for abdominal aortic aneurysm before scheduled screening

Group	Elective*	Emergency	Total (%)
Scanned (n=12 203)	20	2	22 (0.2)
Not scanned (n=8 297)	198	29	227 (2.7)
Total invited (n=19 352)	218	31	249 (1.3)
Control (n=19 352)	191	33	224 (1.2)

*Includes emergency symptomatic cases.

Participation in screening and prevalence of abdominal aortic aneurysm

There was no difference between the numbers of men in the two groups who had had surgery for abdominal aortic aneurysm before scheduled screening (table 1, P = 0.47, χ^2 test). Within the men invited for screening, the prevalence of previous surgery for abdominal aortic aneurysm was highest among those who did not attend (2.7%). Similar numbers of men in the two groups died between randomisation and scheduled screening, including 25 deaths from rupture (13 in invited group, 12 in control group). After correcting the lists for deaths, we sent letters of invitation to 19 352 men. Of these, 12 213 underwent a screening examination, a crude response fraction of 63.1%. If we excluded 1836 men who would generally be considered ineligible this figure increased to 70% (fig 1).

The overall crude prevalence of any aortic aneurysms (aorta ≥ 30 mm) was 7.2%, increasing from 4.8% in men aged 65-69 years to 10.8% in the oldest men. Of the 875 cases detected, 699 (80%) aortas were 30-44 mm in diameter, 115 (13%) were 45-54 mm in diameter, and 61 (7%) were ≥ 55 mm in diameter.[17]

Procedures and deaths after scheduled screening

Table 2 shows the numbers of procedures for and deaths from abdominal aortic aneurysm after scheduled screening. Table 3 shows the corresponding numbers of events that occurred between randomisation and the end of follow up. The overall mortality within 30 days was 4.3% (7/161) after elective surgery and 24% (4/17) after surgery for ruptured aneurysms (table 2), with no difference between study groups (P = 0.59, χ^2 test). Twice

Fig 2 Cumulative mortality due to abdominal aortic aneurysm after date of screening
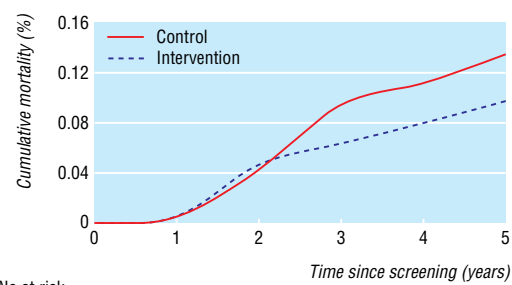
No at risk						
Control	19 352	19 243	18 777	18 011	17 242	16 429
Invited	19 352	19 106	18 610	18 061	17 444	16 851

as many men in the intervention group underwent elective surgery for abdominal aortic aneurysm compared with the number in the control group (107 v 54, P = 0.002, χ^2 test).

Between scheduled screening and the end of follow up 18 men died from abdominal aortic aneurysm in the intervention group and 25 in the control group (table 2), yielding a mortality rate ratio of 0.61 (95% confidence interval 0.33 to 1.11). The age standardised mortality for those who actually attended screening was 60% lower than in the control group (7.48 v 18.91 deaths per 100 000 man years, table 2). Between randomisation and the end of follow up there were 31 deaths from abdominal aortic aneurysm in the intervention group and 37 in the control group, yielding a mortality rate ratio of 0.85 (0.53 to 1.36, table 3). Figures 2 and 3 show the cumulative mortality from abdominal aortic aneurysm. Men in the intervention group initially had a higher mortality, but after one year the mortality curves crossed, such that the difference between them was not significant.

Table 4 summarises the mortality from abdominal aortic aneurysm in men aged 65-74 years and ≥ 75 years. There were no deaths among men aged 65-74 years who underwent screening and only two deaths (after scheduled screening) among those who were invited but did not attend compared with 10 in the

Table 2 Elective and emergency procedures and crude and age standardised mortality from abdominal aortic aneurysm between scheduled screening and the end of follow up

	Elective		Emergency					
	Operation	Postoperative death (%)	All ruptures	Operation	Postoperative death	Fatal rupture without surgery	Total deaths (%)	Age standardised mortality* (95% CI)
Intervention group								
Scanned (n=12 203)	86	4 (4.7)	3	0	0	3	7 (0.06)	7.48 (1.91 to 13.05)
Not scanned (n=7 149)	21	0	30	9	1	10	11 (0.15)	18.27 (7.08 to 29.46)
Total invited (n=19 352)	107	4 (3.7)	33	9	1	13	18 (0.09)	11.51 (6.16 to 16.86)
Control group								
Total (n=19 352)	54	3 (5.6)	38	8	3	19	25 (0.13)	18.91 (10.97 to 26.85)

*Age standardised per 100 000 in strata of one year to age structure of Western Australian male population aged 65-83 years.

Table 3 Elective and emergency procedures, deaths, and crude and age standardised mortality from abdominal aortic aneurysm between randomisation and the end of follow up

	Elective		Emergency					
	Operation	Postoperative death (%)	All ruptures	Operation	Postoperative death	Fatal rupture without surgery	Total deaths (%)	Age standardised mortality* (95% CI)
Intervention group								
Scanned (n=12 203)	86	4 (4.7)	3	0	0	3	7 (0.06)	7.48 (1.91 to 13.05)
Not scanned (n=8 297)	26	1 (3.9)	35	11	2	21	24 (0.29)	46.56 (24.7 to 68.4)
Total invited (n=20 500)	112	5 (4.5)	38	11	2	24	31 (0.15)	23.55 (13.79 to 33.31)
Control group								
Total (n=20 500)	60	4 (6.7)	41	10	5	28	37 (0.18)	27.83 (16.89 to 38.77)

*Age standardised per 100 000 in strata of one year to age structure of Western Australian male population aged 65-83 years.
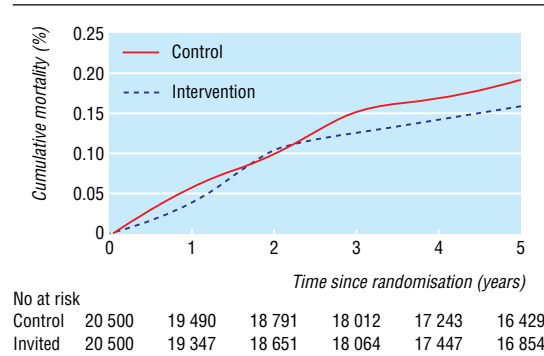
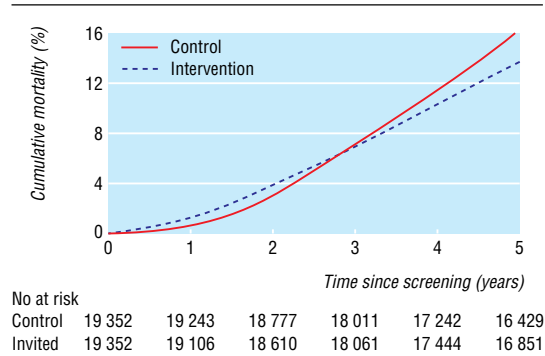**Fig 3** Cumulative mortality due to abdominal aortic aneurysm after date of randomisation

Fig 4 Cumulative all cause mortality after date of screening

control group, an odds ratio of 0.19 (0.04 to 0.89, P=0.01). When we included deaths between randomisation and scheduled screening, however, we found no benefit in the younger age group (odds ratio 0.82, 0.37 to 1.84, P=0.6).

Table 5 and figures 4 and 5 show the cumulative and age standardised all cause mortality. There is clear evidence of response bias among men who took up the invitation to be screened; their mortality experience was close to half that of invited men who did not undergo a scan. Overall, however, there were no meaningful differences in the age standardised mortality rates for all causes for the invited and control groups.

Discussion

The main conclusion from our population based randomised controlled trial of ultrasound screening for abdominal aortic aneurysm in Western Australia is that associated mortality for men aged 65-83 years is not significantly reduced by a screening programme. Although there was substantial benefit for the men who attended for screening, the overall benefit was reduced by

deaths among men who did not attend. The multicentre aneurysm screening study (MASS) has already provided convincing evidence that screening men aged 65-74 years has the potential to reduce the mortality.[15] In light of these findings, a target group aged 65-74 years may have been more suitable for our study. Indeed, subgroup analysis indicated that this group benefited the most from screening. For several reasons, however, we had to include 13 688 (33.4%) men aged 75-83 years. These men cannot be excluded post hoc and our primary intention to treat analysis included all randomised men aged 65-83 years.

Method of recruitment

In addition to the differences in target age range, our trial and the multicentre study used quite different methods of recruitment (electoral roll and general practice lists). As systematic screening is often based on centralised population databases rather than general practice lists, our trial is probably more representative of what would occur in many countries if screening were to be introduced. Because we used a centralised database, however, we could not exclude various categories of "ineligible" men before randomisation (fig 1). Thus we included men who

Table 4 Cumulative mortality from abdominal aortic aneurysm in men aged 64-75 years and ≥75 years

	65-74 years		≥75 years	
	No of men (person years)	Deaths	No of men (person years)	Deaths
From randomisation				
Intervention group:				
Scanned	8 641 (30 462)	0	3 562 (13 011)	7
Not scanned	5 200 (17 876)	11	3 097 (10 746)	13
Total invited	13 841 (48 338)	11	6 659 (23 757)	20
Control group	13 464 (46 912)	13	7 036 (25 046)	24
Odds ratio (95% CI)	0.82 (0.37 to 1.84)		0.88 (0.49 to 1.6)	
From scheduled screening				
Intervention group:				
Scanned	8 641 (30 462)	0	3 562 (13 011)	7
Not scanned	4 657 (16 104)	2	2 492 (8 743)	9
Total invited	13 298 (46 566)	2	6 054 (21 754)	16
Control group	12 938 (45 177)	10	6 414 (22 949)	15
Odds ratio (95% CI)	0.19 (0.04 to 0.89)		1.13 (0.56 to 2.29)	

Table 5 Cumulative and age standardised all cause mortality over five years after real or virtual date of screening

Subgroup of men	No of men	Person years	Cumulative deaths (%)	Age standardised mortality* (95% CI)
Scanned	12 203	43 473	1071 (8.8)	1501 (1377 to 1625)
Not scanned	7 149	24 847	1161 (16.2)	2885 (2691 to 3079)
Total invited	19 352	68 320	2232 (11.5)	1976 (1945 to 2117)
Control	19 352	68 126	2571 (13.3)	2020 (1948 to 2092)
Non-randomised men	8 801	29 067	1166 (13.2)	2238 (2075 to 2401)
Overall total	47 505	165 513	5949 (12.5)	2112 (2041 to 2184)

*Age standardised per 100 000 in strata of one year to age structure of Western Australian male population aged 65-83 years.
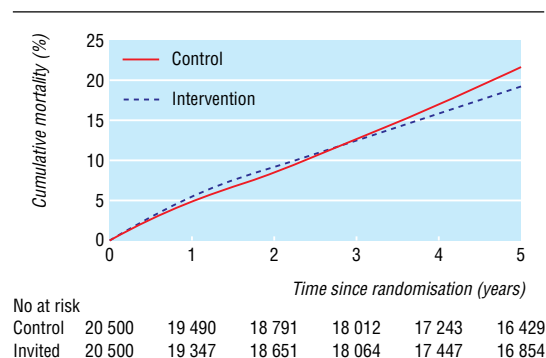
Fig 5 Cumulative all cause mortality from date of randomisation

were not randomised into the multicentre study (through being too old, too ill, or resident in a nursing home). The exclusion of such men optimises the effectiveness of screening by increasing the level of participation. It also removes a group with a relatively high incidence of ruptured abdominal aortic aneurysm. When we applied the criteria for eligibility used in the multicentre study to our study, the response fraction is about 70%. Although attendance fell with increasing age,[17] the lower response seen in our trial was not simply due to inclusion of older men; attendance in men aged 65-74 years was 74% compared with the 80% achieved in the multicentre study.[15] It is possible that men are more likely to participate if they are invited by their general practitioner rather than a research group.

The mortality from abdominal aortic aneurysm was high in the group of men who were invited but did not attend for screening (table 2). The multicentre study investigators were able to minimise the size of this group by exclusion before randomisation. Strict criteria for considering an individual as "ineligible for screening" may be easier for a general practitioner to apply in the setting of a randomised controlled trial than in real life. A proportion of patients with "other serious health problems" (an exclusion criterion in the multicentre study) will die from ruptured abdominal aortic aneurysm and may have benefited from elective surgery—especially if stenting proves to be more suitable than open repair in high risk cases.

Low mortality from abdominal aortic aneurysm in the control group

Although our sample size calculation was based on published rates of mortality in Western Australia,[3] mortality from abdominal aortic aneurysm in our control group was lower than expected (37 v 55 deaths). It was also lower than that seen in the multicentre study. The crude cumulative all cause mortality in the control group at four years was similar (12%) in both studies. In contrast, the crude cumulative mortality from abdominal aortic aneurysm in the control group was 0.33% in the multicentre study and, despite inclusion of older men, only 0.11% in our study. Contamination of our control group through ad hoc screening during the trial period may have resulted in the diagnosis and successful treatment of some abdominal aortic aneurysm in this group. More notably, however, linkage to hospital morbidity records showed that a surprisingly large proportion (1%) of all randomised men had already had elective surgery for an abdominal aortic aneurysm (table 1). This is substantially greater than in the multicentre study, where the prevalence of survivors of surgery for abdominal aortic aneurysm seemed to be 0.26%. The high frequency of previous surgery in Western Australia may be due to a higher incidence of abdominal aortic aneurysm or greater rates of diagnosis and treatment before screening.

What is already known on this topic

A screening programme for 65-74 year old men identified as eligible by their general practitioners reduces mortality from abdominal aortic aneurysm.

Such a screening programme is likely to be cost effective.

What this study adds

A screening programme for all 65-83 year old men does not reduce mortality from abdominal aortic aneurysm.

Men aged 65-74 years may benefit from screening provided there are no deaths between recruitment and actual screening

A high background rate of diagnosis and successful treatment may reduce the magnitude of benefit

In men aged 65-83 years less than 1% of all deaths are due to abdominal aortic aneurysm

While the overall prevalence of any aneurysm (aortic diameter ≥30 mm) was higher in our study than in the multicentre study (7.2% v 4.9%), the proportion of the largest aortas (≥55 mm in diameter) in Western Australia was almost half that seen in the multicentre study (7% v 12%). As the prevalence of large aortas increases with age, this difference is even more remarkable considering the greater age of our cohort. We can only speculate about the reasons for these differences. One possibility is the longstanding and easy availability of imaging (ultrasound and computed tomography) to general practitioners in Australia. This may have resulted in a relatively high level of incidental detection and treatment of large aortas over the past two decades. This aspect of a healthcare system needs to be taken into account when screening for abdominal aortic aneurysm is considered.

Deaths between randomisation and screening

In our trial, all men were randomised at the beginning of the screening period and inevitably there were deaths from abdominal aortic aneurysm between randomisation and the date of screening. These deaths were not included in our primary analysis and they did not occur in the multicentre study as randomisation was undertaken as the trial progressed. In an ideal world there should be no delay between becoming eligible for screening and actual screening, although in practice this may be a problem.

The chief reasons for our overall result seem to be our failure to identify and exclude men who were unlikely to attend and may have been ineligible for surgery had they attended and a high background level of detection and treatment of abdominal aortic aneurysms in the study community. The success of screening will depend on choosing the best target age group (probably men aged 65-74 years), excluding ineligible men, and minimising delay between becoming eligible for screening and actual screening. It is also important to assess the current rate of elective surgery as in some communities this may already approach a level that reduces the potential benefit of population based screening.

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Education and debate

> **Summary points**
>
> Composite end points are outcomes that capture the number of patients experiencing one or more of several adverse events
>
> The validity of composite end points depends on similarity in patient importance, treatment effect, and number of events across the components
>
> When large variations exist between components the composite end point should be abandoned

infarction with subsequent disability far more important than a short admission for acute coronary syndrome with rapid return to previous function.

The answers to the other two questions are also negative. Hospital admissions occurred far more frequently than the two more important events (table). Biological rationale fails to support a presumption that the invasive strategy will have similar effects on all three end points. Indeed, the investigators explicitly state that they expect an increase in short term deaths with surgery, while achieving benefits in terms of decreased angina and associated hospital admissions. The trend toward increased deaths, with a large reduction in admissions, with the invasive strategy provides support for this hypothesis. The composite end point thus fails all three criteria and provides little useful information for clinical decision making.

Conclusions

The widespread use of composite end points reflects their elegant simplicity as a solution to the problem of declining event rates. Unfortunately, use of composite end points makes the interpretation of the results of randomised trials for clinical decision making challenging. Investigators and their sponsors may claim treatment effects over a broad range of outcomes, whereas the effect may in fact be limited to one component. Occasionally, composite end points prove useful and informative for clinical decision making. Often, they do not. These users' guides will help clinicians differentiate between these situations.

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> **Corrections and clarifications**
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> *Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm*
> Tables 2 and 3 of both the abridged and the full versions of this paper by Paul E Norman and colleagues contain some incorrect values (*BMJ* 2004;329:1259-62). In table 2, for the emergency procedures the "all ruptures" values are 19 and 22 for the "not scanned" and "total invited" groups respectively and 27 in the control group; in table 3, the corresponding values are 32, 35, and 38. The authors state, however, that this amendment does not alter their analyses or conclusions.
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> *Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies*
> In our haste to correct this paper by Etminan and colleagues (*BMJ* 2005;330:63-5, 8 Jan), some of the authors' late corrections were not carried out properly—either at proof stage of the abridged print version or in the correction that we subsequently published on the web relating to the full version only. In the abridged version, the relative risk for migraine with aura in table 2 should be 2.88 (not 2.28); in table 1, the upper confidence limit for migraine with aura for Schwaag should be 3.53 (not 3.35), and the cases:controls for the Collaborative Group should be 430:151 (not 430:451). In the results section of the full version, the references for the data on migraine with and without aura are numbers 2, 3, 12-14, 17-19; in table 1, the cases:controls with migraine is 26:26 for Donaghy (not for Chang as stated in the previous correction).
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> *Minerva*
> The eighth Minerva item (about a study published in *Neurology*) in the issue of 22 January (*BMJ* 2005;330:204) may have misled readers by including as its first sentence: "Survival in patients with Parkinson's disease is less than in the general population." This statement applies generally and is contradictory to the actual finding of the study, which is presented in the rest of the item. We should and could have made it clearer that the first statement was intended, as in most Minerva items, as background.