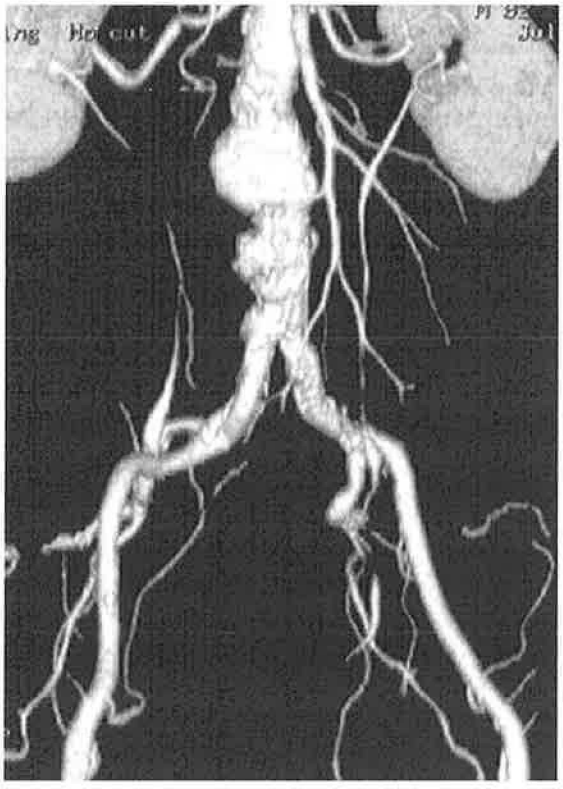
Dodging the Sniper: Screening for Abdominal Aortic Aneurysms



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Dodging the Sniper: Screening for Abdominal Aortic Aneurysms

Introduction

The abdominal aortic aneurysm (AAA) is one of several diseases that have been called "snipers" because they are clinically furtive. The term refers to the characteristic of these illnesses of often eluding detection even after death.[1] Other sniper diseases include hereditary hemochromatosis, pulmonary embolism, pheochromocytoma and suicide in the elderly. All affect substantial proportions of undiagnosed individuals.

Our understanding of disease prevalence is distorted when death by sniper is ascribed to the wrong illness. This, in turn, affects our assessment of whether a disease is common enough to warrant routine screening. Approximately 9,000 deaths in the United States every year are attributed to ruptured AAA.[2] However, there is undoubtedly more to this iceberg than its tip. Because AAA is known to be well represented among the 300,000 who die from sudden death without receiving medical care, it is believed that the true annual death rate from AAA rupture may be as high as 30,000. This compares with the annual mortality for prostate cancer (32,000) and breast cancer (42,000).[3] A likely undiagnosed reservoir of AAA is confirmed by the technique of "epidemiologic necropsy," which measures the necropsy detection rate of unsuspected AAA .[4] These estimates are consistent with more recent population-based studies.

An AAA is defined by an aortic diameter more than 1.5 times the diameter at the renal arteries. Since the normal diameter of the abdominal aorta is about 2.0 cm, a diameter of 3.0 cm or more is considered an aneurysm in most studies.

The U.S. Preventive Services Task Force uses a rigorous "Generic analytic framework" to determine the advisability of population screening (Figure 1).[5]

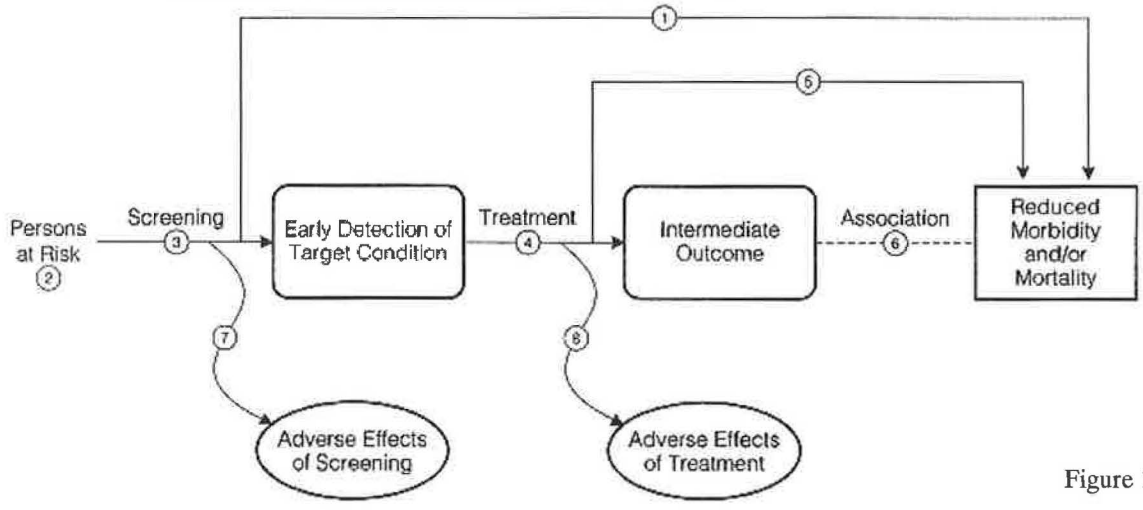


Figure 1

The most recent, second edition of the *Guide to Clinical Preventive Services*, published in 1996, applies this methodology to an extensive review of the available literature and concludes: "There

is insufficient evidence to recommend for or against routine screening of asymptomatic adults for abdominal aortic aneurysm with abdominal palpation or ultrasound."[6] The Task Force does offer an amendment to their general recommendation: "Although direct evidence that screening for AAA reduces mortality or morbidity is not available in any population, clinicians may decide to screen selected high-risk patients, due to the significant burden of disease and the availability of effective surgical treatment for large aneurysms."

Since the *Guide's* publication several large randomized trials and observational studies have been published, providing the outcomes data that the Task Force found lacking in 1996. Applying the Task Force "analytic framework" to these data suggests that high-risk patients would benefit from wider use of screening in clinical practice. Further, a compelling case can now be made for selective population-based screening for AAA.

Modified Analytic Framework

A modified version of the series of questions that constitute the U.S. Preventive Services Task Force criteria, adapted for application to AAA screening, is suggested:

1. What is the prevalence of disease in the target group? Can a high-risk group be reliably identified? What is the magnitude of morbidity and mortality caused by the disease ("burden of suffering")?
2. What is the efficacy of the screening test?
3. What is the effectiveness of early detection?
4. Does screening have adverse effects?
5. What is the cost and cost-effectiveness of screening?
6. What is the effectiveness of treatment?

1. What is the prevalence of disease in the target group? Can a high-risk group be reliably identified? What is the magnitude of morbidity and mortality caused by the disease ("burden of suffering")?

Abdominal aortic aneurysms are found in 4% to 8% of older men, usually remain asymptomatic for 5 to 10 years, and cause death from rupture in about one third if not treated.[7-10] The diameter of small AAAs enlarges 0.2 to 0.3 centimeters yearly and rarely rupture before reaching 6.0 centimeters.[11, 12] Elective repair at a high-volume center has a mortality of less than 4% to 6%. After rupture, approximately 80% of patients die before reaching the hospital or after emergency surgery. While AAAs are usually asymptomatic, patients may present with abdominal pain, back pain, aortic tenderness to palpation or intermittent claudication.

Detailed information on AAA prevalence and associated risk factors come from the Department of Veterans Affairs (VA) Aneurysm Detection and Management (ADAM) study. ADAM included a cross-sectional screening study of 122,272 men and 3,450 women between the ages of

50 and 79 at 16 VA medical centers. The study identified AAAs of 3.0 cm or larger in 4.3% of men and 1.0% of women ($P < .001$).[8, 13, 14]

Screening initiatives are aimed at sub-populations most likely to benefit from improved outcomes in order to enhance cost-effectiveness and to minimize inconvenience and risk to individuals not likely to have the disease. A number of studies over many years have consistently found AAA to be associated with the male sex, older age, history of smoking cigarettes and atherosclerotic disease. Family history of AAA is a significant risk factor.[8-10, 13-16] Some studies have suggested an important association with hypertension and with chronic obstructive pulmonary disease, but more recent investigations have found these to be less significant.

In ADAM, men were between three and six times more likely to have an AAA than women. Women were one fourth as likely to have an AAA of 3.0 cm or larger and one tenth as likely to have an AAA of at least 4.0 cm. Even after adjusting for other risk factors and covariates such as height and weight, men are still more than twice as likely to have AAA. The association of age, smoking and family history of AAA is similar in women and men. Several smaller studies have identified a stronger association between AAA and cerebral vascular disease in women than in men. This relationship was noted in ADAM, but was not statistically significant.

The age of 65 years has been suggested as the optimal time for AAA screening. More than 95% of deaths from ruptured AAA occur in individuals older than 65.[17] Population screening studies generally exclude those older than 80 years. Furthermore, a normal ultrasound at age 65 virtually excludes later death from ruptured AAA. A cohort study of 223 65 year old men in Gloucestershire, England who had an abdominal aorta of less than 26 mm diameter had repeat ultrasonography in 1993 and again in 2000. During the two intervals between the scans, a total of 8 men were lost to follow-up and 86 died. None of the deaths were attributed to ruptured AAAs. Also, there was no clinically significant increase in mean aortic diameter during the 12 years (Figure 2).[18]

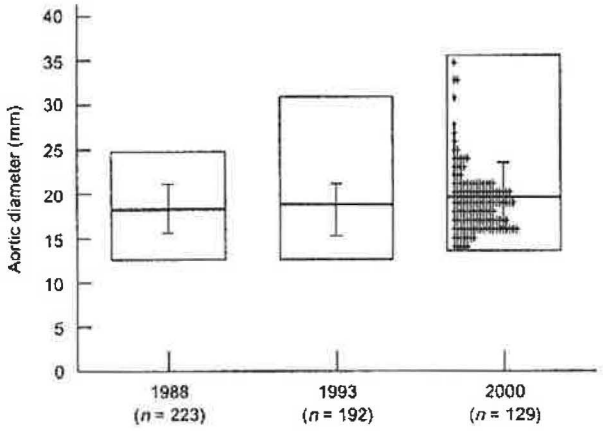


Figure 2

In a study in Chichester, England a group of 649 men with an aortic diameter of less than 3 cm on ultrasound were rescreened at two-year intervals. Twenty-seven new AAAs were detected (Table 1).[17]

Table 1

	Initial scan	Repeat scans of "normals"					Total
	Age 65	Age 67	Age 69	Age 71	Age 73	Age 75	New AAA
AAA detected	32	11	7	6	3	0	27
No. men in sample	681	559	469	383	166	54	
Prevalence	4.7%	2.0%	1.5%	1.6%	1.8%	0.0%	
Cumulative prevalence	4.7%	6.3%	7.3%	8.2%	8.7%	8.7%	

However, all of these new AAAs measured less than 4 cm. A larger group of 2691 men with normal scans at age 65 were followed up for 10 years and causes of death were ascertained. Only two of these men died from ruptured AAA (cause-specific mortality rate 0.07%, 95% confidence interval [CI] 0.02-0.30).

Smoking is by far the most important controllable risk factor for development of AAAs and death from ruptured AAA.[8, 14] It appears to be the only variable besides age and sex that is useful for determining a higher prevalence target population for AAA screening (Table 2).[8]

Table 2: Multivariable Models of Associated Factors for Abdominal Aortic Aneurysm of at Least 4.0 cm in Diameter vs Normal Infrarenal Aortic Diameter

	Odds Ratios (95% Confidence Intervals)		
Factors	First Cohort (985/66,638)†	Second Cohort (583/47,781)†	Combined Group (1568/114,419)†
Age (per 7 y‡)	1.65 (1.53-1.78)	1.81 (1.65-1.99)	1.71 (1.61-1.82)
Female sex	0.22 (0.07-0.68)	0.12 (0.02-0.88)	0.18 (0.07-0.48)
Black race (vs white)	0.49 (0.35-0.69)	0.59 (0.39-0.91)	0.53 (0.40-0.69)
Other race (vs white)	0.91 (0.63-1.33)	1.19 (0.79-1.79)	1.02 (0.77-1.35)
Height (per 7 cm‡)	1.21 (1.12-1.30)	1.17 (1.06-1.28)	1.19 (1.12-1.26)
Weight (per 16 kg‡)	1.08 (0.95-1.23)	1.01 (0.86-1.19)	1.06 (0.96-1.17)
Waist circumference (per 11 cm‡)	1.15 (1.03-1.29)	1.19 (1.03-1.38)	1.16 (1.07-1.27)
Family history of AAA	1.95 (1.56-2.43)	1.94 (1.45-2.59)	1.94 (1.63-2.32)
Ever smoked regularly§	5.57 (4.24-7.31)	4.45 (3.27-6.05)	5.07 (4.13-6.21)
Hypertension	1.16 (1.01-1.32)	1.14 (0.96-1.36)	1.15 (1.03-1.28)
High cholesterol level	1.54 (1.31-1.80)	1.29 (1.06-1.58)	1.44 (1.27-1.63)
Coronary artery disease	1.62 (1.41-1.84)	1.36 (1.14-1.62)‖	1.52 (1.37-1.68)
Claudication	0.96 (0.74-1.25)	1.26 (0.88-1.80)	1.05 (0.85-1.30)
Cerebral vascular disease	1.19 (0.99-1.42)	1.45 (1.15-1.84)	1.28 (1.11-1.47)
Any atherosclerosis¶	1.68 (1.47-1.92)	1.60 (1.35-1.90)	1.66 (1.49-1.84)
Deep venous thrombosis	0.67 (0.50-0.88)	0.67 (0.46-0.99)	0.67 (0.53-0.84)
Diabetes mellitus	0.54 (0.44-0.65)	0.50 (0.39-0.65)	0.52 (0.45-0.61)
Chronic obstructive pulmonary disease	1.26 (1.09-1.50)	1.08 (0.86-1.36)	1.21 (1.06-1.38)
Nonskin cancer	0.90 (0.74-1.09)	0.64 (0.48-0.84)‖	0.80 (0.68-0.93)
Abdominal imaging in past 5 y	0.80 (0.67-0.94)	0.73 (0.57-0.93)	0.77 (0.67-0.89)
Second cohort (vs first)	...	...	0.86 (0.77-0.95)

Normal infrarenal aortic diameter is defined as less than 3.0 cm. AAA indicates abdominal aortic aneurysm; ellipses, not applicable.
†Numbers in parentheses represent number of cases/controls.
‡Approximately 1 SD.
§More than 100 cigarettes during lifetime.
‖The association differed significantly between cohorts (P<.05 for interaction with second-cohort term).
¶From a separate logistic model in which coronary artery disease, cerebral vascular disease, and claudication were combined into a single variable.

Screening is three to five times more likely to detect AAA in smokers and accounted for 75% of AAAs greater than 4.0 cm in ADAM. Men who have never smoked have a low prevalence of AAAs this size, between 0.2% and 0.8%, depending on age[14] (Figure 3).[19] The prevalence of AAAs 3.0 cm or greater is approximately the same in men who never smoked (1.6%) and women who have ever smoked (1.5%)

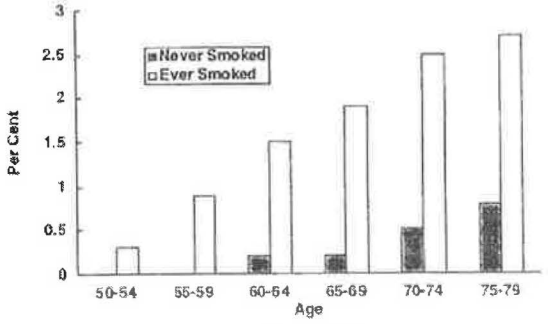


Figure 3

Many other studies have confirmed the importance of smoking as an independent risk factor for AAA, although there is some controversy about the relative effect of level of exposure versus duration. The Chichester study found level of exposure to be more important.[20] On the other hand, a case-control study found the duration of exposure rather than the level of exposure to be the most important risk factor for AAA.[21] Both studies found a very gradual decline in risk of AAA after smoking cessation. This slow decline, along with the finding that smokers have a higher relative risk for small (> 2.9 and < 4.0 cm) rather than large ($\geq$ 4 cm) aneurysms, led the authors of the case-control study to suggest that smoking may be an initiating event for AAAs.

History of atherosclerosis is associated with detection of AAA at screening. A prospective cohort study of 8,006 men was published in an article in *Circulation* in 1992 entitled, "Are Aortic Aneurysms Caused by Atherosclerosis?" This study answered the question in the affirmative, concluding "...the risk factors for aortic atherosclerosis and probably atherosclerosis itself are necessary elements in the causal pathway for the great majority of aortic aneurysms..."[22] Statistically combining coronary artery disease, cerebral vascular disease and claudication into a single classification variable, ADAM found an odds ratio of 1.66 (CI 1.49-1.84) }(Table above).[8] The long-term population-based Chicago Heart Association (CHA) study of 10,574 men and 8,700 women also found a statistically significant association with coronary artery disease, cerebrovascular disease and peripheral artery disease.[23]

A number of studies have found an inconsistent relationship with serum cholesterol level. ADAM found an odds ratio of 1.44 (95% confidence interval 1.27-1.63), a weaker association than those previously mentioned. The CHA study did find an association with baseline serum cholesterol level (proportional hazard ratio 1.39, $p<0.001$). However, a case-control study from Winnipeg, Canada found no association with levels of total cholesterol, LDL cholesterol or HDL cholesterol. Other studies have not found serum cholesterol levels to be associated with rapid expansion in the size of AAAs[24-27] or with increased risk of AAA rupture.[28] The relative weakness of this association is consistent with current understanding of the different pathophysiology of aneurysmal, as opposed to occlusive vascular, disease.

The association with hypertension is also somewhat equivocal. ADAM found a relatively weak relationship. Other studies have variously found an association with both diastolic and systolic blood pressure,[23] just diastolic blood pressure,[20, 29] or neither diastolic nor systolic blood pressure.[27] Also, studies have not found a significant effect of hypertension on the growth rate of existing aneurysms.[20, 24-26]

The relationship between diabetes and AAA also tends to support an underlying pathogenesis that may fundamentally differ from occlusive vascular disease. Several studies have identified an inverse association between diabetes mellitus and AAA (Table above).[8, 14, 29] In vascular smooth muscle, elastin is the main load-bearing structural protein and collagen functions as a "safety net." AAAs form when this architecture is weakened. Elastin has a half-life of 70 years and is not synthesized in the adult aorta, presumably explaining the predominance of AAAs in older individuals.[30] Aneurysm expansion is associated with proteolysis and inflammation. Metalloproteases are believed to be particularly important in aneurysm formation.[31]

African American race has also been found to inversely associated with AAA.[8]

Finally, individuals with a family history of AAA are at increased risk for having AAA themselves. An Australian study compared the incidence of AAA among 1,254 siblings of 400 index AAA patients with an age- and sex-matched control group recruited from patients having abdominal CT scans for non-vascular diagnoses. Overall, 25% of siblings had AAAs, with a higher rate observed among male siblings.[32] This led the authors to advise ultrasound screening for all siblings of AAA patients and to also consider screening their children when they reach age 50 or 60. A systematic review of the published literature found studies suggesting a 12-19% chance of AAA patients having one or more first-degree relatives with an aneurysm.[33] The authors suggest that pattern of inheritance is likely autosomal dominant with incomplete penetrance.

An understanding of these risk factors should inform the clinician's vigilance for AAAs. However, the question remains: can these factors be used to select a target population that minimizes the expense of screening large numbers of individuals without missing the detection of AAA in a significant number of individuals? This question is especially important when formulating public health policy. The answer seems to be that using factors other than age, sex, smoking (history of having ever smoked) to target screening is probably not worthwhile.[34] One study found that excluding normotensive patients who stopped smoking for more than ten years reduced the number of individuals meeting screening criteria by 27% but would have missed 19% of AAAs.[35] The screening requirement for the current cohort of men over the age of 65 would not be greatly reduced by using smoking history, since only 34% of them in the United States have never smoked.[36]

2. What is the efficacy of the screening test?

Although several modalities are available,[37, 38] ultrasonography is the screening technique of choice (Table 3).[38]

Table 3: Comparison of Available Imaging Modalities

Imaging modality	*Advantages*	*Disadvantages*
Ultrasonography	Lower cost Widely available	Suboptimal in obese patients Suboptimal in patients with increased bowel gas
	Noninvasive	Increased interobserver variation
Aortography	Visualize renovascular disease Identifies anomalous vessels	Invasive Higher cost
	Aids placement of endovascular stent grafts	Increased patient morbidity Underestimates aneurysm size Exposure to iodinated contrast
MRI	Noninvasive Lack of ionizing radiation	Higher cost Motion artifact Contraindications with metal clips and pacemakers Patient claustrophobia Availability of scanner and software

CT	Noninvasive	Use of ionizing radiation
	Highly predictive of aneurysm size	Higher cost compared with ultrasonography
	Localize proximal extent of aneurysm Identify other abdominal pathology Procedure of choice for suspected rupture	Limited information regarding arterial anatomy
Helical CT and CTA	Noninvasive	Higher cost
	Faster scanning time	Lack of availability of scanner and software
	Use in conjunction with endovascular stent grafts	Use of ionizing radiation

MRI = magnetic resonance imaging; CT = computed tomography; CTA = computed tomographic angiography.

The advantages of ultrasonography include wide availability, noninvasive technology without radiation exposure, low cost and high degree of accuracy. The sensitivity, specificity and positive and negative predictive value of ultrasonography are nearly 100%.[39] All randomized trials of screening for AAA have used ultrasonography. Computed tomography, magnetic resonance imaging and angiography are generally used to determine surgical technique rather than for screening. While a high degree of precision is possible in measuring AAAs, variations of up to 0.5 cm are not uncommon and must be considered in managing patients.[37]

A "quick-screen" hand-held ultrasound technology is now available to screen for AAAs. This approach typically takes four or five minutes (versus 24 minutes for a conventional duplex ultrasound).[40] Using duplex ultrasound as the reference, the sensitivity of the hand-held device in detecting AAAs is 93%; specificity is 97%; positive predictive value is 89%; negative predictive value is 98%. The diagnostic accuracy of the portable device is 98% when compared with conventional ultrasonography.[41]

In the hands of an experienced professional, ultrasound is a highly reliable technology. As it happens, it is also highly reliable in the hands of a not-so-experienced professional. In an intriguing study, internal medicine residents quickly learned to use a hand-held device to obtain images of the abdominal aorta.[42] The training program consisted of a 20-minute videotape, a one-hour seminar on ultrasonography and AAAs, and a one-hour hands-on training session. All training was accommodated within the scheduled time for the residents' clinic. Ten of 16 residents attained the highest skill level; an average of 3.4 ultrasound exams per resident were required to reach that level. Counting all ultrasound exams (not just those by residents who reached the highest level of competence), no AAAs were missed (Table 4).[42]

Table 4

Resident positive, vascular lab positive 4	Resident positive, vascular lab negative 0
Resident negative, vascular lab positive 0	Resident negative, vascular lab negative 75

The equipment used in the study cost $50,000 to $100,000, but was later replaced with equipment that produced much better images, was more portable and easier to use, and cost $15,000.

Screening by Physical Examination

The oldest screening test for AAA is the abdominal examination (see Appendix A: Abdominal Palpation for Abdominal Aortic Aneurysm). In a study of the accuracy of the abdominal exam, two internists blinded to each other's findings and to the ultrasound results examined 200 subjects, 99 with and 101 without AAA.[43] The overall accuracy of palpation to detect AAA was: sensitivity 68% (CI 60%-76%); specificity 75% (CI 68%-82%); positive likelihood ratio 2.7 (CI 2.0-3.6); negative likelihood ratio 0.4 (CI 0.33-0.56). Factors independently associated with correct examination included AAA diameter (OR, 1.95 per centimeter increase; CI 1.06-3.58); abdominal girth (OR, 0.90 per cm increase; CI 0.87-0.94); and examiner's assessment that the abdomen was "not tight" (OR, 2.68; CI 1.17-6.13).

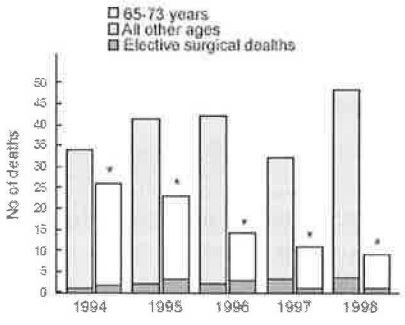
Lederle has reviewed 15 studies of patients who were screened with both ultrasound and abdominal exam.[44] He concludes that while abdominal palpation will detect most AAAs of sufficient size to suggest surgery, examination does not reliably exclude the diagnosis. This review points out that the pooled results of these studies finds a positive predictive value of 42%, meaning that less than half of high-risk patients, and fewer low-risk ones, found to be positive on palpation will actually have one.

Cost is always an issue when screening large numbers of individuals. A recent British study explores the use of physical examination to screen for AAA at what must be the lowest possible cost. Here, patients themselves were instructed in self-examination. Examinations by doctors, nurses, and patients were similar in both diagnosing and excluding AAA.[45]

3. What is the effectiveness of early detection?

The Preventive Services Task Force declined to endorse screening for AAA in 1996 because of inadequate evidence, particularly from controlled trials, demonstrating improved outcomes (reduced morbidity or mortality; improved quality of live) from screening. However, since publication of the Task Force report a number of studies have found screening to reduce mortality from ruptured AAA.

The first is an observational study of a cohort of men from the county of Gloucestershire, UK (total population 520,000). Men reaching the age of 65 between 1990 and 1998 were offered ultrasound examination at 96 of the county's 97 general practices. This cohort had a significant reduction in AAA related deaths when compared with men in all other age groups (Figure 4).[46] During the eight years after screening was initiated, the number of elective AAA operations grew steadily (especially among screened men) and the total number of AAA operations increased slightly.



Total number of aneurysm-related deaths in men in Gloucestershire, 1994-1998. *P<0.001

Figure 4

A second nonrandomized study reported a statistically significant decrease in AAA rupture among men invited for screening as compared with the period before being invited.[47] However, this study is considered

methodologically flawed because individuals who were not considered surgery candidates (and may have been more likely to have AAA rupture) were placed in the "before" group and because mortality from elective surgery was not included as an outcome.[36]

There have also been four randomized trials since the Guide to Clinical Preventive services last addressed the issue AAA screening. These studies originated in Chichester, UK;[10, 15, 16] Viborg, Denmark:[9] multiple centers in the UK (Multicentre Aneurysm Screening Study [MASS]);[7] and Western Australia.[48] They are summarized in a review by Lederle (Table 5).[36]

Table 5

Study (Reference)	Sex	Age	Group	Randomly Assigned Patients	Patients Who Attended Screening	Patients with AAA Detected	Elective Repairs
		y		*n*	%		*n*
Chichester	Men	65–80	Invited	3000	74	7.6	36
			Control	3058			17
	Women	65–80	Invited	4682	65	1.3	3
			Control	4660			2
Viborg	Men	65–73	Invited	6339	76	3.9	53
			Control	6319			14
MASS	Men	65–74	Invited	33 839	80	4.9	322
			Control	33 961			92
Australia	Men	65–83	Invited	19 583	62	7.2	113
			Control	19 583			59

* AAA = abdominal aortic aneurysm.

All trials noted a decline in mortality related to AAAs, from 21% to 68%; two of the four are statistically significant (Figure 5).[36] Together, they present the most compelling evidence so far that screening followed by elective repair in appropriately selected patients reduces AAA-related mortality.

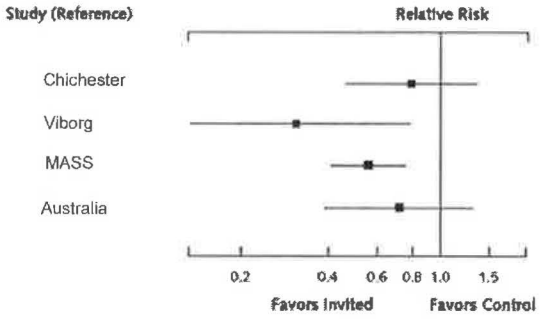


Figure 5

These studies report between five and ten years of follow-up. The methodologies of these trials are similar. Patients are randomly assigned to the group invited for screening by letter from their primary care physician or assigned to the control group. Analysis is by intention-to-treat, meaning that the experimental group consists of all invited patients, regardless of whether they are actually screened. Between 1.3% and 7.6% were found to have an AAA. As expected, elective repairs increased in the invited group in each study.

The Chichester trial has reported results at five years[16] and ten years[10] of follow-up. Patients with AAAs of 3.0-4.4 cm were rescanned annually; those with AAAs of 4.5-5.9 cm were rescanned every 3 months. Elective repair was considered for: an aortic diameter of $\geq$ 6 cm, an increase of $\geq$ 1 cm per year, or symptoms attributable to the aneurysm. There was a 41% reduction in AAA-related deaths among men at five years and a 21% reduction (relative risk 0.79; CI 0.53-1.40) at ten years, neither attaining statistical significance. The prevalence of AAA in women (1.3%) was one sixth that in men (7.6%) and at five and ten years was the same in screened and control groups.[15]

The hospital-based Viborg study found a 68% reduction in AAA-related mortality in the invited group (OR 0.31; CI 0.11-0.90; P<0.01). However, outcome ascertainment may be considered incomplete since data on outpatient mortality was not obtained.

The MASS study is the largest and most comprehensive randomized trial reported to date. Men in the invited group who had a normal aortic diameter (<3 cm) did not have repeat scans. Those with aortic diameters of 3.0 cm-4.4 cm had repeat ultrasounds yearly and those with diameters of 4.5 cm-5.4 cm were rescanned every 3 months. Referral to a vascular surgeon was advised for patients with an aortic diameter of 5.5 cm or greater, those with an aortic enlargement of 1 cm or more in one year, or those with symptoms attributed to their AAA. There was a 42% reduction in AAA-related mortality, with 65 deaths in the invited group and 113 in the control group, producing a hazard ratio of 0.58 (CI 0.42-0.78; p=0.0002) (Table 6).[7] The invitation for screening was accepted by 80% of the men. Among those who actually attended screening the risk reduction was 53% (CI 30-64).

Table 6	**Control Group** (n=33 961)	**Invited Group** (n=33 839)
Person–yrs of observation (1000)	132-6	132-3
Deaths within 30 days of elective surgery	9	15
Deaths from ruptured AAA	91	37
Deaths from ruptured AAA unspecified site	13	13
TOTAL AAA-Related deaths	113	65
Rate per 1000 person-yrs (95% Cl)	0-85-(0-71-1-02)	0-49 (0-39-0-63)
Hazard ratio (95% Cl)	1-00 (reference)	0-58 (0-42-0-78)

The reduced mortality reflects a decline in deaths from ruptured AAAs, offset by a small increase in deaths attributed to the surgery itself (those occurring within 30 days of elective surgery). Because elective surgery occurs sooner after randomization in the invited group, the reduced AAA-related mortality in the invited group is counted after the first year of follow-up, as noted (Figure 6).[7]

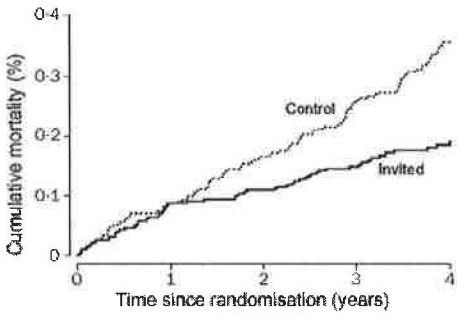


Figure 6

MASS is the only study so far to report all-cause mortality, and it was not statistically significant (proportional hazard ratio 0.97; CI, 0.93-1.02). This is not unexpected, since AAAs caused less than 3% of total mortality. It is generally considered impractical to conduct a randomized screening trial large enough to find a reduction in all-cause mortality. Even breast and colon cancer screening are not supported by randomized trials demonstrating a reduction in all-cause mortality.[36, 49]

The western Australia trial has not yet been published but is reported as an abstract from a presentation.[48] It is said to show a 28% reduction in AAA-related deaths but was not statistically significant.[36]

Repeat Screening

Repeat screening of individuals who do not have an AAA after age 65 has a very low yield and does not appear to be warranted. Several studies rescreened men at intervals of between four and 12 years.[17, 18, 50] They showed progression to aortic diameters of greater than 3.0 cm or larger at rates of between 2.2% and 4.2%, but nearly all were less than 4.0 cm and none were considered likely to be future candidates for elective surgery.

4. Does screening have adverse effects?

Screening affects many people with the expectation that only a few will benefit. Therefore, even a small adverse effect from the screening itself could outweigh the advantages. For example, individuals identified as having hypertension but found to be normal on repeat testing nevertheless had persistent symptoms of depression and a diminished state of general health.[51] Other studies find that false positive results in screening trials (for congenital hypothyroidism, breast cancer, and Down's syndrome) provoke high anxiety that does not quickly resolve when subsequent testing is negative.[52] It is true that negative screening results are reassuring to patients, more when they are given the result rather than told that "no news is good news."[51] There is also a concern about the "certificate of health effect" where, for example, "people who screen negative for cancer may feel safe continuing smoking, and those with low serum cholesterol eating their unhealthy diets."[52]

There are no known direct adverse health consequences of ultrasonography and false positives are not a significant problem in AAA screening. The effect of diagnosing a small AAA appears unsettled, with one study finding no difference in levels of anxiety and depression between the screened and control group,[53] but a more recent study finding permanent and progressive impairment of quality of life (as measured by a standardized questionnaire).[54]

The risk of unnecessary intervention in patients with small AAAs is an important issue. There is convincing evidence that there is no survival advantage of elective repair of AAAs smaller than 5.5 cm.[11, 12] However, patient anxiety as well as the interests of endovascular graft manufacturers, interventional radiologists, and vascular surgeons have been cited as factors encouraging repair of small AAAs.[36] Screening clearly has the potential to increase repairs of AAAs that would have never ruptured. This would be extremely unfortunate. While the mortality from AAA repair is low in the context of published randomized studies and at large centers, overall approximately 15% of AAA-related death is a consequence of elective intervention.[55, 56] Even the decision to operate on AAAs large than 5.5 cm can be difficult in this group of patients who tend to be elderly and often very ill.

5. What is the cost and cost-effectiveness of screening?

The current literature does not adequately assess the likely cost-effectiveness of mass screening for AAA in the United States. The few studies that have included cost data have been conducted in countries with a very different cost structure than the US such as Denmark[9] or the UK[57] where the cost of elective surgical AAA repair is less than $7,000 versus approximately $33,000 in this country. Other studies have assumed that AAAs of 4.0 cm or 5.0 cm would be repaired,[40, 58] while current data suggests repair at 5.5 cm. These studies have found cost-effectiveness ratios (CER) varying between $2,000 and $42,000 per life-year saved. This compares with CERs of $9,500 for coronary artery bypass graft surgery for left main disease and $16,000 for breast cancer screening with mammography; most generally accepted interventions have CERs below $60,000.[40]

Only 15% of the cost of AAA screening comes from the screening test, with the remainder attributed to treatment.[59] To the extent that screened patients are more likely to have elective intervention (average hospital cost $33,000) rather than emergency repair (average cost $126,000), some cost savings might be anticipated (Table 7).[60] However, it is not clear how population screening would affect the frequency of either procedure. A review of 20 years of data from the National Hospital Discharge Survey found no increase in elective AAA repairs or decrease in ruptured AAAs on a per capita basis despite the growing use of sophisticated imaging technologies during this time.[40]

Table 7: Average Hospital Cost per AAA

	Elective ($)	Ruptured ($)
Blood products	400.45	2,118.05
SICU days	11,960.00	55,380.00
SICU Medical supplies	92.40	4,132.20
SICU labs	1,352.40	6,262.20
Ward days	13,352.40	38,950.00
Ward supplies	108.10	321.03
Ward labs	434.70	1,291.50
OR cost	5,465.46	5,697.84
Return trips to OR/dialysis	0.00	12,152.30
Total	33,165.91	126,305.21

While cost-effectiveness in the general population remains an open question, the direct cost to our patients is a more immediate issue. Medicare and other major insurers do not pay for AAA screening. In response to a recent inquiry, the radiology department at the Aston Ambulatory Care Center will now offer a screening sonogram for AAA for $150.00 (CPT code 76775). The *Legs for Life* program, sponsored by the Society for Interventional Radiology, offers free screening clinics, usually during the month of September (www.legsforlife.org).

6. What is the effectiveness of treatment?

The usefulness of any screening program depends on effective treatment of patients whose screening test is positive. Management depends on the size of the AAA, with surgery reserved for AAAs greater than 5.5 cm.

Large AAAs

Individual referral centers report 30-day postoperative mortality rates of 1% to 5% for open elective surgical repair of AAAs.[61, 62] State and national population-based data indicate mortality rates of 4% to 8%.[55, 56] In the population series, mortality rates increased with age, cerebral vascular occlusive disease, preoperative renal insufficiency, multiple comorbidities, small hospital size and sex (female, 1.6 OR, CI 1.3-1.9).[55]

A less invasive option is endovascular aneurysm repair (EVAR), available since the early 1990s. The graft is introduced through the femoral or iliac artery and into the lumen of the aneurysm. Advantages of EVAR include shorter lengths of stay, less blood loss, quicker recovery, and fewer significant complications in the immediate postoperative period. However, it is not clear that there is a significant improvement in postoperative mortality, more careful follow-up is required, and the long-term durability of the grafts has not been established. A complication known as endoleak occurs in 10% to 20% of patients, where blood continues to flow into the aneurysm sac after graft placement. Some forms of endoleak are not threatening or heal spontaneously, while others require surgery, stent placement, or embolization, sometimes emergently. Some patients are precluded from EVAR due to technical considerations related to the anatomy of their aneurysm. Several randomized trials comparing EVAR with open repair are in progress.[61]

Not all patients with AAAs larger than 5.5 cm have them repaired. A prospective cohort study monitored 198 veterans for whom AAA repair was precluded by medical contraindication or patient refusal. The one year incidence of probable rupture varied by initial diameter: 9.4% for 5.5 cm to 5.9 cm; 10.2% for 6.0 cm to 6.9 cm; 32% for AAA 7.0 cm or greater.[63]

Small AAAs

The rupture risk for small aneurysms is relatively low; most patients (66%) die from a different cardiovascular disease. However, the risk of rupture increases sharply at a diameter of 5.5 cm (Figure).[31] Two randomized studies, the ADAM trial[11] in the United States and the United Kingdom Small Aneurysm Trial,[64] have shown that elective surgery for aneurysms of less than 5.5 cm does not improve long-term survival.

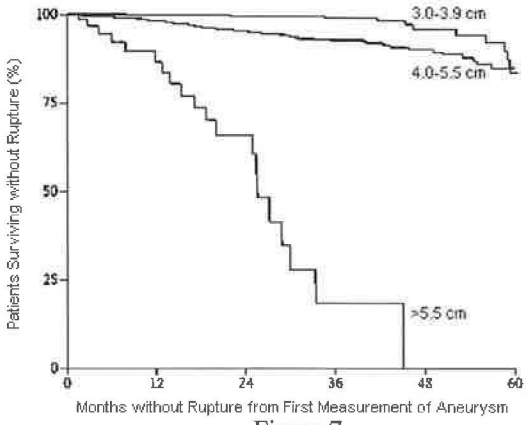


Figure 7

In ADAM, patients 50 to 79 years old with AAAs of 4.0 cm to 5.4 cm and who were not considered high surgical risks were randomly assigned to open repair of monitoring every six months with ultrasonography or CT scan. In the surveillance group, patients were referred for surgery under any of the following circumstances: the AAA enlarged to 5.5 cm; it enlarged by at least 0.7 cm in six months or 1.0 cm in one year; the AAA became symptomatic. No patient had surgery because of the rate of aneurysm enlargement. The mean follow-up was 4.9 years (range 3.5 to 8.0 years).

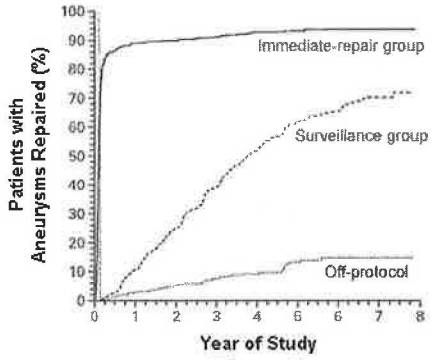


Figure 8

As would be expected, the rate of repair gradually increased in the surveillance group (Figure 8).[11] However, there was no significant difference between the groups in rate of death from any cause (relative risk, 1.21 for repair vs. surveillance; CI 0.95-1.54) (Figure 9, below).[11] The only predictors of increased rate of enlargement were larger initial diameter and absence of diabetes.

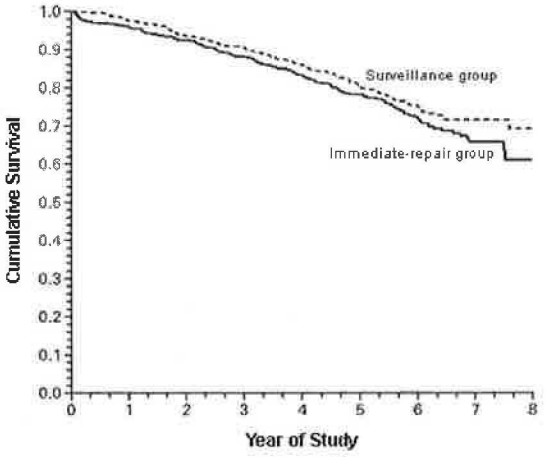


Figure 9

The UK Small Aneurysm Trial used a similar methodology and followed participants for a mean of 8 years (range, 6 years to 10 years). There was no long-term difference in mean survival between the early-surgery and surveillance groups. The curves crossed at three years. At eight years the small advantage in overall survival in the early-surgery group (7.2%, P=0.03) is attributed to improved health habits, particularly smoking cessation, in that group (Figure 10).[64]

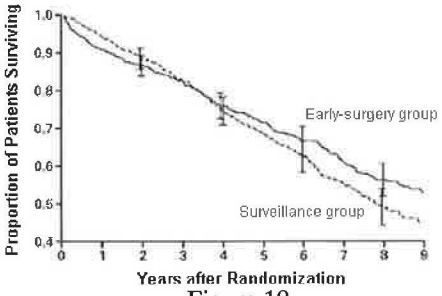


Figure 10

Patients who are eligible for repair should have repeat ultrasonography every six months for AAA diameters of 4.0 cm to 5.4 cm and screening intervals of two to three years have been advised for diameters of 3.0 cm to 4.0 cm.[11, 12, 65, 66] Such a program of "watchful waiting" requires a high degree of patient compliance, which may be problematic for certain individuals.[67]

Smoking increases the growth rate of AAAs by 20% to 25% and smoking cessation may reduce enlargement.[24, 26, 68] No other risk factor modification or medical therapy has been demonstrated to be effective in limiting enlargement. Blood pressure and cholesterol levels do not predict expansion. Cardiovascular risk factor modification is likely to improve longevity by effects unrelated to their AAA.[24, 31] Medical management has not been effective in limiting AAA enlargement. Propranolol has not been found useful.[69, 70] Trials directed at limiting inflammation have not been successful. A macrolide antibiotic,[71] doxycycline[72] and a statin[73] have been tested and do not appear to be effective.

Published Guidelines

The U.S. Preventative Services Task Force has not revised its recommendations for AAA screening since the publication of the randomized trials mentioned in this review. A recent consensus statement jointly sponsored by the Society for Vascular Surgery, the American Association of Vascular Surgery and the Society for Vascular Medicine and Biology applies broad criteria and would markedly increase the number of patients screened for AAAs (Appendix C).

Recommendations

Based on current evidence, the following is advised for patients who are surgical candidates:

- **One-time ultrasound exam for men age 65 to 79 who have ever smoked.**

Abdominal palpation to detect AAA should be part of the routine physical examination for patients as young as age 50, particularly men who have smoked, have a history of clinical atherosclerotic disease, or a family history of AAA. Selected patients may be referred for ultrasonography in the absence of AAA on palpation, especially those with a family history of AAA, including women.

Conclusion

As a sniper disease, AAAs have managed to avoid the notoriety commonly attributed to other forms of cardiovascular disease or to cancer. Ultrasound screening of high-risk individuals would expose this otherwise hidden illness and allow patients to dodge the sniper before it presents catastrophically. Although ultrasound screening is not currently reimbursed by standard health insurance, limited screening ultrasound exams and in particular hand-held ultrasound technology offer patients a high quality, convenient and relatively low cost service.

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Appendix A

Abdominal Palpation for Abdominal Aortic Aneurysm[1]

- Patient supine, knees raised, relaxed abdomen.
- Palpate deeply for aortic pulsation, several centimeters cephalad of umbilicus, to left of midline.
- With both palms down, place index fingers on either side of pulsation; it may be easier to probe one side of aorta at a time.
- Width, not intensity of pulsation, determines AAA.
- Normal aorta less than 2.5 cm (1 in); after allowing for skin thickness, refer patient with larger diameter for ultrasound.
- Palpation for AAA rarely indicated for patients younger than age 50.
- There are no reports of AAA rupture due to palpation.

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Appendix B

Screening for Abdominal Aortic Aneurysm: A Consensus Statement[1]

Recommendations

On the basis of available data, we recommend baseline ultrasound screening for AAA in the following patient cohorts:

- All men aged 60 to 85 years
- Women aged 60 to 85 years with cardiovascular risk factors
- Men and women older than 50 years with a family history of AAA

Patients who appear unfit for any intervention should be screened. On the basis of available data, we recommend subsequent surveillance of screened patients as follows:

- Aortic diameter less than 3 cm, no further testing
- AAA 3 to 4 cm in diameter, yearly ultrasound examination
- AAA 4 to 4.5 cm in diameter, ultrasound examination every 6 months
- AAA greater than 4.5 cm in diameter, referral to a vascular specialist

1. Kent KC, Zwolak RM, Jaff MR, et al. Screening for abdominal aortic aneurysm: a consensus statement. *Journal of Vascular Surgery.* Jan 2004;39(1):267-269. (Cosponsored by the Society for Vascular Surgery, the American Association of Vascular Surgery and the Society for Vascular Medicine and Biology)

Appendix C

Glossary[1]

Confidence Interval (CI): Range between two values within which it is probable that the true value lies for the whole population of patients from whom the study patients were selected.
Cost Analysis: An economic analysis in which only costs of various alternatives are compared. This comparison would inform only the resource-use half of the decision (the other half being the expected outcomes).
Cost Benefit Analysis: An economic analysis in which both the costs and the consequences (including increases in the length and quality of life) are expressed in monetary terms.
Cost-Effectiveness Analysis: An economic analysis in which the consequences are expressed in natural units. Some examples would include cost per life saved, or cost per unit of blood pressure lowered.
Cost Minimization Analysis: An economic analysis conducted in situations where the consequences of the alternatives are identical, and so the only issue is their relative costs.
Cost-Utility Analysis: A type of cost-effectiveness analysis in which the consequences are expressed in terms of life-years adjusted by peoples' preferences. Typically, one considers the incremental cost per incremental gain in quality adjusted life-years or QALYs.
Cross-Product Ratio (or Odds Ratio or Relative Odds): A ratio of the odds of an event in an exposed group to the odds of the same event in a group that is not exposed.
Efficacy[2]: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions.
Effectiveness[2]: A measure of the accuracy or success of a diagnostic or therapeutic technique when carried out in an average clinical environment.
Hazard Ratio: The weighted relative risk of an outcome (e.g., death) over the entire study period; often reported in the context of survival analysis.
Health-Related Quality of Life (HRQL):
Measurements of how people are feeling, or the value they place on their health state.
Incidence: Number of new cases of disease occurring during a specified period of time; expressed as a percentage of the number of people at risk.
Intention-to-Treat Analysis (or Intention-to-Treat Principle): Analyzing study participant outcomes based on the group to which they were randomized even if they dropped out of the study or for other reasons, did not actually receive the planned intervention. This analysis preserves the power of randomization, thus maintaining that important unknown factors that influence outcome are likely equally distributed across comparison group.
Kappa Statistic (or Weighted Kappa): A measure of the extent to which observers achieve agreement beyond the level expected to occur by chance alone. Kappa can take values from 0 (poor agreement) to 1.0 (perfect agreement).
Likelihood Ratio: For a screening or diagnostic test (including clinical signs or symptoms), the relative likelihood that a given test result would be expected in a patient with (as opposed to one without) the target disorder.
Negative Predictive Value (NPV): Proportion of people with a negative test who are free of disease.
Observational Studies (or Observational Study Design): Studies in which participant or clinician preference determines whether a participant receives treatment or control.
Odds Ratio (or Cross-Product Ratio or Relative Odds): A ratio of the odds of an event in an exposed group to the odds of the same event in a group that is not exposed.
Outcome (or Dependent Variable): The target variable of interest. The variable that is hypothesized to depend on or be caused by another variable, the independent variable.

P-value: The probability that results as or more extreme than those observed would occur if the null hypothesis were true and the experiment were repeated over and over. A P-value < 0.05 means that there is a less than 1 in 20 probability of the result occurring by chance alone if the null hypothesis were true.
Positive Predictive Value (PPV): The proportion of people with a positive test who have the disease.
Power: The ability of a study to reject a null hypothesis when it is false (and should be rejected). It is linked to the adequacy of the sample size; if a sample size is too small, the study will have insufficient power to detect differences between groups, if differences exist.
Prevalence: Proportion of persons affected with a particular disease at a specified time. Prevalence rates obtained from high quality studies can inform pretest probabilities.
Prognostic Factors: Patient or study participant characteristics that confer increased or decreased risk of a positive or adverse outcome.
Quality-Adjusted Life-Year (QALY): A unit of measure for survival that accounts for the effects of suboptimal health status and the resulting limitations in quality of life. For example, if a patient lives for 10 years and her quality of life is decreased by 50% because of chronic lung disease, her survival would be equivalent to 5 quality-adjusted life-years.
Randomized Controlled Trial (or Randomized Trial or Controlled Trial):
Experiment in which individuals are randomly allocated to receive or not receive an experimental preventative, therapeutic or diagnostic procedure and then followed to determine the effect of the intervention.
Relative Risk (or Risk Ratio): Ratio of the risk of an event among an exposed population to the risk among the unexposed.
Screening: Services, designed to detect people at high risk of suffering from a condition associated with a modifiable adverse outcome, to be offered to persons who have neither symptoms of, nor risk factors (other than age or gender) for a target condition.
Sensitivity: The proportion of people who truly have a designated disorder who are so identified by the test. The test may consist of, or include, clinical observations.
Specificity: The proportion of people who are truly free of a designated disorder who are so identified by the test. The test may consist of, or include, clinical observations.
Standard Error: The standard deviation of an estimate of a population parameter (thus, the standard error of the mean is the standard deviation of the estimate of the population mean value).
Surrogate Outcomes or Endpoints (or Substitute Outcomes or Endpoints):
Outcomes that are not in themselves important to patients, but are associated with outcomes that are important to patients, (eg, bone density for fracture, cholesterol for myocardial infarction, and blood pressure for stroke).
Target Endpoints (or Target Outcomes or Target Events): In treatment studies, the condition the investigators or clinicians are particularly interested in identifying and which it is anticipated the intervention will decrease (such as myocardial infarction, stroke, or death) or increase (such as ulcer healing).

1. Evidence Based Medicine Glossary. http://www.cebm.utoronto.ca/glossary/index.htm#s.
2. Stedman's Online Medical Dictionary. www.stedmans.com.