Patients with abdominal aortic aneurysm: Are we missing the opportunity for cardiovascular risk reduction?

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Introduction: **Antiplatelet agents, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statin drugs), angiotensin converting enzyme (ACE) inhibitors, and β-adrenergic receptor blockers (β-blockers) reduce cardiovascular risk and mortality in patients with specific manifestations of cardiovascular disease and risk factors. Occlusive arterial disease, in particular, coronary heart disease, is prevalent in patients with abdominal aortic aneurysm (AAA) and results in reduced life expectancy. The purpose of this study was to investigate the prevalence of cardiovascular disease and risk factors in patients with AAA. In particular, numbers of patients in whom pharmacologic therapy is indicated and numbers of patients who are receiving adequate treatment were determined.**

Methods: **This was a prospective study of 313 patients with AAA in Leicestershire over the 15 months between September 2002 and December 2003.**

Results: **Data that enabled determination of an indication for antiplatelet agents and statin drugs were available for 262 patients (84%), and for a β-blocker and ACE inhibitor for 313 patients (100%). An antiplatelet agent was indicated in 242 of 262 patients (92%), a statin drug was indicated in 196 of 262 patients (75%), a β-blocker was indicated in 107 of 313 patients (34%), and an ACE inhibitor was indicated in 178 of 313 patients (57%). In patients with an indication, 146 of 242 patients (60%) were using an antiplatelet agent, 81 of 196 (41%) were using a statin drug, 41 of 313 (38%) were using a β-blocker, and 69 of 313 (39%) were using an ACE inhibitor.**

Conclusion: **Cardiovascular disease, for which there is evidence for the survival benefit of pharmacologic risk reduction, is prevalent in patients with AAA. The data show that current treatment of cardiovascular risk is suboptimal and could be improved, with an expected reduction in cardiovascular morbidity and mortality. (J Vasc Surg 2004;40:691-7.)**

Antiplatelet agents, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statin drugs), angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic receptor blockers (β-blockers) reduce cardiovascular risk in patients with specific manifestations of atherosclerotic occlusive arterial disease.[1-4] Used individually, the relative risk for fatal and nonfatal cardiovascular events is reduced by approximately 25%, and when used in combination the risk reduction may be as great as 75%.[5] Atherosclerotic occlusive arterial disease, in particular, coronary heart disease (CHD), is prevalent in patients with abdominal aortic aneurysm (AAA), and results in reduced life expectancy compared with the rest of the population.[6,7]

Despite the strong association between AAA and cardiovascular risk, the potential role of pharmacologic risk reduction in patients with AAA has not been thoroughly investigated, and remains unclear. There is sparse mention of AAA in recommendations aimed at targeting patients for cardiovascular risk reduction, and little is known about the adequacy of current risk reduction in patients with AAA. To test the hypothesis that cardiovascular risk reduction is consequently suboptimal in patients with AAA, the goal of this study was to determine the number of patients with AAA in whom a statin drug, antiplatelet agent, β-blocker, and ACE inhibitor is indicated and the number of patients who are currently receiving adequate evidence based cardiovascular risk reduction therapy.

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Competition of interest: none.
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0741-5214/$30.00

doi:10.1016/j.jvs.2004.06.039

METHODS

A prospective study was conducted in 313 patients with AAA in Leicestershire over the 15 months between September 2002 and December 2003. Patients were recruited during routine vascular surgery outpatient clinic visits, before or after AAA repair; at admission to hospital for AAA repair; or during attendance at the Leicestershire AAA screening program. The screening program identifies men aged 65 from general practitioner (primary care physician) patient lists, and they are offered abdominal ultrasound scanning to measure the diameter of the aorta. Those with a small AAA (<5.5 cm) are followed up in the program with scanning at 3-month to 12-month intervals, depending on diameter; and those with a large AAA (>5.5 cm) are referred to the vascular outpatient department for consideration of surgical repair. All study patients had a general practitioner, and patients attending the vascular surgery outpatient clinic or admitted to hospital were under the care of a vascular surgeon. Although no vascular medicine specialist is present in the vascular surgery outpatient clinic, lifestyle advice regarding smoking cessation and exercise is

given, and medication is prescribed if it is thought appropriate.

A single investigator (G.L.) interviewed all patients, using a standardized form, and information supplied by patients was confirmed and supplemented with reference to medical records. Data were collected on patient age and sex, size of the AAA or size when repaired, smoking history, previous diagnosis of myocardial infarction (MI), angina, stroke, hypertension, peripheral vascular disease (PVD), and diabetes, and a record was made of all medication being taken at the time of recruitment into the study. The date and results of blood lipid measurements were obtained from the local pathology laboratory computer database. This database comprehensively records the results of all blood tests performed in the region. In each patient a blood pressure measurement was taken in the right arm with the patient seated. In patients in whom previous resting outpatient blood pressure measurements were recorded in the medical notes, mean blood pressure was calculated.

In patients with no history of occlusive arterial disease, prediction of their risk for CHD over 10 years was estimated with a CHD risk assessment calculator, based on the Framingham Heart Study data.[8] This risk assessment calculation is based on attaching weighting to patient age, sex, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol (HDL-C) concentrations, diabetes, and smoking habit. In the United Kingdom it is generally accepted as a minimum standard of care that a statin drug is indicated in the primary prevention of cardiovascular disease in patients without arterial occlusive disease with a 30% or greater predicted risk for CHD in the next 10 years.[9] An antiplatelet agent is recommended in the primary prevention of cardiovascular disease in patients with a 10-year risk for CHD of 15% or greater, and we have used these criteria as indication for an antiplatelet agent and statin drug in patients with no evidence of occlusive arterial disease.[9-11]

Patients with occlusive arterial disease were considered suitable for an antiplatelet agent, statin drug, and ACE inhibitor in accordance with evidence from the Antithrombotic Trialists' Collaboration, the Heart Protection Study, and the Heart Outcomes Prevention Evaluation (HOPE), which have demonstrated that all patients with occlusive arterial disease, defined as a history of MI, angina, ischemic stroke, or PVD, benefit from an antiplatelet agent, statin drug, and ACE inhibitor.[1-3] The HOPE study also demonstrated that patients with diabetes plus an additional risk factor (hypertension, smoking, high total cholesterol concentration, low HDL-C concentration, documented microalbuminuria) benefit from an ACE inhibitor, and we have used these criteria as indication for treatment.[3] β-Blockers reduce mortality after MI, and their use in patients with angina lowers the frequency of ischemic episodes.[4] We have therefore considered patients with MI or angina suitable to receive β-blockers. Hypertension has been defined as blood pressure 140/90 mm Hg or greater, in accordance with the British Hypertension Society classification of hypertension.[12] In addition, it is universally accepted that smoking cessation is beneficial in all persons.

Statistical analysis was performed with SPSS version 9, and the χ^2 test was applied.

RESULTS

Two hundred eighty (89%) patients with AAA were men, and 33 (11%) were women. Their median age was 71 years (range, 53-91 years). Seventy patients (22%) had previously undergone AAA repair, and 243 patients (78%) were undergoing AAA surveillance or consideration of elective AAA repair at the time of the study. Mean AAA diameter when recruited into the study or at the time of AAA repair was 5.2 cm (range, 3-10 cm). Sixty-nine patients (22%) had a history of MI, 38 (12%) had angina but no history of MI, 46 (15%) had a history of ischemic stroke, and 80 (26%) had PVD.

Of the total 313 patients, 202 (65%) had a blood lipid measurement in the previous 5 years; mean total cholesterol concentration was 5.0 mmol/L (range, 2.9-8.5 mmol/L). Two hundred twenty-eight patients (73%) were undergoing treatment of hypertension. Mean systolic blood pressure was 146 mm Hg, and mean diastolic blood pressure was 84 mm Hg. Two hundred eight patients (66%) had systolic pressure 140 mm Hg or greater, or diastolic pressure 90 mm Hg or greater. Twenty-one patients (7%) had diabetes. Twenty-seven (9%) patients denied ever having smoked cigarettes, 75 (24%) were current smokers, and 211 (67%) were former smokers. Patients with a history of cigarette smoking had a mean pack-year history of 38.2 years.

One hundred seventy-four patients (56%) had evidence of occlusive arterial disease (MI, angina, PVD, stroke), thereby having indication for an antiplatelet agent, statin drug, and ACE inhibitor. One hundred seven of 174 patients (61%) had a history of MI or angina, and therefore, in addition, had an indication for a β-blocker (Table I; Fig 1).

One hundred thirty-nine patients (44%) with AAA were not known to have occlusive arterial disease, and therefore an indication for a statin drug was based on demonstration of a 10-year CHD risk of 30% or greater (Fig 1). Fifty-one of 139 patients (37%) had not had a recent blood lipid measurement. Eighty-eight patients (63%) had total cholesterol and HDL-C concentration measurements, thereby enabling 10-year CHD risk calculation. Mean 10-year CHD risk in the 88 patients was 22% (range, 5%-53%). Twenty-two of the 88 patients (25%) had a 10-year CHD risk of 30% or greater, thereby having an indication for a statin drug. Of the 88 patients with a determinable 10-year CHD risk, 68 (77%) had a 10-year risk of 15% or greater, thereby having an indication for antiplatelet prophylaxis. Statin drug and anitplatelet use, depending on lipid measurement and indication, is shown in Fig 2. Four patients without occlusive arterial disease had diabetes and an additional cardiovascular risk factor, and in accordance with the results of the HOPE study should use an ACE inhibitor.

Table I displays the total numbers and percentages of the 313 patients with AAA with indication for specific

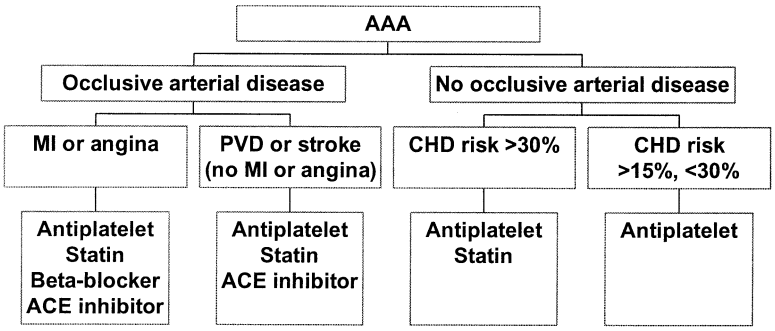

Fig 1. Algorithm for pharmacologic cardiovascular risk reduction in patients with abdominal aortic aneurysm *(AAA)*. In all patients hypertension should be treated if present, and smoking should be stopped. Occlusive arterial disease is defined as myocardial infarction *(MI)*, angina, peripheral vascular disease *(PVD)*, or ischemic stroke. *CHD,* Coronary heart disease; *ACE,* angiotensin converting enzyme.

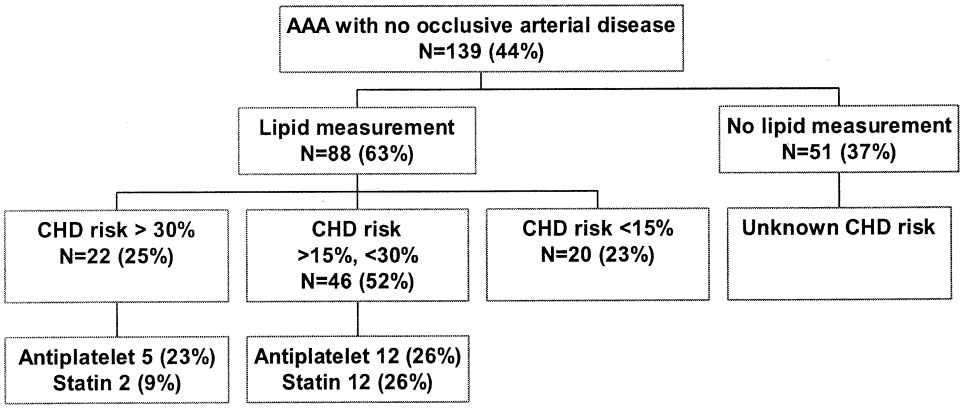

Fig 2. Summary of lipid measurement, 10-year risk for coronary heart disease *(CHD)*, and antiplatelet and statin drug use in 139 patients with abdominal aortic aneurysm *(AAA)* without evidence of occlusive arterial disease.

therapy, and those patients undergoing appropriate pharmacologic risk reduction. Table II gives a breakdown of vascular disease in the 313 patients with AAA, and the total number and percentage of patients using an antiplatelet agent, statin drug, ACE inhibitor, and β-blocker.

There was no significant difference in adequacy of treatment in patients who had undergone AAA repair compared with those who had not. Comparing appropriate treatment use in patients with an indication who had undergone AAA repair versus those who had not undergone AAA repair respectively revealed that antiplatelet agents were used by 31 of 52 patients versus 115 of 190 patients ($P = .905$), statin drugs were used by 18 of 42 patients versus 63 of 154 patients ($P = .82$), β-blockers were used by 11 of 25 patients versus 30 of 82 patients ($P = .504$), and ACE inhibitors were used by 13 of 37 patients versus 56 of 141 patients ($P = .611$; χ^2 test).

DISCUSSION

The high prevalence of cardiovascular disease and risk factors in patients with AAA means that most have an indication for an antiplatelet agent, statin drug, ACE inhibitor, or β-blocker. Seventy-five percent of 174 patients with occlusive arterial disease and 88 patients without evidence of occlusive arterial disease who had a lipid measurement had a clear indication for a statin drug. If the 51 patients without occlusive arterial disease who did not have a lipid measurement are included in the analysis and it is assumed that the proportion of the 51 patients with indication for a statin drug is the same as in the patients without occlusive arterial disease who had a lipid measurement (25%), then 67% would have an indication for a statin drug. An antiplatelet agent was indicated in 92% of patients with AAA, excluding the 51 patients who had not had a lipid measurement. Again, if it assumed that the proportion of the 51 patients with indication for an antiplatelet agent is the same as in the patients without occlusive arterial disease with a lipid measurement (77%), then 90% would have an indication for an antiplatelet agent. Thirty-four percent of patients had an indication for a β-blocker, because of a history of MI or angina, and 57% had an indication for an ACE inhibitor, in accordance with the findings of the HOPE study.[3,4]

Table I. Numbers and percentages of patients with occlusive arterial disease and without occlusive arterial disease, and total number of patients with indication for specific therapy and numbers and percentages appropriately treated

	Patients with OAD with indication*		*Patients with OAD treated*		*Patients without OAD with indication*		*Patients without OAD treated*		*Total patients with indication*		*Total patients treated*	
Therapy	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Antiplatelet	174	100	129	74	68	77	17	25	242	92	146	60
Statin	174	100	79	45	22	25	2	9	196	75	81	41
β-blocker	107	61	41	38	—		—		107	34	41	38
ACE inhibitor	174	100	67	39	4	3	2	50	178	57	69	39

In the consideration of patients in whom an antiplatelet agent or statin are indicated, the 51 patients without occlusive arterial disease in whom 10-year coronary heart disease risk could not be established have been excluded.
OAD, Occlusive arterial disease.
*OAD is defined as myocardial infarction, angina, peripheral vascular disease, or ischemic stroke.

Table II. Breakdown of associated manifestations of occlusive arterial disease in patients with AAA and the numbers and percentage receiving an antiplatelet agent, statin, β-blocker, and ACE inhibitor

Cardiovascular pathologies (N = 313)	*Total no. of patients treated*		*Patients using statin*		*Patients using antiplatelet*		*Patients using β-blocker*		*Patients using ACE inhibitor*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
AAA only	139	44	24	17	35	25	33	24	35	25
AAA and PVD	38	12	8	21	18	47	12	32	11	29
AAA and CHD	63	20	36	57	53	84	30	48	23	37
AAA and stroke	23	7	8	35	16	70	8	35	6	26
AAA, PVD and CHD	27	9	18	67	23	85	5	19	16	59
AAA, PVD and stroke	6	2	2	33	3	50	1	17	2	33
AAA, CHD and stroke	8	3	3	38	8	100	3	38	2	25
AAA, CHD, Stroke and PVD	9	3	4	44	8	89	3	33	7	78

PVD, Peripheral vascular disease; *CHD,* coronary heart disease.

However, suboptimal cardiovascular risk management is demonstrated; only 60% of patients were using an antiplatelet agent, 41% were using a statin drug, 38% were using a β-blocker, and 39% were using an ACE inhibitor, when indicated. In addition, 35% of patients had not had a blood lipid measurement in the previous 5 years, and the finding that 66% of patients had blood pressure 140/90 mm Hg or greater suggests that hypertensive control could be improved. It is established that smoking cessation can reduce the risk for MI by half, and the finding that one fourth of the patients were current smokers highlights a further opportunity for intervention to reduce cardiovascular risk.[5]

The presence of AAA is an indicator of high cardiovascular risk.[13,14] In 1980 Hertzer et al[15] demonstrated that patients who have undergone AAA repair have an annual CHD mortality rate of 1.9% to 3.9%, and on this basis the American 2001 Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP-III) document[16] considers AAA to be a CHD risk equivalent, a condition conferring a 20% or greater 10-year risk for CHD. More recent studies have reported similar findings; the United Kingdom Small Aneurysm Trial observed a 28% incidence of mortality due to cardiovascular causes over an 8-year period, and 5-year survival rates between 60% and 74% have been demonstrated.[7,18-20]

The 2003 Heart Protection Study, a randomized controlled trial of 20,536 patients aged 40 to 80 years with occlusive arterial disease receiving 40 mg of simvastatin daily or placebo demonstrated a reduction of approximately 25% in cardiovascular events and death in patients receiving simvastatin, irrespective of baseline cholesterol level.[2] There is growing evidence that statin drugs may also reduce perioperative mortality in patients undergoing major vascular surgical procedures, and long-term statin drug use after AAA repair is associated with reduced all-cause and cardiovascular mortality.[21-23] Although ATP-III recommends aggressive low-density lipoprotein cholesterol–lowering therapy in patients with AAA, at present the evidence for routine use of statin drugs in patients with AAA is limited.[16] This study demonstrates that most patients with AAA have associated cardiovascular disease for which statin drugs confer survival benefit, strengthening the case for routine statin therapy in most patients with AAA.

Risk for bleeding in patients using aspirin is constant, irrespective of the severity of cardiovascular disease, and cardiovascular benefit appears linearly dependent on absolute cardiovascular risk.[24] The Antithrombotic Trialists' Collaboration in their meta-analyses of 287 randomized trials of antiplatelet therapy versus control or one antiplatelet regimen versus another demonstrated that an antiplatelet agent reduces vascular events by 25% and vascular mortality by one sixth in patients at increased risk for occlusive vascular events.[1] In primary prevention, aspirin use cannot be justified without formal CHD risk estimation. The precise level of CHD risk necessary to justify antiplatelet treatment is controversial. In the United States treatment has been recommended in patients with 10-year CHD risk levels of 6% and 10%, whereas in the United Kingdom treatment in patients with risk of 15% or greater is generally recommended.[10,25,26] The estimation that the presence of AAA confers a 20% or greater 10-year CHD risk provides the rationale for the Antiplatelet in Vascular Surgery Consensus Statement, which recommends that an antiplatelet agent should be strongly considered in patients with AAA without evidence of occlusive arterial disease.[27] Our demonstration that 92% of patients with AAA overall, and 77% without evidence of occlusive arterial disease, have an indication for an antiplatelet agent supports this, but at present no studies have determined the actual risk reduction associated with antiplatelet use in patients with AAA.

In patients who have had an MI, a β-blocker reduces mortality by as much as 40%, and although there is no evidence that β-blocker use in patients with stable angina improves survival, its use reduces the frequency of ischemic episodes.[4,28] Perioperative use of β-blockers in patients at high risk for cardiovascular disease or undergoing major vascular surgery significantly lowers risk for MI and cardiac death in the perioperative period and up to 2 years postoperatively.[29,30]

ACE inhibitors confer a proved survival benefit in patients with left ventricular systolic dysfunction, and improve outcome in patients after MI.[31] The HOPE study of 9297 patients at increased risk for vascular disease randomized to receive either the ACE inhibitor ramipril or placebo expanded the indication for treatment by demonstrating that ramipril lowered the risk for MI, stroke, or cardiovascular death by 22% in this patient group.[3] We have demonstrated that, by virtue of meeting the criteria laid out in the HOPE study, more than half of patients with AAA should be using an ACE inhibitor.[3]

Secondary prevention of cardiovascular disease has been simplified and indications expanded by the demonstration that all patients with evidence of occlusive arterial disease benefit from a statin drug, antiplatelet agent, and ACE inhibitor.[1-3] The effects of each agent appear to be independent and additive, and it has been estimated that when these are used in combination, two thirds to three fourths of future vascular events can be prevented.[5] In the 4 categories of treatment discussed, at least 1 non-proprietary agent exists, resulting low-cost antiplatelet agents (aspirin 75 mg, $0.30 per 28 days), β-blockers (propranolol 10 mg, $1.00 per 28 days), and ACE inhibitors (captopril 12.5 mg, $2.00 per 28 days). However, at present, even the cheapest statin drug is relatively expensive (fluvastatin 20 mg, $23.00 per 28 days).[32] The significant benefit of treatment, combined with relative safety, has led to advocates of a "polypill" suggesting that all patients older than 55 years or those with manifestations of occlusive vascular disease should take a combined pill containing a statin drug, aspirin, 3 antihypertensive agents, and folic acid.[33] However, at present, cardiovascular risk reduction remains dependent on identifying patients with indication for specific therapy. The lack of studies investigating the potential benefit of similar therapeutic measures in patients with AAA means that little direct evidence exists for the benefit of pharmacologic cardiovascular risk reduction. Currently, identification of patients with AAA who will benefit from using an antiplatelet agent, statin drug, β-blocker, or ACE inhibitor depends on demonstrating associated cardiovascular disease for which there is evidence for their use. A recent study of patients with PVD, a condition where there is clear evidence of the benefit of pharmacologic cardiovascular risk reduction, demonstrated that 93% of patients were using an antiplatelet agent, 56% were using a statin drug, and 54% were using an ACE inhibitor.[34] Although this is clearly not optimal treatment, it is superior to that in patients with AAA. Typically in the United Kingdom vascular medicine specialists are not present in the vascular surgery clinic, and we would expect our results to be comparable with those in most UK centers.

Side effects of the pharmacologic agents discussed are less common than previously thought, and more therapeutic options within each drug class are becoming available. Patients who are intolerant of aspirin can often tolerate alternative antiplatelet agents.[27,35] Symptoms sufficiently severe to stop β-blocker treatment occur in only 0.8% of patients, and, although cited as a relative contraindication, most patients with PVD satisfactorily tolerate a β-blocker.[36] Statin drugs are safe, with liver failure and rhabdomyolysis the only serious adverse effects, occurring at a rate of only 1 case per million person-years.[37] The only absolute contraindication to statin drug use is active or chronic liver disease.[37] ACE inhibitors are well tolerated, with unwanted symptoms sufficiently severe to stop treatment occurring in 0.1% of patients. However, they can cause a decline in renal function or hypotension, and therefore their use requires monitoring.[3,36] The large proved benefit of these therapies means that, unless an absolute contraindication to treatment exists, treatment should be initiated and patient tolerance established.

The main limitation of this study is that the identification of cardiovascular disease depends on the accuracy of a previous diagnosis. Only a small number of patients have assessment of left ventricular function available, so we have made no mention of this in our analysis of patients who should receive an ACE inhibitor. Although this approach will tend to underestimate the number of patients with an indication for cardioprotective therapy, it enables an accurate evaluation of adequacy of current cardiovascular risk factor reduction in patients with known indications. We have used a 10-year CHD risk of

30% or greater as the indication for statin therapy in patients with no occlusive arterial disease, to avoid overestimating the number of patients with indication for treatment. Generally, 10-year CHD risk of 30% or greater is considered the minimum accepted standard of care, and although initiating treatment at predicted risk levels as low as 15% has been advocated, local recommendations depend in part on available resources.[38]

Despite the strong association between AAA and cardiovascular disease, identification and treatment of cardiovascular risk in patients with AAA is suboptimal. The growing popularity of AAA screening programs will result in the increasing identification of patients with AAA and therefore patients at high cardiovascular risk. Frequently patients with AAA are not under the care of a cardiovascular physician, and provided long-term monitoring can be conducted in primary care, the vascular surgery clinic would be an appropriate setting for the initiation of treatment. This approach will no doubt increase the life expectancy of patients with AAA.

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Submitted Apr 15, 2004; accepted Jun 30, 2004.